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Editorial**Parvo: Canine Enemy No. 1****Mohsin Masud Jan**

Editor

Today, we'll digress from our usual routine of topics and exit the human world to delve into the world of man's best friend. Records show that dogs are the first ever domesticated animals. And over these thousands of years of human canine partnership, seldom has there been an occasion when dogs have been needed to be protected by humans, but alas, along came Parvovirus.

Now, a little background, what exactly is Parvo? Canine parvovirus type 2 (CPV2, colloquially parvo) is a contagious virus mainly affecting dogs, and is thought to originate in cats. The current consensus is that the feline panleukopenia mutated into CPV2. Parvo is highly contagious and is spread from dog to dog by direct or indirect contact with their feces. Vaccines can prevent this infection, but mortality can reach 91% in untreated cases. Treatment often involves veterinary hospitalization. Canine parvovirus may infect other mammals; however, it does not infect humans. The major symptoms associated with the intestinal form of a canine parvovirus infection include severe, bloody diarrhea, lethargy, anorexia, fever, vomiting, and severe weight loss. The intestinal form of CPV affects the body's ability to absorb nutrients, and an affected animal will quickly become dehydrated and weak from lack of protein and fluid absorption. The wet tissue of the mouth and eyes may become noticeably red and the heart may beat too rapidly. On abdominal examination, the dog may respond with pain or discomfort. Dogs that have contracted CPV may also have a low body temperature (hypothermia), rather than a fever.

The timely diagnosis of parvo can make all the difference between life and death for a pup. Diagnosis is made by the following methods: physical examination, biochemical tests, urine analysis, abdominal radiographs, and abdominal ultrasounds. A chemical blood profile and a complete blood cell count will also be performed. Low white blood cell levels are indicative of CPV infection, especially in association with bloody stools. Biochemical and urine analysis may reveal elevated liver enzymes, lymphopenia, and electrolyte imbalances. Abdominal radiograph imaging may show intestinal obstruction, while an abdominal ultrasound may reveal enlarged lymph nodes in the groin, or throughout the body, and fluid-filled intestinal segments.

Treatment usually involves extensive hospitalization, due to the severe dehydration and damage to the intestines and bone marrow. A CPV test should be

given as early as possible if CPV is suspected in order to begin early treatment and increase survival rate if the disease is found. Treatment ideally also consists of crystalloid IV fluids and/or colloids (e.g., Hetastarch), antinausea injections (antiemetics) such as maropitant, metoclopramide, dolasetron, ondansetron and prochlorperazine, and broad-spectrum antibiotic injections such as cefazolin/enrofloxacin, ampicillin/enrofloxacin, metronidazole, timentin, or enrofloxacin.^[5] IV fluids are administered and anti nausea and antibiotic injections are given subcutaneously, intramuscularly, or intravenously. The fluids are typically a mix of a sterile, balanced electrolyte solution, with an appropriate amount of B-complex vitamins, dextrose and potassium chloride. Analgesic medications can be used to counteract the intestinal discomfort caused by frequent bouts of diarrhea; however, the use of opioid analgesics can result in secondary ileus and decreased motility. In addition to fluids given to achieve adequate rehydration, each time the puppy vomits or has diarrhea in a significant quantity, an equal amount of fluid is administered intravenously. The fluid requirements of a patient are determined by the animal's body weight, weight changes over time, degree of dehydration at presentation and surface area.

Once the dog can keep fluids down, the IV fluids are gradually discontinued, and very bland food slowly introduced. Oral antibiotics are administered for a number of days depending on the white blood cell count and the patient's ability to fight off secondary infection. A puppy with minimal symptoms can recover in 2 or 3 days if the IV fluids are begun as soon as symptoms are noticed and the CPV test confirms the diagnosis. If more severe, depending on treatment, puppies can remain ill from 5 days up to 2 weeks.

However, even with hospitalization and all forms of extensive treatment, there is no guarantee that the dog will be cured and will survive. Now, in Pakistan, Parvo is highly endemic, widely spread, and is responsible for the deaths of hundreds of pups all over the country no matter how well kept and bred they may be. Hence, in case you're getting a pup, prevention is the best treatment, you can afford. Generally once the pup crosses the age of 6 months, the incidence of parvo decreases drastically. So for the first few months, keep your furry little best friends isolated from other dogs until, at the very least, all his vaccinations are complete.

Sentinel Lymph Node Biopsy in Early Breast Carcinoma

Ambreen Munir, Farzana Bibi, Shiraz Shaikh, Zameer Hussain Laghari, Muhammad Rafique Pathan and Sohail Ahmed Memon

ABSTRACT

Objective: The objective of this study is to determine the success rate of sentinel node dissection and sensitivity of sentinel node to determine the presence of axillary node metastasis in women with clinically node negative breast cancer.

Study Design: Observational / descriptive study.

Place and Duration of Study: This study was conducted at the Department of Surgery, Liaquat University Hospital Jamshoro from January 2014 to December 2014.

Materials and Methods: Thirty (30) female patients admitted with biopsy proven early breast carcinoma with clinically negative axillary lymph nodes were prospectively enrolled in the study. All patients underwent complete general and local physical examination. All routine and specific investigations were carried out and after obtaining informed consent, patients were prepared for surgery. A proforma was filled-in including clinical data and all the data was analyzed on SPSS 16.0.

Results: Thirty female patients with mean age of 45.8 ± 1.10 and 60% patients having pain with lump in the breast was found in the study. The family history of breast carcinoma was found positive in 20% of cases while 26% women having history of oral contraceptives. The left breast was more frequently involved and found in 76.6% of cases. Majority of the patients (93.4%) underwent mastectomy. In 56.44% of the cases, 3 to 4 sentinel lymph nodes were detected. In postoperative histopathology, invasive ductal carcinoma was found in 46.6% of the cases with grade II was in 56.7% of the patients.

Conclusion: The sentinel node notion in breast cancer has been broadly validated & is the standard care for lymphatic staging in early breast carcinoma.

Key Words: Breast carcinoma, Sentinel node, Mastectomy

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INTRODUCTION

Over the past 10 years, axillary lymph node was generally acknowledged as the most specific predictive device accessible in accessing axillary nodal status & henceforth breast malignancy staging^{1,3}. In account of breast cancer treatment, sentinel lymph node biopsy (SLNB) is proved to be less invasive tool^{4,5}. The adverse effects concerned with ALND are associated with extensive complications i.e. post surgical lymphedema, seroma formation, neuropathy, paresthesia, chronic shoulder pain, joint distraction, weakness & immobility^{2,3,6-8}. That's why SLNB is preferred in females with breast cancer needing full dissection⁹, for better quality of life & less hospital time. Though SLNB method have side effects, but with fewer risks as compared to ALND^{10,11}.

As breast cancer ration has increased in Malta, with highest ranking in Europe at 34.4/100,000 million¹², staging procedures with less difficulties were being specified. The SLNB was commenced in May 2009. With the notion of the organized chain of lymph node metastasis, which involve one or few lymph nodes (sentinel node/s, (SN/s)) primarily approached by metastasizing cells from tumour dissemination^{13,14}. To reduce morbidity, all SNs must be surgically cropped while SLNB to stage the cancer. Presence of more than 1 sentinel node is considered as milieu of breast cancer as it could give rise to multiple lymphatic channels from existing lesion¹⁵⁻¹⁷. In 75% to 95% of cases, the lymphatic drainage of the breast (SN) is restricted to the ipsilateral axilla, even though disparity in the lymphatic flow is present^{11,18-19}.

The purpose of my study is to determine the importance of sentinel lymph node biopsy in early carcinoma of breast at Liaquat University Hospital Jamshoro.

MATERIALS AND METHODS

This study was carried out in Department of Surgery of Liaquat University Hospital Jamshoro. All patients with unifocal biopsy proven carcinoma of breast < 5cm in diameter, clinically positive axillary lymph nodes,

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multifocal tumours of breast, any previous axillary or breast surgery, neoadjuvant therapy, pregnancy and inflammatory carcinoma were excluded from the study. After ethical committee approval, informed written consent after explaining the patient about the procedure, thirty female patients were included in the study. All patients underwent complete general and local physical examination. All routine and specific investigations were carried out, patients were prepared for surgery. A proforma was filled-in including clinical data and all the data was analyzed on SPSS 21.0.

RESULTS

Total 30 patients were included in the study, mean age of 45.8 ± 1.10 , in these women, age of menarche was 12.8 ± 1.37 and age of menopause in our series was detected with mean 48.12 ± 3.07 years, while lactation period was noted as 14.4 ± 10.6 . (Table: 1). According to the complaints, most patients (60%) having pain with lump, while 40% only presented with lump. (Table: 2). In the 20% of the patients, family history found to be positive for breast carcinoma while in 26% history of contraceptive pills was found positive.

According to the site, left breast involvement was found in the 76.6% of the women, right breast involvement was noted in 23.4% of the cases. Mostly tumours were found in the upper quadrant of the breast with the percentage of 73.4%, lower quadrant were found with tumour 20% and only 6.6% women having tumour in the region of the breast (Table: 3).

Table No. 1: Age distribution of the patients n=30

Age	Mean $\pm$ SD
Age of Women (years)	45.8 ± 1.10
Age of Menarche (years)	12.8 ± 1.37
Age of Menopause (years)	48.12 ± 3.07
Lactation Period (months)	14.4 ± 10.6

Table No. 2: Presenting complaint of the patients n=30

Complaint	Frequency (%)
Lump with pain	18 (60.0%)
Lump without pain	12 (40.0%)

Table No. 3: Assessment of the breast n=30

History	Frequency (%)
Breast Involved	
Left	23 (76.6%)
Right	07 (23.4%)
Tumour Site	
Upper quadrant	22 (73.4%)
Lower quadrant	06 (20%)
Central region	02 (6.6%)
Tumour Size	
Index=AP+T(Mean $\pm$ SD)	11.32 ± 5.4

Table No. 4: Operative analysis of the cases n=30

Operative analysis	Frequency (%)
Injecting Site	
Intradermally	19 (63.3%)
Peritumoural	11 (36.7%)
Type of Surgery	
Breast Conservative	02 (6.6%)
Mastectomy	28 (93.4%)
Number of SLN detected	
1 – 2	12 (40%)
3 – 4	16 (53.4%)
< 4	02 (6.6%)
Berg's Level of SLN	
Level I	30 (100%)
Level II	00
Analytic Method of SLN	
Methylene blue	30 (100%)
Other	00

Table No. 5: Histopathological findings of tumour n=30

Finding	Frequency (%)
Ductal carcinoma in situ	01 (3.3%)
Ductal carcinoma	03 (9.9%)
Invasive intraductal cell carcinoma	01 (3.3%)
Infiltrating ductal carcinoma	07 (23.3%)
Invasive ductal carcinoma	14 (46.6%)
Invasive lobular carcinoma	04 (13.3%)
Total	30 (100%)

Table No. 6: Grading of the tumor and ER-PR score n=30

History	Frequency (%)
Grading of the tumour	
I	13 (43.3%)
II	07 (56.7%)
Score	
ER Score	5.6 ± 3.06
PR Score	3.4 ± 3.02

Table No. 7: Complications of SLNB n=30

Complications	Frequency (%)
Allergic reaction	00
Pain or discomfort	04 (13.3%)
Fluid collection	00
Skin discoloration	01 (3.3%)
Infection	02 (6.6%)
Bleeding	02 (6.6%)
Necrosis	01 (3.3%)
Abscess formation	02 (6.6%)

Out of Thirty, Nineteen (63.3%) cases were selected for intradermally injecting site while Eleven (36.7%) were selected for peritumoural injection (Table: 4). Majority of the cases 93.4% were underwent mastectomy and only 6.6% women were underwent breast conservative surgery. In the majority of the cases

53.4%, 3 to 4 SLN were detected, 1 to 2 were detected in the 40% of the cases while 6.6% of the cases were found with more than 4 SLN detected. According to the Berg's level of SLN, completely patients were found with level I (Table: 4).

According to the histopathology of the removal tumour, invasive ductal carcinoma was found in 36.6% of the cases, second most common variety was infiltrating ductal carcinoma which accounts for 20% of the cases (Table: 5). In the grading of tumour, grade II was most common and accounts for 56.7% while 43.3% tumours found in grade I. Total ER score was found as (Mean $\pm$ SD) 5.6 $\pm$ 3.06. and total PR score was noted as (Mean $\pm$ SD) 3.4 $\pm$ 3.02 (Table: 6).

The complications of SLNB was described in table: 7.

DISCUSSION

The world's most widespread female's cancer accounting for almost 1/4th of all cancers is the breast cancer^{20, 21}. females of all races, ethnicities & geographic areas are affected. nonetheless, ethnicity & area based disparities in breast cancer pathology is an well-known trait²²⁻²⁴. The frequency, clinical appearance & endurance rates differ in dissimilar geographic areas, races & ethnicities²⁵. In developed countries there is higher occurrence & decreased mortality rates have been reported. 45% of all cases & 55% of all mortalities are occurring in the poor & average income countries.

The mean age of 47 $\pm$ 12 years in the patients with breast cancer reported by Khokhar S, et al²⁹. In our series mean age was found as 45.8 $\pm$ 1.10. Mean age has been accounted as 48 years by Malik, et al²⁷, and Shariq, et al²⁸ also reported as findings.

Nulliparity augment lifetime occurrence of breast cancer. As compared to meta-analysis from Nordic countries, It was related to 30% raised risk³⁰. Pregnant females have 2/3 folds less likelihood of mounting breast cancer. with every consecutive nativity, there is 7% decrease risk is renowned. There are less chances of cancers when child parity occurs earlier than 30 years of age³⁰. In a Pakistani study, it was illustrated that in women who had no issue (12.06%) breast cancer was common, & (9.37%) in women who deliver infants after 30 years of age³¹. In this study, majority (60%) of tumours were found in the women with low parity.

In One third of the population, familial breast cancer cases are due to BRCA-1 gene mutation on chromosome number 17. In 4-47.3% positive familial record of breast tumors were instituted in Pakistan²⁷. there is 2/4 fold increased risk of cancer in females having first degree relative (mother, daughter/sister) with breast cancer³². Risk of cancer dramatically amplified If family member developed cancer before 50 years of age³². Positive familial history was found in 25% of our population. Similarly in this study, family history was found in the 20% of the patients.

There is increased risk of BRCA-1 mutation carriers with the use of oral contraceptives.³² premenopausal breast cancer is noted in young ladies who utilize oral

contraceptives for four years or more before first time parity. There is contrary alliance was renowned among oral contraceptive & breast cancer³³. In our study, 26% of women were found with the history of use of contraceptive pills. In finding of another study from Pakistan stated that oral contraceptive utilization is radically related with breast cancer³⁴.

In the study of Hajrah Doutani et al³⁵, reported that right breast in 44.8% of cases, the left breast in 47% and bilateral involvement in 8% of cases with breast cancer. In our study, according to the site, left breast involvement was found in the 76.6% of the women,, right breast involvement was noted in 23.4% of cases. Mostly tumors were found in the upper quadrant of the breast with the percentage of 73.4%, lower quadrant were found in 20% and only 6.6% women having tumour in the central region of the breast.

In the study of Hajrah Doutani et al³⁵ suggested the histomorphological types seen among 272 breast cancer patients indicated that there were 212 cases (78%) with histology of invasive ductal carcinoma which was found to be the most common type. According to Muhammad et al³⁶, infiltrating ductal carcinoma with nonspecific features was the commonest type, found in 38 patients (82.6%). Similarly in the present study histopathology of the removal tumour, invasive ductal carcinoma was found most common and accounts for 36.6% of the women, second most common variety is infiltrating ductal carcinoma and was found in 20%.

CONCLUSION

The sentinel node notion in breast cancer has been broadly validated. It is the standard care for lymphatic staging of breast & facilitates accurate, less invasive lymphatic staging in avoiding the morbidity of regular lymph node dissection for node negative breast cancer females.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Chakravorty, N. Sanmugalingam, A. Shrestha. Axillary Nodal Yields: A comparison between primary clearance and completion clearance after sentinel lymph node biopsy in the management of breast cancer. *Eur J Surg Oncol* 2011;37(2): 122-126.
2. E.A. Newman, L.A. Newman. Lymphatic mapping techniques and sentinel lymph node biopsy in breast cancer. *Surgical Clinics of North Am* 2007; 87(2):353-364.
3. Namwongprom S, Boonyaprapa S, Ekmahachai M. Breast lymphoscintigraphy for sentinel lymph node identification in breast cancers with clinically-negative axillary nodes. *Singapore Med J* 2005;46 (12):688-692.
4. Sun X, Liu JJ, Wang YS. Roles of preoperative lymphoscintigraphy for sentinel lymph node biopsy

- in breast cancer patients. *Jap J Clin Oncol* 2010; 40(8):722-725.
5. Keshitgar MRS, Waddington WA, Lakhani SR. The sentinel node in surgical oncology. Springer Verlag Berlin 1999;49-89.
 6. Pesek S, Ashikaga T, Krag LE. The false negative rate of sentinel node biopsy in patients with breast cancer, a meta-analysis. *World J Surg* 2012;36(9): 2239-2251.
 7. Bokhari, Q. Tahir, S. Rasul. Early experience of sentinel lymph node biopsy in breast cancer. *J Surg Pak Int* 2009;14(1):29-32.
 8. Vijayakumar V, Boerner PS, Jani AB. A critical review of variables affecting the accuracy and false-negative rate of sentinel node biopsy procedures in early breast cancer. *Nuclear Med Comm* 2005;26:395-405.
 9. Pechlivanides G, Vassilaros D, Tsimpanis A. Sentinel node biopsy for breast cancer patients: issues for discussion and our practice. *Pathol Res Int* 2011;1-8.
 10. Mansel RE, Fallowfield L, Kissin M. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer. The ALMANAC trial. *J Natl Cancer Inst* 2006;98(9):599-609.
 11. Leikola J. Sentinel lymph node biopsy as a diagnostic tool in the treatment of breast cancer. Academic Dissertation 2008;1-90.
 12. European commission "Eurostat", causes of death statistics explained 2012.
 13. Camilleri G, Grima KB, Zarb F. Correlation of number and identification of sentinel nodes during radiographer led lymphoscintigraphy prior to sentinel lymph node biopsy in breast cancer patients. *Radiogra* 2011;18(1):9-14.
 14. Zakaria S, Degmin AC, Kleer CG. Sentinel lymph node biopsy for breast cancer. How many nodes are enough? *J Surg Oncol* 2007;96(7):554-559.
 15. Buscombe J, Paganelli G, Burak Z. Sentinel node in breast cancer procedural guidelines. *Europ J Nuclear Med Molecular Imag* 2007;34(12): 2154-2159.
 16. Collins CD. The sentinel node in breast cancer. An update. *Cancer Imag* 2005;5: S3-S9.
 17. Nieweg OE, Tanis PJ, Kroon BBR. The definition of a sentinel node. *Eur J Nuclear Med Molecul Imag* 2001;8(6):538-541.
 18. Goyal RG, Newcombe RE, Mansel. Role of routine preoperative lymphoscintigraphy in sentinel node biopsy for breast cancer. *Eur J Cancer* 2005;41(2): 238-243.
 19. Mcmasters KM, Wong SL, Tuttle TM. Preoperative lymphoscintigraphy for breast cancer does not improve the ability to identify axillary sentinel lymph nodes. *Ann Surg* 2000;231(5): 724-731.
 20. Marchal F, Rauch P, Morel O. Results of preoperative lymphoscintigraphy for breast cancer are predictive of identification of axillary sentinel lymph nodes. *World J Surg* 2006;30(1):55-62.
 21. Ferlay J, Shin H, Bray F. Cancer incidence and mortality worldwide: IARC Cancer Base No 10 Lyon France. Int Agency Res Cancer 2010.
 22. Echeverria SE, Borrell LN, Brown D, et al. A local area analysis of racial, ethnic and neighborhood disparities in breast cancer staging. *Cancer Epidemiol Biomarkers Prev* 2009;18:3024-29.
 23. Jemal A, Siegel R, Ward E, et al. Cancer statistics. *Ca Cancer J Clin* 2009;59:1-25.
 24. Bhikoo R, Srinivasa S, Yu T, et al. Systematic review of breast cancer biology in developing countries. *Asian Subcontinent and South East Asia Cancer* 2011;3:2382-401.
 25. Gorin SS, Heck JE, Cheng B, et al. Delays in breast cancer diagnosis and treatment by racial / ethnic group. *Arch Int Med* 2006;166: 2244-52.
 26. Samina K, Muhammad UQ, Masooma R, et al. Clinicopathologic profile of breast cancer patients in Pakistan: Ten years data of a local cancer hospital. *Asian Pacific J Cancer Prev* 2012;13: 693-98.
 27. Malik IA. Clinicopathological features of breast cancer in Pakistan. *J Pak Med Assoc* 2002;52: 100-104.
 28. Sharif MA, Mamoon N, Mushtaq S, et al. Morphological profile and association of HER-2/neu with prognostic markers in breast carcinoma in Northern Pakistan. *J Coll Phys Surg Pak* 2009; 19:99-103.
 29. Ewertz M, Duffy SW, Adami HO, et al. Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. *Int J Cancer* 1990;46:597-603.
 30. Wohlfahrt J, Melbye M. Age at any birth is associated with breast cancer risk. *Epidemiol* 2001; 12:68-73.
 31. Memon GA, Solangi RA, Dahri AM, et al. An experience with breast cancer at P.M.C.H Nawabshah. *Med Channel* 1999;5:7-14.
 32. McPherson K, Steel CM, Dixon JM. ABC of breast diseases: breast cancer epidemiology, risk factors and genetics. *BMJ* 2000;321:624-8.
 33. Wrensch M, Chew T, Farren G, et al. Risk factors for breast cancer in a population with high risk incidence rates. *Breast Cancer Res* 2003;5: 88-102.
 34. Muhammad FI, Muhammad KI, Imran AJ, et al. Risk factors of breast cancer in patients treated at NORI hospital Islamabad. *J Pak Med Assoc* 2007; 15(5):242-44.
 35. Hajrah D, Shahab-ud-din, Jamila D, et al. Clinical and Histopathological characteristics of breast cancer in people of Baluchistan and adjoining territory of Afghanistan. *Current Res J Biolog Sci* 2012;4(6)676-681.
 36. Naeem M, Khan N, Aman Z, et al. Pattern of breast cancer: experience at Lady Reading Hospital Peshawar. *J Ayub Med Coll Abbott* 2008;20(4): 22-25.

Diagnostic Accuracy of Spot Urine Protein-Creatinine Ratio in Women with Pre-Eclampsia

Nusrat Nisar, Naheed Akhtar and Saira Dars

ABSTRACT

Objective: To determine the diagnostic accuracy of spot urine protein-creatinine ratio in women with pre-eclampsia as compared with 24-hr urine protein excretion.

Study Design: Descriptive / cross-sectional study

Place and Duration of Study: This study was conducted at Obstetrics and Gynecology Department of Liaquat University Hospital, Hyderabad for duration of one year from February 20, 2015 to February 19, 2016.

Materials and Methods: Subjects for this study were collected by using non-probability consecutive sampling technique. Women of all parity having systolic blood pressure (SBP) ≥ 140 mmHg or a diastolic BP (DBP) ≥ 90 mmHg were included for this study. Women with medical disorders like renal disease, diabetes mellitus, were excluded.

Information regarding demographic data, medical history, obstetrical history, general physical examination and ultrasonography were recorded. A spot mid-stream urine sample was obtained from every patient after that 24-hour urine collection was started. Patients having confirmed proteinuria were considered and treated for pre-eclampsia. All information were recorded on a predesigned proforma. SPSS version 16.0 was used for data analysis.

Results: Total 404 pregnant hypertensive women were included in this study. The mean $\pm$ SD age of the subjects was 27.08 ± 5.84 years. The mean $\pm$ SD systolic blood pressure of the subjects was 161.68 ± 19.59 mmHg, whereas the mean $\pm$ SD diastolic blood pressure of the subjects was 104.70 ± 12.6 mmHg. On dipstick test 140 (34.7%) presented with 1+. The results of 24-hours urine collection showed that 158 (39.1%) subjects were negative for proteinuria while urine protein-creatinine ratio revealed that 358 (88.6%) subjects were positive for preeclampsia.

Conclusion: The present study indicates that for the clinical purposes, spot urine protein-creatinine ratio is a satisfactory and reliable substitute for determination of proteinuria than in a 24 hour urine collection.

Key Words: Preeclampsia; proteinuria; protein-creatinine ratio; 24h urine collection; sensitivity; specificity; diagnostic accuracy

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INTRODUCTION

Hypertension complicating pregnancy along with hemorrhage and infection are one of the deadly triad that contributes to the major proportion of maternal death and disability.^{1,2} Hypertension in pregnancy with proteinuria is known as pre-eclampsia.³ The worldwide incidence of pre-eclampsia is 10%⁴ and it is responsible for 15% of all direct maternal deaths.⁵

In Pakistan the reported rate of maternal death due to pre-eclampsia and eclampsia is about 11.7%⁶.

Preeclampsia is diagnosed when woman is having raised blood pressure of 140/90 or higher after 20-weeks of gestation along with proteinuria.^{7,8} Proteinuria

is a significant component of pre-eclampsia and defined as 300-mg or more excretion of protein per 24-hrs⁹.

When proteinuria is overt and persistent, then the risk of maternal and fetal morbidities increases. Hence the quick and error free detection and measurement of proteinuria is essential for the management and prevention of complication in pregnant women with preeclampsia. In pregnancy protein measurement in the 24-hour urine sample is used as a traditional standard method¹⁰. But recent studies suggested that this Gold standard method is inconvenient and costly besides this it can delay the clinical diagnosis and may prolong the hospital stay¹¹. Therefore an alternative method has been considered that is protein-creatinine ratio¹². The correlation between spot protein-creatinine ratio and 24-hour urine protein excretion has been reported significant with p-value up to 0.001¹³.

The protein-creatinine ratio in a single urine specimen has been used for rapid and accurate detection of proteinuria.¹⁴

It avoids collection error and gives physiologically more relevant information. Hence, there is a need to evaluate these tests which can be used to overcoming the limitations of routinely performed tests¹⁵.

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Lot of data is available from western part of world where patients may have different genetics and available diagnostic resources are very much advanced. Very scarce data is available from low resource countries like Pakistan. The purpose of is to determine the diagnostic accuracy of spot urine protein-creatinine ratio, as compared to conventional 24-hr urine protein excretion. The results of this study may aid in saving resources and time.

MATERIALS AND METHODS

This was a descriptive cross-sectional study. This study was carried out at Obstetrics and Gynecology Department of Liaquat University Hospital, Hyderabad. The duration of this study was one year from February 20, 2015 to February 19, 2016.

Sampling Technique: Subjects for this study were collected by using non-probability consecutive sampling technique.

Sample Size: Sample size was calculated by taking the $P=10\%$ and $d=7\%$, with 95% confidence interval, spot urine protein-creatinine sensitivity 92%¹³ and specificity 88%¹³. Thus, the sample size calculated was 404 cases of pregnant hypertensive Patients.

Inclusion Criteria: Women of all parity with more than 20-weeks gestation according to dating ultrasonograph presenting with systolic blood pressure (SBP) ≥ 140 mmHg or a diastolic BP (DBP) ≥ 90 mmHg were selected for this study.

Exclusion Criteria: Women presenting with ruptured membranes and those who delivered during urine collection period were excluded from the study. Women with urinary tract infection and other associated medical disorders like renal disease, diabetes mellitus, women who had bed-rest longer than 24-hours at presentation were not included.

Data Collection: An informed consent was obtained from women who fulfill the inclusion criteria. All information regarding demographic data, medical history, obstetrical history, general physical examination and ultrasonography were recorded. A spot mid-stream urine sample was obtained from every subject and protein creatinine ratio of 0.20 was set as cut off point, immediately after which 24-hour urine collection was started i.e. from 08:00 a.m. to 08:00 a.m. next morning. Total protein concentration was measured by biuret colorimeter assay and creatinine level was measured by modified Jaffe test. Protein-creatinine ratio in urine was obtained by dividing the urinary protein concentration by urine creatinine concentration. Subjects having confirmed proteinuria were considered and treated for pre-eclampsia. All information was recorded on a predesigned Proforma.

Data Analysis: Relevant descriptive statistics, frequencies and percentages were calculated for quantitative data like presence of hypertension, proteinuria and parity. Mean with standard deviation

were calculated for continuous data like age, parity, systolic blood pressure, diastolic blood pressure, 24-hr urinary protein excretion.

The diagnostic accuracy of the spot urine protein-creatinine ratio was obtained by sensitivity, specificity, PPV and NPV calculated by their respective standard formulae by using 2x2 table; taking 24-hr urinary protein excretion ≥ 300 -g as gold standard for comparison. SPSS version 16.0 was used for data analysis. All results are presented in the form of frequency distribution tables.

RESULTS

Total 404 pregnant hypertensive patients were included in this study. The demographic details of the patients were given in table 1. The mean $\pm$ SD age of the women was 27.08 $\pm$ 5.84 years and range was from 16-years to 40 years. 86 (21.29%) women in age group of up to 20 years, 223 (55.2%) and 95 (23.51%) women were age group of 21-30 years and 31-40 years respectively.

Twenty-three (5.69%) patients presented with gestational age of 20-25 weeks, 33 (8.19%) were at the gestational age of 26-30 weeks, while 61 (15.1%) and 287 (71.04%) were presented at 31-35 weeks and >35-weeks of gestational age respectively. The mean $\pm$ SD gestational age of the subjects was 36.26 $\pm$ 4.59 weeks.

Among 404 patients 84 (20.8%) were primiparous, 221 (54.7%) were multiparous and 99 (24.5%) were grand-

multiparous. Majority 248(61.4%) of the patients belongs to rural areas. While only 156 (38.6%) patients were from urban areas. Table 1.

Table No.I: Demographic data (n=404)

Age Group	Number	Percentage
≤ 20 years	86	21.29
21-30 years	223	55.20
>30 years	95	23.51
Mean $\pm$ SD age= 27.08 $\pm$ 5.84 years		
Gestational Age		
20-25 weeks	23	5.69
26-30 weeks	33	8.19
31-35 weeks	61	15.1
>35 weeks	287	71.04
Mean $\pm$ SD gestational age = 36.26 $\pm$ 4.59 weeks.		
Parity		
Primiparous (para 1)	84	20.8
Multiparous (para 2-5)	221	54.7
Granmultiparous	99	24.5
Area of Residence:		
Rural	248	61.4
Urban	156	38.6

Data is presented as numbers and percentages

The mean $\pm$ SD systolic blood pressure of the patients was 161.68 $\pm$ 19.59 mmHg, whereas the mean $\pm$ SD diastolic blood pressure was 104.70 $\pm$ 12.65 mmHg.

On the urine dipstick 106 (26.2%) patients presented with traces of protein urea, 140 (34.7%) presented with 1+ while 94 (23.3%) and 64 (15.8%) presented with 2+ and 3+ respectively.

Table No.2: Blood Pressure readings and values of three methods used for detection of Proteinuria (n=404)

Blood Pressure	Mean	SD
Systolic Blood Pressure (mmHg)	161.68	19.59
Diastolic Blood Pressure (mmHg)	104.70	12.65
Dipstick Values		
Value	Number	Percentage
Traces	106	26.2
1+	140	34.7
2+	94	23.3
3+	64	15.8
Preeclampsia according to 24-h urine collection protein		
PROTEINURIA		
Negative	158	39.1
Positive	246	60.9
Preeclampsia according to protein-creatinine ratio		
Proteinuria	Number	Percentage
Negative	46	11.4
Positive	358	88.6
Mean±SD protein-creatinine ratio = 1.23±1.58		

Data is presented as numbers and percentage

Table No.3: Diagnostic accuracy of Protein-Creatinine ratio (n=404)

		24-h Urine Collection Protein		Total
		True	False	
Protein-Creatinine Ratio	Positive	240	118	358
	Negative	46	40	86
	Total	286	158	444

Sensitivity = $TP/(TP+FN) = 240/246 = 0.975$

Specificity = $TN/(TN+FP) = 40/158 = 0.253$

PPV = $TP/(TP+FP) = 240/358 = 0.670$

NPV = $TN/(TN+FN) = 40/86 = 0.465$

The results of 24-hours urine collection showed that 158 (39.1%) women were negative for proteinuria and 246 (60.9%) women were positive for proteinuria i.e. they presented with >300-mg protein. The mean±SD protein in 24-hours urine collection was 1447.06±2045.27-mg.

The results of protein-creatinine ratio showed that 46 (11.4%) women were negative for preeclampsia and 358 (88.6%) women were detected positive for preeclampsia the mean±SD protein-creatinine ratio was 1.23±1.58. As given in table 2

The Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of protein-creatinine ratio was 97.5%, 25.3%, 67% and 86.9% respectively, as detailed in Table 3

DISCUSSION

Pre eclampsia is differentiated from gestational hypertension by the presence of significant proteinuria. An accurate and quick detection of proteinuria is important not only for the management of Preeclampsia but also for prevention of complications related with the severity of the disease.

The gold standard for the diagnosis of significant proteinuria remains the 24-hours urine protein. A 24-hr collection is needed there is high degree of variation in the urine protein concentration during the course of the day. Though the method of 24 hours urine collection was considered as Gold standard but it is time consuming and can be inaccurate because of incomplete collection.

For these reasons simpler methods which can measure urinary protein in spot samples like urinary dipstick and urine protein-creatinine ratio are proposed and we evaluated it in present study.

Consistent with many previous reports^{16,17} the present study indicated positive and significant correlation of urine protein-creatinine ratio with 24-hour urine result. One study conducted by Sethuram et al. they assess the diagnostic value of protein creatinine ratio in preeclampsia by correlating it to 24hour urinary protein. There sensitivity was 83% and specificity 92% it is similar to our study.¹⁸ Another similar study was conducted Chandka Medical College Hospital, Larkana. There results indicated that relationship of random urine protein creatinine ratio and 24hour urinary protein excretion is very much significant and positive in mild to severe proteinuria but it is not significant in massive proteinuria.¹⁹

a systematic review; done by Cote MA et al, they reviewed thirteen studies for spot protein creatinine ratio and albumin creatinine ratio as diagnostic test for significant proteinuria in women with Hypertension during pregnancy. The conclusion of that review was that spot urine protein creatinine ratio is a reasonable "rule out" test for significant proteinuria of 0.3g/dl or more in pregnancy²⁰. Similarly Thomas et al conducted a similar study in pre-eclamptic women. They also found significant correlation of random spot protein creatinine ratio with 24hour urinary protein levels.²¹

The present study indicated that a urine Protein/Creatinin ratio of 0.20 corresponded with a protein excretion rate of 300 mg/24 h. these findings were Consistent with literature. We also detected a strong

correlation ($r = 0.84$) between the spot P/C ratio and the 24-hour urine protein similar to literature¹⁶⁻¹⁷. But there are some reports with conflicting results. The variation in results could be due to different reasons like the variation in laboratory methods for detection of proteinuria, use of different cutoff points and different units for the urinary P/C ratio²².

In one study by Durnwald and Mercer²³, the authors reported a poor correlation between the random urinary P/C ratio and the 24-hour urine total protein and they advised against replacing the spot P/C ratio for the 24-hour urine protein collection. The variation of findings between their report and ours may be due to the difference in the study population and the wider exclusion criteria in our population may explain the higher positive and negative predictive values. Furthermore, the patient recruited in their study were from outpatient Department, who could have incomplete urine collections, which may be associated with lower levels of 24-hour urine total protein that increases the false negative rate²³.

Our results indicated that the random urine P/C ratio is a highly accurate test for differentiating between insignificant and significant proteinuria. The key concern regarding clinical use of this test is the false-negative results, as 8% of patients with preeclampsia may be missed.

To obtain the optimal cutoff, we suggest that while increasing specificity one need to maintain a sensitivity of higher than 90% this will be reducing the possibility of missing the diagnosis of preeclampsia.

The present study have some limitation we need further Research in the future s focusing on the evaluation of clinical outcomes and the cost-effectiveness of the use of a random urinary P/C ratio for prediction of significant proteinuria. In addition, studying the test in an outpatient basis should be further considered in order to apply it in ambulatory management of preeclamptic patient. We suggest that the test be done also in severely preeclamptic women, as they tend to excrete greater amounts of protein, in order to determine a cutoff value for prediction of the 24-hour urine protein excretion of greater than 5 g.

CONCLUSION

The present study indicates that this method for quantification of proteinuria, when properly interpreted, and validated by laboratory can provide valuable information regarding diagnosis and severity of the disease. Hence for the clinical purposes, spot urine protein-creatinine ratio is a satisfactory and reliable substitute for determination of proteinuria than in a 24 hour urine collection.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Berg CJ, Chang J, Callaghan WM, et al. Pregnancy- related mortality in the United States 1991-1997. *Obstet Gynecol* 2003; 101: 289.
2. MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from pre-eclampsia and eclampsia. *Obstet Gynecol* 2001; 97: 533-38.
3. Shennan A. Hypertensive disorder. In: Edmonds DK, editor. *Dewhurst's text book of obstetrics and gynecology*. London: Blackwell; 2006. p.227-35.
4. Cunningham FG, MacDonald PC, Gant NF. Hypertension disorders in pregnancy. In: Cunningham FG, Mac-Donald PC, Gant NF, editors. *Williams obstetrics*. Norwalk, CT: Appleton & Lange; 1989:653-94.
5. Ashelby L, Winter C, Fox R. Fluid Balance in Pre-eclampsia, what we know and what we don't know. In: Stud J, Tan SL, Chervenak F, editors. *Progress in Obstetrics Gynecology*. UK: Elsevier; 2006. p.125-141.
6. Wasin T, Gull M, Siddiq S. Eclampsia, a major cause of maternal & perinatal morbidity and mortality. *Professional Med J* 2004;11(3):328-33.
7. Salgado SS, Pathmeswaran A. Effects of placental infarctions on the fetal outcome in pregnancies complicated by hypertension. *J Coll Physician Surg Pak* 2008;18:213-6.
8. James DK, Stear PJ, Weiner CP, Gonik B, editors. *High risk pregnancy: management options*. 3rd ed. Philadelphia, PA: WB Saunders; 2006.
9. Lussely DM, Baker P. Preeclampsia and non-proteinuric hypertension. An evidence text book of MRCOG. London: Arnold; 2004.p.179-86.
10. Phelan LK, Brown MA, Davis GK, Mangos G. A prospective study of the impact of automated dipstick urinalysis on the diagnosis of pre-eclampsia. *Hypertens Preg* 2004; 23: 135-42.
11. Aggarwal N, Suri V, Soni S, Chopra V, Kohli HS. A prospective comparison of random urine protein-creatinine ratio vs 24-hours urine protein in women with preeclampsia. *Medscape J Med* 2008;10(4): 98. [online]
12. Cote AM, Brown MA, Lam E, von Dadelszen P, Firoz T, Liston RM, et al. Diagnostic accuracy of urinary spot protein creatinine ratio for proteinuria in hypertensive pregnancy omen: systematic review. *Br Med J* 2008;336:1003-6.
13. Shahbazian N, Hosseini-Al F. A comparison of spot urine protein-creatinine ratio with 24-hour urine protein excretion in women with preeclampsia. *Iranian J Kidney Dis* 2008;2(3): 127-31.

14. Report of the National High Blood Pressure Education Programme Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000; 183: S1-S22.
15. Papanna R, Mann LK, Kouides RW, et al. Protein/Creatinine ratio in pre eclampsia: A systematic review. *Obstet Gynecol* 2008; 112: 135.
16. Saudan PJ, Brown MA, Farrell T, Shaw L. Improved methods of assessing proteinuria in hypertensive pregnancy. *Br J Obstet Gynaecol* 1997;104:1159-64.
17. Yamasmit W, Chaithongwongwatthana S, Charoenvidhya D, Uerpaiojkit B, Tolosa J. Random urinary protein-to creatinine ratio for prediction of significant proteinuria in women with preeclampsia. *J Matern Fetal Neonatal Med* 2004; 16:275-9.
18. Rodriguez-Thompson D, Lieberman ES. Use of a random urinary protein-to-creatinine ratio for the diagnosis of significant proteinuria during pregnancy. *Am J Obstet Gynecol* 2001;185:808-11.
19. Sethuram R, Kiran TS, Weerakkody AN. Is the urine spot protein / creatinine ratio a valid diagnostic test for preeclampsia? *J Obstet Gynaecol* 2011; 31(2):128-30.
20. Shaikh SA, Shaikh S, Shaikh GS. Optimal diagnostic value of random urine protein-to-creatinine ratio over 24 hours urine protein excretion in women with preeclampsia at Chandka Medical College Hospital Larkana. *Medical Channel* 2010;16(3):413-6.
21. Thomas L, Wheeler I, Dawn W, Blockhurst, Eric H, Dellinger, et al. Usage of spot protein to creatinine ratios in the evaluation of preeclampsia. *AJOG* 2007; 65-1:465e4.
22. Rahman MM, Azad K, Ahmed N, Haque MR, Wahab M.A, Asad H.B, et al. Spot morning urine protein creatinine ratio and 24hour urinary total protein excretion rate. *Mymensingh Med J* 2006; 15:146-9.
23. Durnwald C, Mercer B. A prospective comparison of total protein/creatinine ratio versus 24-hour urine protein in women with suspected preeclampsia. *Am J Obstet Gynecol* 2003;189: 848-52.

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Meconium Aspiration Syndrome in Neonates

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ABSTRACT

Objective: To determine the frequency of the factors leading to meconium aspiration syndrome in neonates.

Study Design: Descriptive case series study.

Place and Duration of Study: This study was conducted at the Neonatal Unit of the Department of Pediatric Medicine, Sheikh Zaid Postgraduate Medical Institute Lahore from 02-08-2013 to 2-02-2014

Materials and Methods: A total of 180 patients were selected for this study. After verbal consent for participating in the study mothers were inquired for factors leading to meconium aspiration syndrome like post maturity and cesarean section with detailed history including date of last menstrual period and mode of delivery and filled in predesigned proforma.

Results: There were 101 (56.1%) male and 79 (43.9%) female patients. Neonates delivered with cesarean section were 73 (40.6%), 85 (47.2%) patients had post maturity and 7 (3.9%) patients had IUGR. There were 13 (7.2%) patients had pneumothorax and mortality was recorded in 8 (4.4%) patients.

Conclusion: Cesarean section, post maturity and IUGR are important risk factors, frequently associated with meconium aspiration syndrome.

Key Words: Meconium aspiration syndrome, cesarean section, IUGR, post maturity.

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INTRODUCTION

Meconium aspiration syndrome is an important cause of respiratory distress in newborn infants. The pathophysiology of meconium aspiration syndrome is complex and involves airway obstruction, surfactant dysfunction and pulmonary inflammation. Meconium aspiration syndrome can be diagnosed in any infant born with meconium staining of amniotic fluid, develops respiratory distress at or shortly after birth and has positive radiographic findings.^{1,2}

The incidence of meconium stained liquor is more in prolonged pregnancies i.e. 19% at 40 weeks of gestational age and 42% at 42 weeks of gestational age and the incidence of passage of meconium during labor also increases with gestational age, it reaches up to 30% at 40 weeks and 50% at 42 weeks.³

Several factors are associated with meconium aspiration syndrome like, cesarean section is associated with 41.8%, intrauterine growth restriction (IUGR) in 6% of cases. While complications associated with meconium aspiration syndrome include pneumothorax in 9.6% of cases and mortality occur in 6.6% of cases.

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Term neonates who are admitted with diagnosis of meconium aspiration syndrome continue to represent a high risk population with significant morbidity and often require intensive therapies.^{4,5}

The results of this study will bring awareness among mothers and obstetricians regarding factors leading to meconium aspiration syndrome like avoidance of post maturity by induction of labor at term pregnancy between 37 and 42 weeks, avoid unnecessary cesarean section without labor pain or cesarean section on request of mother at term pregnancy and plan for normal vaginal delivery and also IUGR was controlled in form of treating maternal infection and maternal malnutrition. So, the better outcome will be achieved.

MATERIALS AND METHODS

This descriptive case series study was carried out in Neonatal Unit of the Department of Pediatric Medicine, Sheikh Zaid Postgraduate Medical Institute Lahore from 02-08-2013 to 2-02-2014.

Sample size of 180 cases is calculated with 95% confidence level, 3.5% margin of error and taking expected percentage of IUGR i.e. (factor leading to meconium aspiration syndrome) i.e. 6% (least among all) in neonates presenting in a tertiary care hospital and collected by non-probability consecutive sampling.

Inclusion criteria:

1. Neonates born after completing 37 weeks or more than 37 weeks of gestation calculated from date of last menstrual period.
2. Neonates referred to Neonatology Unit because of meconium aspiration syndrome.

Exclusion criteria

1. Sick new born with other co morbid conditions like neonatal sepsis
2. Birth asphyxia.

Data collection procedure: Total number of 180 patients admitted in the Neonatal Unit, Department of Pediatrics, SheikhZaid Hospital Lahore, fulfilled the inclusion criteria were included in the study. After taking informed consent of parents, their biodata including name, date of birth, sex, address and date of admission were recorded. There will be no ethical issue regarding privacy and safety of the patients. Information regarding factors leading to meconium aspiration syndrome like post maturity and cesarean section were obtained by history that was by asking date of last menstrual period and mode of delivery. IUGR information was obtained by taking and plotting weight, length and head circumference of neonates on percentile chart. Outcome was determined in terms of development of pneumothorax and mortality in neonates during hospital stay. Pneumothorax was diagnosed with hyper lucent shadow that was more dark shadow with no lung marking on chest x-ray.

Statistical analysis: Data was entered in SPSS version 16 and analyzed. The qualitative variables like gender, factors leading to meconium aspiration syndrome (i.e. post maturity, cesarean section and IUGR) and outcome (pneumothorax and mortality) were presented in the form of frequency and percentages.

RESULTS

There were 101 (56.1%) male and 79 (43.9%) female patients (Table 1). The mean weight of the patients was 3.0 ± 0.4 kg. There were 7 (3.9%) patients in the weight range of up to 2.0 kg, 95 (52.8%) patients in the weight range of 2.1-3.0 kg and 78 (43.3%) patients in the weight range of 3.1-4.0 kg.

The mean length of the patients was 49.2 ± 2.3 cm. There were 7 (3.9%) patients had length range of 40-45cm, 113 ((62.8%) patients in the length range of 46-50cm and 60 (33.3%) patients in the length range of 51-55cm. The mean head circumference of the patients was 35.0 ± 0.9 cm. There were 132 (73.3%) patients in the head circumference range of 31-35cm and 48 (26.7%) patients in the head circumference range of 36-40cm (Table 2).

In the distribution of patient's mode of delivery by cesarean section, there were 73 (40.6%) patients, who delivered with cesarean section and 107 (59.4%) patients who were not delivered with cesareans section. Post maturity was seen in 85 (47.2%) patients while 95 (52.8%) were normal term babies. IUGR affects 7 (3.9%) patients, and 173 (96.1%) patients had not IUGR. Graph 1 showing all the factors contributing in meconium aspiration.

Complications of meconium aspiration like pneumothorax, was present in 13 (7.2%) patients, in

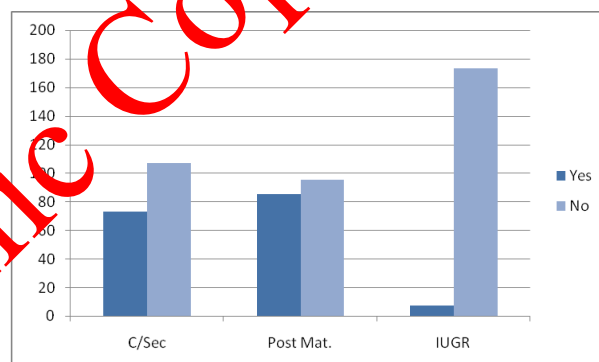
167 (92.8%) patients pneumothorax is not seen. (Table 3)

Table No.1: Distribution of patients by sex (n=180)

Sex	No. of patients	Percentage
Male	101	56.1
Female	79	43.9
Total	180	100.0

Table No.2: Demographics of patients(n=180)

Weight (Kg)	No. of patients	Mean $\pm$ SD
Upto 2.0	7 (3.9%)	3.0 ± 0.4
2.1-3.0	95(52.8%)	
3.1-4.0	78(43.3%)	
Length (cm)		
40-45	7(3.9%)	49.2 ± 2.3
46-50	113(62.8%)	
51-55	60(33.3%)	
Head circumference		
31-35	132 (73.3%)	35.0 ± 0.9
36-40	48 (26.7%)	

**Graph No.1: Various factor of meconium aspiration****Table No.3: Distribution of patients by pneumothorax (n=180)**

Pneumothorax	No. of patients	Percentage
Yes	13	7.2
No	167	92.8
Total	180	100.0

DISCUSSION

Meconium aspiration syndrome is a disease of the term and near-term infant that is associated with considerable respiratory morbidity. It is characterized by early onset of respiratory distress in a new born, with poor lung compliance and hypoxemia clinically and patchy opacification and hyperinflation on radiography.^{6,7}

At least one third of infants with MAS require intubation and mechanical ventilation, and newer neonatal therapies, such as high-frequency ventilation (HFV), inhaled nitric oxide (iNO), and surfactant administration are often brought into play.⁸⁻¹¹

In the past few decades, there is decline in the incidence of MAS in many centers in developed world. The apparent reduction in the risk of MAS has been attributed to better obstetric practices, in particular, avoidance of post maturity and expeditious delivery where fetal distress has been noted.^{12,13}

In previous epidemiologic studies, some important risk factors for the development of MAS have been identified, either within the general birth population or among infants born through meconium-stained amniotic fluid (MSAF). The presence of fetal compromise, indicated by abnormalities of fetal heart rate tracings and/or poor Apgar scores, is known to increase the risk of MSAF and of MAS in the meconium-stained infant. Cesarean delivery is also associated with a heightened incidence of MAS. There is an apparent relationship between maternal ethnicity and risk of MSAF and the suggestion in several reports of an increased risk of MAS in black Americans and Africans and Pacific Islanders. Advanced gestation has also been recognized as a risk factor, both for MSAF and for MAS.^{14,15}

Therapy for infants with MAS, in particular, those requiring intubation, is evolving rapidly. There is, however, a paucity of longitudinal data examining the proportional uptake of newer therapies in ventilated infants with MAS. Similarly, whereas it is clear that severe MAS is associated with a relatively high risk of pneumothorax and a relatively long duration of respiratory support and oxygen therapy. The mortality rate is lying between 5% and 37%, with the marked disparity in published figures being attributable to the difficulties in identifying the cause of death (respiratory versus non respiratory) and the skewed populations in which the mortality risk is calculated.^{6,7}

In this study 40.6% infants were delivered with cesarean section. As compared with the study of Dargaville and Copneli 41.8% infants delivered with cesarean section, which is comparable with our study. While post maturity was found in 47.2% patients which is more or less similar with the study of Adhikari et al post maturity was found in 54% patients.^{4,16}

Intrauterine growth restriction (IUGR) which was found in 3.9% patients while the study of Dargaville and Copneli observed intrauterine growth restriction in 6% patients, which is almost comparable with this study.

In this study pneumothorax was found in 7.2% patients. As compared with the study of Dargaville and Copneli pneumothorax was found in 9.6% patients, which is comparable with our study.⁴

Mortality was found in 4.4% patients compared with study by Nangia S (4.6%) neonate not intubated. In

another study conducted by Adhikari et al mortality was found in 14% patients. Study by Nangia S 10.34% deaths in neonate intubated for meconium aspiration syndrome.^{17,18}

CONCLUSION

It is concluded from this study that presence of post maturity, cesarean section and IUGR are important risk factors for meconium aspiration syndrome. The pneumothorax (7.2%) and mortality (4.4%) are outcome variables for meconium aspiration syndrome during hospital stay. The monitoring of labor was the most significant factor in the reduction of meconium aspiration syndrome.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Sylvia C, Alfonso L, David H, Fred M. Meconium inhibits phagocytosis and stimulate respiratory burst in alveolar macrophages. *J Pediatr Res* 2005; 57:113-8.
2. Yeh TE. Core concepts: Meconium aspiration syndrome: pathogenesis and current management. *Neon Reviews* 2010;11:503-12.
3. Amjad N, Imran T, Ahmad AN. Fetomaternal outcome of pregnancy between 40 and 42 weeks. *J Professional Med* 2008;15:317-22.
4. Dargaville PA, Copneli B. The epidemiology of meconium aspiration syndrome. *Pediatrics* 2006; 117:1712-21.
5. Singh BS, Clark RH, Powers RJ, Spitzer AR. Meconium aspiration syndrome remains a significant problem in the NICU. *J Perinatol* 2009;29:497-503.
6. Cleary GM, Wiswell TE. Meconium-stained amniotic fluid and the meconium aspiration syndrome: an update. *PediatrClin North Am* 2008;45:511-29.
7. Wiswell TE, Bent RC. Meconium staining and the meconium aspiration syndrome: unresolved issues. *PediatrClin North Am* 2003; 40:955-81.
8. Coltart TM, Byrne DL, Bates SA. Meconium aspiration syndrome: a 6-year retrospective study. *Br J Obstet Gynaecol* 2004; 96:411-14.
9. Wiswell TE, Tuggle JM, Turner BS. Meconium aspiration syndrome: have we made a difference? *Pediatrics* 2000; 85:715-21.
10. Bhutani VK, Chima R, Sivieri EM. Innovative neonatal ventilation and meconium aspiration syndrome. *Indian J Pediatr* 2003; 70:421-27.

11. Wiswell TE. Advances in the treatment of the meconium aspiration syndrome. *Acta Paediatr* 2001;90:28–30.
12. Sriram S, Wall SN, Khoshnood B, Singh JK, Hsieh HL, Lee KS. Racial disparity in meconium-stained amniotic fluid and meconium aspiration syndrome in the United States, 1989–2000. *Obstet Gynecol* 2003;102:1262–8.
13. Yoder BA, Kirsch EA, Barth WH, Gordon MC. Changing obstetric practices associated with decreasing incidence of meconium aspiration syndrome. *Obstet Gynecol* 2002;99:731–9.
14. Fugikura T, Klionsky B. The significance of meconium staining. *Am J Obstet Gynecol* 1975; 121:45-50.
15. Peng TC, Guther GR, Van Dorsten JP. A selective aggressive approach to the neonate exposed to meconium-stained amniotic fluid. *Am J Obstet Gynecol* 2006;175:296–301.
16. Alexander GR, Hulsey TC, Robillard PY, De Caunes F, Papiernik E. Determinants of meconium-stained amniotic fluid in term pregnancies. *J Perinatol* 2004;14:259–63.
17. Adhikari M, Gouws E, Velaphi SC, Gwamanda P. Meconium aspiration syndrome: importance of the monitoring of labor. *J Perinatol* 1998;18:55-60.
18. Nangia S, Sunder S, Biswas R, Saili A. Endotracheal suction in term non vigorous meconium stained neonates-A pilot study. *Resuscitation* 2016;105:79-84.

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Comparing the Two Treatment Regimes for Scabies, Topical Permethrin 5% with Oral Ivermectin

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ABSTRACT

Objective: Comparing the efficacy of oral ivermectin with topical permethrin in treating scabies.

Study Design: Randomized control trial study.

Place and Duration of Study: This study was conducted at the Department of Dermatology, Nishtar Hospital Multan from May 2016 to January 2017.

Materials and Methods: One hundred and forty (140) patients were selected for the study. SPSS version 20 was used to analyze the data. Categorical variables presented as frequencies and percentages and numerical variables presented as mean $\pm$ standard deviation.

Results: A total of One hundred and forty 140 (100%) patients of scabies disease were included in this study in which 101 (72.1%) were male and 39 (27.9%) were female. Mean of patients in group A (permethrin) was 30.65 ± 6.47 and in group B was 29.85 ± 6.59 . It was observed that in Group A 49 (70%) patients were cured and in Group B 47 (67.1%) patients were cured. When we applied chi-square test to check the association, it was observed that cure was associated with severity of itching for both the groups and not associated with Nocturnal pruritus.

Conclusion: It was concluded that for 7 days treatment (Permethrin) had better outcomes and for 14 days treatment, Group B (Ivermectin) had better outcomes.

Key Words: Ivermectin per oral, Permethrin, Skin disease, Scabies

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INTRODUCTION

Scabies usually proceed by contagious ectoparasite infecting on skin, affecting all ages, gender and social classes, with higher rate of prevalence in developing countries.¹ usually associated with overpopulation and unsatisfactory unhygienic living which facilitate its cross spread.^{2,3,4,5} but due to high incidence of Human Immune Virus infection, also involving developed societies.⁵

Clinical diagnosis is made on history of Itching all over the body with worsening of condition at night and having same pattern of symptoms in persons living together. Lesions having characteristics of tortuous burrows which are slightly raised especially in web spaces.

Lesions of having excoriation with features of urticarial papules, eruptions with itching properties along with crusts. Diagnosis was confirmed either having burrow in web spaces, presence of microscopically detected eggs and feces. Available regimes of treatment are topical like permethrin, Lindane, chrotamotone, Benzyle benzoate etc. which having usual drawback off burden to apply its messy characteristic, having smell and time taking which lead to non compliance of patient.^{6,7,8} 5% Permethrin is most commonly and efficiently used topical scabidical agent.¹¹

Only available scabidical agent having its limitation due to cost and high drug resistance. Ivermectin is only oral agent having scabidical properties available in market. Ivermectin is synthetic macrolid and vermicial usually used in multiple disorders for example filariasis and onchocerciasis. FDA not yet approved this agent for the treatment of scabies but still it widely used as a treatment option for scabies patients, scabies with crusts, patients having scabies in pemphigus disease, HIV disease and connective tissue disorder. In for mention situation it's quite difficult to use topical therapy.⁹ its use is quite convincing for the treatment of institutional based scabies epidemics. It is easy to administer with cost effectiveness, minimum drug interactions and side effects like rashes, joint pains, fever, headache muscle pain, palpitations, hypotension,

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vomiting, nausea, pain in abdomen, lymphadenopathy and itching. It's advisable not to use in pregnant ladies, lactating mothers and children weight less than 15 kg and age less than five years. Hyper sensitivity to drug and nervous disorders are contra-indications.⁶ In a study conducted by Usha and Nair⁵ reported that efficacy comparable to topical permethrin when a dose of 200 microgram/ kg used.

MATERIALS AND METHODS

In our clinical trial study, one hundred and forty patients with age range from 14–53 years, having mean age of 42 ± 14 with confirmed diagnosis of scabies were enrolled from January 2016 to December 2016. Patients age less than 14 years, pregnant ladies, lactating mothers, having past history of seizures, severe systemic diseases, immune suppressant disorders and scabies with crusts were excluded from our clinical trial. Excluded consents were taken from all patients. Patients who had not taken any oral or topical acaricidal agent one month before included in our study. The 5% permethrin cream and ivermectin for oral use were packed in similarly looking boxes and evaluation team not known to contents of these packets. It was ensured that blinding of contents remain maintained throughout the contacts of clinical trial likewise all members of treatment team who taking part in applying medication. Before enrolling the patient for clinical trial a thorough examination and detailed history of any medication infestation and other particles were noted in perform. Age and gender were recorded to make demographic comparison. scabies was diagnosed on the confirmation of egg, mites on feces and confirmed microscopically following three criteria; typically scabies lesions in classical sites, night time itching and having history of similar symptoms enclosed living persons. Two groups were made randomly by dividing the patients with lottery method. In 1st group of patients and their close living persons permethrin cream was used (Group A), but other patients were given oral ivermectin (Group B). 1st group using permethrin treatment was received two applications of topical agents for seven and fourteen days. Ivermectin was given orally as a single dose in patients of group B but in group A permethrin topical cream was asked to apply on whole body and take shower after 12 hours in each occasion. A physician having clinical experience of five years was dedicated to evaluate the efficacy of treatment during evaluation physician recorded the sites of lesion using body diagram shape. A follow up schedule for seven and fourteen days was done. Patients with history of no itching and purities were labeled as effectively cured. Patient having new lesions after fourteen days confirmed by light microscopy and those who still having itching and purities after fourteen days were labeled as treatment failure. Treatment failure was defined as a patient with microscopically-

confirmed new lesions at 14 days and who was not considered cured at 14 weeks. The results of the study were analyzed using computer software SPSS ver. 20. To account for statistical differences in the two groups, chi square test was used. P less than 0.05 were considered statistically significant.

RESULTS

A total of one hundred and forty patients of scabies were included in this study in which 101 (72.1%) were male and 39 (27.9%) were female. These patients were divided in two equal groups; Group A permethrin (70 patients), and group B (70 patients). Mean age of patients in group A (permethrin) was 30.65 ± 6.47 and in group B was 29.85 ± 6.59 (Table-1). It was observed that Group A cured the 49 (70%) patients and Group B cured the 47 (67.1%) patients. Nocturnal pruritus in Group A was 52 (74.3%) and 18 (25.7%) were not. Nocturnal pruritus of in group B was 47 (67.1%) and 23 (32.9%) were not. Severity of itching in group A was 14 (20%) mild, 42 (60%) moderate, and 14 (20%) were severe. And it was also noted that severity of itching in Group B 19 (27.1%) mild, 37 (52.9%) moderate, 14 (20%) were severe patients (Table-2).

Table No. 1: Demographic Variables

Characteristics	Frequency	Percentage (%)
Gender		
Male	101	72.1 %
Female	39	27.9 %
Age		
Groups	Mean $\pm$ SD	
Group A	30.65 ± 6.473	
Group B	29.85 ± 6.592	

Table No.2: Frequency of Nocturnal Purities, Severity of itching

Nocturnal Pruritus			
Groups		Frequency	Percentage
Group A	No	18	25.7
	Yes	52	74.3
Group B	No	23	32.9
	Yes	47	67.1
Severity of itching			
Group A	Mild	14	20.0
	Moderate	42	60.0
	Severe	14	20.0
Group B	Mild	19	27.1
	Moderate	37	52.9
	Severe	14	20.0

When the drug were given to the patients, after given both drugs 7 day it was observed that in group A cured 51 (72.85%) and 19 (27.14%) were not cured and in

group B 26 (37.1%) were cured and 44 (62.85 %) were not cured respectively (Table-3). Administration of drug at 14 days shows opposite results as in group A 28 (40%) patients were cured and 42 (60%) were not cured and in group B 57 (81.42 %) were cured and 13 (18.57%) were not cured (Table-3).

When we applied chi-square test to check the association, it was observed that cure was associated with severity of itching for both the groups $P=0.001$ for group A and 0.000 for group B significant values, and not associated with Nocturnal pruritus for both the groups $P=0.660$ and 0.065 (Table-4-5).

Table No.3: Frequency (Percentage %) of Cure at 7 and 14 days

Groups		Frequency	Percentage (%)
Cure at 7 Days			
Group A	Cured	65	92.9 %
	Not Cured	5	7.1 %
Group B	Cured	62	88.6 %
	Not Cured	8	11.4 %
Cure at 14 Days			
Group A	Cure	51	72.9 %
	Not cured	19	27.1 %
Group B	Cured	62	88.6 %
	Not cured	8	11.4 %

Table No.4: Inferential Results

Groups	Nocturnal Pruritus	Cure		Total
		Not Cured	Cured	
Group A	No	1	17	0.596
	Yes	5	47	
	Total	6	64	
Group B	No	3	20	0.668
	Yes	8	39	
	Total	11	59	

Table No.5: Inferential Results

Groups	Severity of itching	Cure		P Value
		Not Cured	Cured	
Group A	Mild	4	10	0.010
	Moderate	1	41	
	Severe	1	13	
	Total	6	64	
Group B	Mild	0	19	0.000
	Moderate	0	37	
	Severe	11	3	
	Total	11	59	

DISCUSSION

No statistical major difference was found in efficacy when a single dose of oral ivermectin and topical permethrin were used for the treatment of scabies. Scabies have high rate of relapse and resistance to treatment against both groups of drugs. Group A treated with permethrin topical showed 73.7 % and 66.7 % cure rate respectively at interval of seven and fourteen days, meanwhile in group P treated by oral ivermectin showed 68.3% and 66.7 % cure rate at seven and fourteen days interval respectively our observation is almost identical to the results of clinical trial conducted by Madan et al. and Meinking et al.^{12, 13} our results are comparable with Abedin et al.¹⁴ regarding the efficacy of both treatment options. In 2007 Akhtar et al. used oral ivermectin in divided dose of 300 microgram/kg in sixty patients. They reported 100% efficacy regardless of age which is nearly identical to our observation. A treatment regime of 12 mg oral ivermectin was used by Auben and Humert in France for the treatment of clustered scabies.¹⁵ Similarly 100% efficacy we reported by Khan and Yamin in 30% based clinical trial. Their results are nearly equivalent to observation made by our study.^{16, 21, 22}

But a clinical trial conducted by Usha and Nire showed 70% patients were cured in a group using oral ivermectin as compare to 97% cure rate in topical permethrin therapy at even days interval, this observation showed that permethrin is superior to oral ivermectin which differ from our observation. But oral ivermectin treated group having almost 70% cure at even days which is comparable our observation 73.3%. But this difference has no statistically significant effect between two groups. This difference most probably due to variation in compliance as in ivermectin group drug was taken by patient under direct supervision as compare to topical permethrin group in which patient applied lotion out of direct supervision that may be the cause of difference in compliance due to inappropriate application. An element of resistance against topical permethrin may be the reason over the year.^{12, 16, 17}

Mainking et al conducted a clinical trial in 1995 labeled as open trial with two follow up visits reported 45% of scabies patients respondents like our study, with 100% response rate at two week interval while using 200 microgram/kg. In multiple clinical trials no laboratory investigation were done while using oral ivermectin as in our clinical trial.^{17, 18, 19, 20}

CONCLUSION

Both drugs are effective in treatment of scabies, at 7 days interval Permethrin 5% is more effective than Ivermectin but at 14 days interval of treatment Ivermectin have better treatment effects.

Limitations: The limitation of our clinical trial was contraindication regarding the use of ivermectin in patients of less than 5 years of age, pregnant ladies and lactating mothers and possibility of ivermectin to cross immature blood brain barriers leading to increase percentage of drug precipitating nervous system disorders. We also face difficult to find out treatment efficacy in all contacts. So further studies are required to check effectiveness of these treatment regimes in above mention groups.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Karthikeyan K. Treatment of scabies: newer perspectives. *Postgrad Med J* 2005;81:7-11.
2. Burns DA. Diseases caused by arthropods and other noxious animals. In: Burns T, Breathnach S, Griffiths C, editors. *Rook's Textbook of Dermatology*. 7th ed. London: Blackwell Science; 2004.p.33.37-41.
3. Ribeiro FA, Taciro E, Guerra MR, Ecklley CA. Oral ivermectin for the treatment and prophylaxis of scabies in a prison. *J Dermatol Treat* 2005; 16:138-41.
4. Scheinfeld N. Controlling scabies in institutional settings; a review of medications, treatment models and implementation. *Am J Clin Dermatol* 2004; 5:31-7.
5. Usha V, Nair TV. A Comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. *J Am Acad Dermatol* 2000; 42:236-40.
6. Arndt KA, Bows KE, editors. *Manual of Dermatologic Therapeutics with Essentials of Diagnosis*. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2002.
7. Bukhari SA, Maan MA, Iqbal J. A randomized controlled trial to compare the efficiency of 1% lindane (scabene) cream and 5% permethrin (lotrix) cream for the treatment of scabies. *J Pak Assoc Dermatol* 2000;10;2-4.
8. Santoro AF, Rezae MA, Lee JB. Current trend in ivermectin usage for scabies. *J Drugs Dermatol* 2003;2:397-401.
9. Dourmishev AL, Dourmishev LA, Schwartz RA. Ivermectin: pharmacology and application in dermatology. *Ind J Dermatol* 2005;44:981-8.
10. Fawcett RS. Ivermectin use in scabies. *Am Fam Physician* 2003;68:1089-92.
11. Chouela E, Abeldaño A, Pellerano G, Forgia M. Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. *Arch Dermatol* 1999;135:651-5.
12. Madan V, Jaskiran K, Gupta U, Gupta DK. Oral ivermectin in scabies patients: a comparison with 1% topical lindane lotion. *J Dermatol* 2001;28: 481-4.
13. Meinking TL, Taplin D, Hermida JL et al. The treatment of scabies with ivermectin. *N Engl J Med* 1995;333:26-30.
14. Akhtar SJ, Maan MA, Iqbal J, Kapadia N. Treatment of scabies simplified. *J Pak Assoc Dermatol* 2007;17:240-9.
15. Abedin S, Narang M, Gandhi V, Narang S. Efficacy of permethrin cream and oral ivermectin in treatment of scabies. *Ind J Pediatr* 2007;74: 915-9.
16. Aubin F, Humbert P. Ivermectin for crusted (Norwegian) scabies. *N Engl J Med* 1995;332:612.
17. Maan I, Yasmin R. Ivermectin in the treatment of scabies. *J Pak Assoc Dermatol* 2007;17:78-83.
18. Walton SF, Currie BJ. Problems in diagnosing scabies, a global disease in human and animal populations. *Clin Microbiol Rev.* 2007;20:268-79.
19. Vorou R, Remoudaki HD, Maltezou HC. Nosocomial scabies. *J Hosp Infect* 2007;65:9-14.
20. Strong M, Johnstone PW. Update of: interventions for treating scabies. *Cochrane Database Syst Rev* 2007; (3):CD000320.
21. Elgart ML. Cost benefit analysis of ivermectin, permethrin and benzyl benzoate in the management of infantile and childhood scabies. *Expert Opin Pharmacother* 2003;4:1521-4.
22. Mounsey KE, Holt DC, McCarthy J, Walton SF. Identification of ABC transporters in *Sarcoptes scabiei*. *J Med Entomol* 2007;44: 1054-63.

Casual Comparative Analysis of Quality of Life in Congestive Heart Failure Patients Presenting With & Without 25-Hydroxy Vitamin D Deficiency

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ABSTRACT

Objective: It is only natural to assume that the course of disease is more aggressive in the face of 25-Hydroxy vitamin D deficiency the prognosis of patients presenting with congestive heart failure would be grim. More important so, their quality of life during the years that they live would be markedly reduced.

Study Design: Observational / descriptive study.

Place and Duration of Study: This study was conducted at the Department of Cardiology, Liaquat University of Medical & Health Sciences, Jamshoro during the month of May 2016.

Materials and Methods: Forty patients (chosen via purposive sampling) presenting with congestive heart failure were included in the study. Data was derived using a structured interview based questionnaire after taking written informed consent. Investigations were also carried out to determine the levels of 25-hydroxy vitamin D levels in the blood. The patient condition and the quality of life was investigated at the time of discharging the patient and comparison was drawn.

Results: Sixty percent of the patients were men, while the remaining forty percent were women. The ratio of the patients with or without 25-hydroxy vitamin D deficiency was 1:1 and the patients with 25-hydroxy vitamin D deficiency were experiencing markedly low levels of quality of life due to aggravated disease.

Conclusion: The deficient levels of 25-hydroxy vitamin D as indicated in literature, alter the metabolism of minerals and lead to myocardial dysfunction in the congestive heart disease patients. It is thus an aggravating factor for pathogenesis of congestive heart failure and leads to marked decrease in the quality of life.

Keywords: Congestive Heart Failure, 25-Hydroxy vitamin D, Vitamin Deficiency

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INTRODUCTION

The cardiac anomaly named congestive heart failure is categorized as a disease in which the ejection fraction of the left ventricle is markedly lessened. It is also, more often than not, associated with retention of bodily salts and water. The 2 primary symptoms of the ailment are weakness of the muscles and early onset of fatigue and tiredness. Congestive heart failure is prevalent worldwide and the levels loom between one percent to three percent in the developed world and with the prevalence climbing particularly in the geriatric population.¹⁻⁴

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The true reason behind such widespread prevalence has still not been unearthed and neither is the disease pathogenesis fully identified. However, we do know that the disease is aggravated once the mineral metabolism is disturbed by any factor, be it deficiency of 25-Hydroxy vitamin D levels or anything else. The said deficiency affects the intracellular management of calcium ions and disturbs the myocardial contractions⁵. In experiments conducted on extracted myocytes from individuals suffering from congestive heart failure, calcium ion transition during the contractile phase of the heart were lessened and the during the relaxation phase they were heightened. The decrease and the consequent increase both matched pathologic level⁶. The use of digitalis and beta-blockers is thus merited in such a condition and for secondary stoppage. These drugs effectively act to enhance the cardiac contraction and thus the ejection fraction⁷⁻⁸.

A review of recent literature brings to light a fresh research that concludes that vitamin D deficiency congestive heart failure occur together far too often for the occurrence to be coincidental⁹. It is important to note that multiple hypothesis exist that hope to explain

how vitamin D deficiency steepens the course of this disease, some going as far as calling it catalytic¹⁰⁻¹². Research also indicate that individuals who are deficient in this crucial vitamin are more likely to have a poor prognosis and have a reduced life span.^{13,14}. Also, the effectiveness of the treatment of this disease is limited if the deficiency is not overcome¹⁵. Circulating levels of 25-Hydroxy vitamin D are thus important and need to be maintained if a good prognosis is to be achieved¹⁶.

MATERIALS AND METHODS

Forty patients (chosen via purposive sampling) presenting with congestive heart failure at Liaquat University Hospital, Department of Cardiology during the month of May 2016 were included in the study. Data was derived using a structured interview based questionnaire after taking written informed consent. Investigations were also carried out to determine the levels of 25-hydroxy vitamin D levels in the blood. The patient condition and the quality of life was investigated at the time of discharging the patient and comparison was drawn.

RESULTS

Sixty percent of the patients were men, while the remaining forty percent were women.

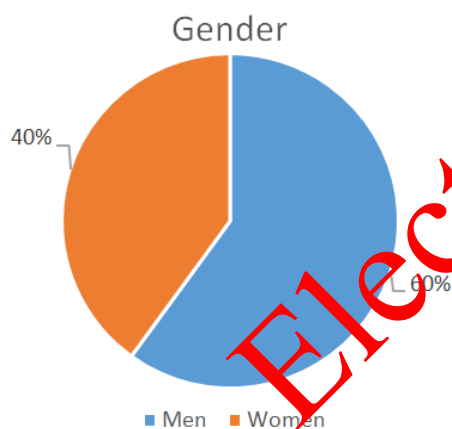
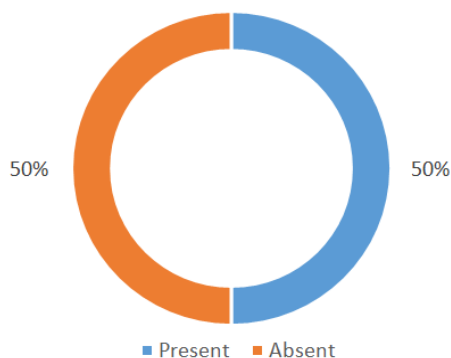


Figure No.1: Congestive heart Failure



FigureNo.2: Patients Ratio

Congestive heart Failure was more common in men and less common in women. The cardio-protective effect of the hormone in women prior to menopause may be the reason behind the disease being less common in women. While aggravating factors like smoking, which are more common in men, may explain the high levels of the disease in men. (Figure 1)

The ratio of the patients with or without 25-hydroxy vitamin D deficiency was 1:1.

The patients with 25-hydroxy vitamin D deficiency were experiencing markedly low levels of quality of life due to aggravated disease

It was important that the ratio be kept same to remove all bias that may have altered the result credibility and validity. (Figure 2).

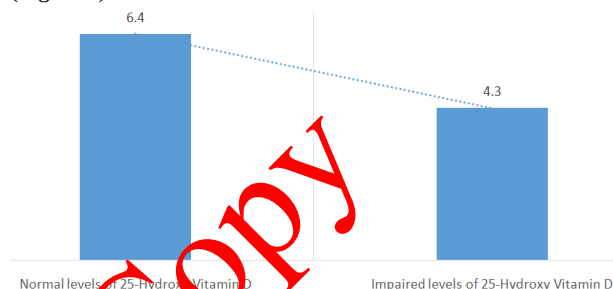


Figure No.3: Impaired Quality of Life

DISCUSSION

The vitamin 25-Hydroxy D casts multiple individual effects on muscle cells. It influences the calcium ion transfer to intracellular region and it is proved by culture studies where the mechanism was studied on a petri dish.¹⁷ The impact that this crucial vitamin casts on cardiac cells is somewhat lower than what it does to the regular muscle cells but still its significant in every aspect.¹⁸⁻²⁰ In diseased individuals, the levels of this vitamin are thus of particular importance.

In the western world, the levels of 25-Hydroxy vitamin D are mostly dependent on the amount of time that an individual spends in broad day light and the area of exposure on body of ultraviolet spectrum of light (a.k.a UV B light).²¹ In normal circumstances, a low level of exposure does not cause the levels of the said vitamin to drop but in diseased individuals who are often bedridden, the exposure level and duration drop to nearly a zero. The diet too of such individuals is not very supportive and so in the face of heightened demand and poor supply, the condition worsens and the disease is aggravated.²²⁻²⁵

The dropped levels of the vitamin, when they aggravate the disease and worsen the adverse symptoms, cause distress to the patients and reduce their quality of life to a large extent.^{26,27} It is noted in our study that individuals suffering from the disease benefit from the use of medication as the use of digitalis and beta-blockers acts to enhance the cardiac contraction and thus the ejection fraction⁷⁻⁸, but it is still not enough to counter the negative effects cast by 25-Hydroxy vitamin D deficiency.

CONCLUSION

The deficient levels of 25-hydroxy vitamin D, as indicated in literature, alter the metabolism of minerals and lead to myocardial dysfunction in the congestive heart disease patients. It is thus an aggravating factor for pathogenesis of congestive heart failure and leads to marked decrease in the quality of life.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure. the Framingham study. *N Engl J Med* 1971;144:1446.
2. McDonald TF, Pelzer S, Trautwein W, Pelzer DJ. Regulation and modulation of calcium channels in cardiac, skeletal, and smooth muscle cells. *Physiol Rev* 1994; 74:365-507.
3. Dargie HJ, McMurray JJ. Diagnosis and management of heart failure. *Br Med J* 1994; 308: 321-328.
4. Statistisches Bundesamt; Statistisches Jahrbuch für die Bundesrepublik Deutschland. Metzler Poeschel Verlag Stuttgart 2000:415-427.
5. Krüger C, Erdmann E, Nabauer M, Beuckelmann DJ. Intracellular calcium handling in isolated ventricular myocytes from cardiomyopathic hamsters (strain BIO 14.6) with congestive heart failure. *Cell Calcium* 1994; 16:500-508.
6. Beuckelmann DJ, Nabauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocardium. *Circulation* 1992;85: 1046-1055.
7. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure. Mechanisms of action and recent clinical developments. *N Engl J Med* 1986; 314:290-299.
8. Kubo H, Margulies KB, Manciano V, Gaughan JP, Houser SR. Patients with end-stage congestive heart failure treated with beta-adrenergic receptor antagonists have improved ventricular myocyte calcium regulatory protein abundance. *Circulation*. 2001; 104:1012-1018.
9. Shane E, Mancini D, Aaronson K. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. *Am J Med* 1997; 103: 197-207.
10. Thomasset M, Parkes C.O, Cuisinier-Gleizes P. Rat calcium-binding proteins. distribution, development, and vitamin D dependence. *Am J Physiol* 1982; 243:E483-E488.
11. Simpson RU, Weishaar RE. Involvement of 1,25-dihydroxyvitamin D3 in regulating myocardial calcium metabolism. physiological and pathological actions. *Cell Calcium* 1988;9:285-292.
12. De Boland AR, Boland RL. Non-genomic signal transduction pathway of vitamin D in muscle. *Cell Signal* 1994; 6:717-724.
13. Weishaar RE, Simpson RU. Involvement of vitamin D3 with cardiovascular function. II. Direct and indirect effects. *Am J Physiol* 1987; 253: E675-E683.
14. Hochhauser E, Barak J, Kushnir T. Mechanical, biochemical, and structural effects of vitamin D deficiency on the chick heart. *Angiol* 1989; 40: 300-308.
15. Wu J, Garami M, Cao L, Li Q, Gardner DG. 1,25(OH)2D3 suppresses expression and secretion of atrial natriuretic peptide from cardiac myocytes. *Am J Physiol* 1995; 268:E1108-E1113.
16. Lerman A, Gibbons RJ, Rodeheffer RJ. Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left-ventricular dysfunction. *Lancet* 1993; 341:1105-1109.
17. Zittermann A, Scheld K, Stehle P. Seasonal variations in vitamin D status and calcium absorption do not influence bone turnover in young women. *Eur J Clin Nutr* 1998; 52:501-506.
18. Haug CJ, Aukrust P, Haug E, Morkrid L, Muller F, Froland SS. Severe deficiency of 1,25-dihydroxyvitamin D₃ in human immunodeficiency virus infection. Association with immunological hyperactivity and only minor changes in calcium homeostasis. *J Clin Endocrinol Metab* 1998; 83: 3832-3838.
19. Selles J, Bellido T, Boland R. Modulation of calcium uptake in cultured cardiac muscle cells by 1,25-dihydroxyvitamin D3. *J Mol Cell Cardiol* 1994; 26:1593-1599.
20. Penpargkul S, Bhan A, Scheuer J; Studies of subcellular control factors in hearts of uremic rats. *J Lab Clin Med* 1976; 88:563-570.
21. Birge SJ, Haddad JG. 25-Hydroxycholecalciferol stimulation of muscle metabolism. *J Clin Invest* 1975; 56:1100-1107.
22. Brunvand L, Haga P, Tangsrud SE, Haug E. Congestive heart failure caused by vitamin D deficiency. *Acta Paediatr* 1995;84:106-108.
23. Gillor A, Groneck P, Kaiser J, Schmitz-Stolbrink A. Congestive heart failure in rickets caused by vitamin D deficiency. *Monatsschr Kinderheilk* 1989; 137:108-110.
24. Avery PG, Arnold IR, Hubner PJ, Iqbal SJ. Cardiac failure secondary to hypocalcaemia of nutritional osteomalacia. *Eur Heart J* 1992; 13:426-427.
25. McKenna M. Differences in vitamin D status between countries in young adults and elderly. *Am J Med* 1992; 93:69-77.
26. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest* 1985; 76:1536-1538.
27. Heaney RP. Vitamin D. How much do we need, and how much is too much. *Osteoporos Int* 2000; 11:553-555.

A Study on Incidence of Endophthalmitis Post Intravitreal Injections in Southern Punjab Rural Population

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ABSTRACT

Objective: To evaluate the incidence of endophthalmitis post intravitreal injection in rural population of southern Punjab (Multan District) of anti-vascular endothelial growth factor.

Study Design: Observational / descriptive study

Place and Duration of Study: This study was conducted at Multan Medical and Dental College, Multan between January 2014 and December 2015.

Materials and Methods: Addresses on National Identity Cards were used to enroll the patients who are residing out of multan municipal area. Patient's medical records were maintained to identify the incidence of endophthalmitis. Patients presenting with post operative endophthalmitis between January 2014 till December 2015 were included in the study. All IVIs were performed by single surgeon using standard sterile technique in operation theatre settings. None of the patients were prescribed with preoperative topical or systemic antibiotics. Postoperatively all patients had a QDS dose of topical ofloxacin.

Results: A total of 416 intravitreal injections were performed during the study period. All patients had bevacizumab as intravitreal anti vascular growth factor (Anti-VEGF). Out of total patients there were two cases of endophthalmitis. This led to an incidence of 0.48%, (95% confidence interval: 0.0026-0.0220%). These two cases had intravitreal specimens which were later found to be culture negative.

Conclusion: The risk of post intravitreal Anti-VEGF in rural southern Punjab was found to be higher than quoted national and international standards though we had a small patient group which demands a similar study with larger sample size.

Key Words: Endophthalmitis, Intravitreal Injections, Bevacizumab

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INTRODUCTION

There has been an increasing role of intravitreal injections of Anti-VEGF in current ophthalmic practice.^{1,2} It has become the main stay of treatment for wet age related macular degeneration and diabetic macular oedema.² Intravitreal injections are given in office as well as operating room settings. At some facilities there are dedicated rooms reserved as it has become a very frequent procedure in ophthalmic practices. International protocols do not point toward a standard settings for the procedure.³

There has been no study published so far from our region which take into account the local socioeconomic factors, hygienic conditions and our rural practice leading to an increased incidence of devastating complication as endophthalmitis.

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Endophthalmitis is not the only complication ophthalmologists come across post intravitreal antibiotic injections. Other complications already documented in the literature include retinal detachment, vitreous haemorrhage and iatrogenic lenticular trauma.⁴ However the risk of mentioned complications is relatively low and if managed appropriately can lead to a satisfactory visual outcome.^{4,5} Mentioned statement, though greatly differs for devastating complication as endophthalmitis. In contrast to other intraocular surgeries, intravitreal injections appears to be associated with more virulent organisms.⁶ Streptococcal strains of organisms appears to be most frequently associated with post injection endophthalmitis. These patients tend to have worse visual outcomes as reported in literature.⁷

There has been multiple large trials published so far looking at the safety of IVI and associated complications. The international documented incidence is relatively low as compared what has been found in our study. The risk of endophthalmitis in published trials range from 1 in 1500 to 1 in 5500 injections.^{5,7,8} Endophthalmitis as mentioned earlier is the most dreadful complication ophthalmologist comes across.⁹ There has been a lot of controversy regarding the best evidence based practice for intravitreal injections to minimize this risk.⁹ In our country, taking into account

the resources, procedure is performed in operation theatres as well as in physician's offices. The use of sterile environment may reduce the incidence of endophthalmitis. It is equally important to conduct such study in our rural population as they comprise the largest group of patients and majority belong to a low income group. In order to test the above mentioned assumption a prospective clinical trial was conducted at Eye Unit, Multan Medical and Dental College. This study also looked at the role of pre and post injection topical antibiotics.

MATERIALS AND METHODS

A study, including the rural population presenting to eye out door at Multan Medical and Dental College, Multan was carried out between January 2014 till December 2015. All patients included in the study had an informed consent of their recruitment prior to intravitreal injections. As this study specifically focused on the rural population which makes approximately 90% of the total out patients, their addresses were confirmed from national identity cards.

All patients had intravitreal bevacizumab as anti vascular endothelial growth factor. Entries were made in hospital register and cross checked prior to compilation of results. Hospital theatre register was used to identify patients presenting and being treated for endophthalmitis. Endophthalmitis was defined as patients presenting with intraocular inflammation and treated with intravitreal antibiotics post vitreous tap following intravitreal injections. Patients who had other intraocular procedures e.g. phacoemulsification, vitrectomy though very few, were excluded from the study. Patients presenting to outdoor clinics with endophthalmitis resulting from treatment elsewhere were also excluded from the study.

All patients had the standard dose of bevacizumab (1.25 mg/0.05 mL) provided by a single local supplier. Source of injections were certified compounding pharmacies based in Lahore. All injections were administered under the sterile conditions in operating theatre. Surgeon used mask, sterile gloves, theatre gowns and had surgical scrub prior to the procedure. Patients had topical anaesthetic drops (Alcaine manufactured by Alcon) preoperatively for local anaesthesia. Injections were administered using standard prefilled insulin syringes with 30 gauge needles on them. Prefilled syringes however, as provided by the local supplier were non sterile as is the common practice in our country. All patients had a thorough cleaning of periocular tissue and lids using 5-10% povidone iodine. Same drops were instilled in the eyes to be operated for two to three minutes in order to achieve the maximum possible sterility. Patients had a self-adhesive surgical drape covering periocular tissue, nose and part of face prior to the procedure. Patients had a sterile speculum inserted followed by the

intravitreal injection. Injections were performed in the inferotemporal quadrant. Needle was inserted 3.5mm from the limbus for phakic and 3.5mm for pseudophakic and aphakic patients. Following the procedure, speculum was removed and patients had a single drop of ofloxacin eye drops combined with a single drop of povidone iodine solution. All patients had a sterile eye pad and were instructed to remove it 2-3 hours post procedure. No topical antibiotics were used preoperatively. All patients were prescribed with topical ofloxacin eye drops. Clear written instructions in native language were provided to them for the use of topical antibiotic drops to be used four times a day for five days in the operated eye, starting on the same day following eye pad removal. Data was thoroughly analyzed by the biostatistician using the Wilson score method.

RESULTS

A total of 416 intravitreal injections were given of anti-vascular endothelial growth factor. All patients (100%) had the standard dose of bevacizumab. There were two documented cases (0.48%) of endophthalmitis, (95% confidence interval: 0.0026-0.0220%). There were no comparative groups as standard protocols were followed for all the procedures and all patients had same drug. Two patients presenting with endophthalmitis had a vitreous tap followed by intravitreal injections, though they were found to be culture negative. Both patients had three ports pars plana vitrectomy afterwards but they ended up losing any functional vision due to severity of the complication.

Case 1 (HAD): A 67 year-old man with diagnosed diabetic macular oedema on clinical assessment and optical coherence tomography had intravitreal bevacizumab. Central macular thickness at the time of presentation was 458 microns. This was his third injection in the same eye. He presented a day later with severe pain and loss of vision in the same eye. On examination his visual acuity at time of presentation had reduced to counting fingers from 6/36. There was anterior chamber hypopyon with hazy view of fundus. Patient had a vitreous tap with intravitreal injections of vancomycin 1.0mg and ceftazidime 0.4mg as per protocol. Vitreous culture failed to grow any organisms. Patient was prescribed a topical combination of tobramycin and dexamethasone, ofloxacin and oral prednisolone following intravitreal antibiotics. He had three ports pars plana vitrectomy with silicone oil 48 hours after initial presentation as there were no clinical signs of improvement. Unfortunately he ended up with a visual acuity of hand movements. He is still being followed up in the out patients.

Case 2 (ZB): A 58-year-old woman with diabetic macular oedema and proliferative diabetic retinopathy presented three days after receiving intravitreal bevacizumab injection. She had a history of poorly

controlled diabetes. Best corrected visual acuity had dropped to hand movements in this particular case. Clinical findings were consistent with acute endophthalmitis. She had the vitreous tap with intravitreal vancomycin and ceftazidime as per protocol. Cultures failed to grow any pathogen. Day after her vision improved to 6/60, which again declined to hand movements four days post intravitreal antibiotics. She had a three ports pars plana vitrectomy with resulting visual acuity of hand movements. She was lost to follow up afterwards.

DISCUSSION

This is a prospective study of 416 intravitreal injections and a very first of its kind to include the rural population of southern Punjab. This prospective analysis was performed to compare the incidence of most devastating complication i.e. endophthalmitis with what has been documented in international trials. It has confirmed the fact that incidence was found to be relatively higher in southern Punjab rural population despite of following standard accepted protocols for the administration of intravitreal antibiotics. Study did not had a comparative group due to its patient pool hence it is not possible to compare the difference between urban and rural population. Moreover no direct comparison was done between administration of injections in operating theatre or outdoor clinics. The higher incidence of endophthalmitis can be explained with the relatively smaller sample size.

One of the largest study published so far looking at the incidence of endophthalmitis post intravitreal injection was the meta analysis by McCannet et al.⁶ This analysis included prospective as well as retrospective data. There were 52 reported cases of endophthalmitis post 105,536 injections administered in outpatient clinics. The incidence rate was found to be 0.049% per injection (95% CI: 0.038-0.065%). This analysis excluded all the studies done outside of United States. Only studies with proven cases of endophthalmitis which had a vitreous tap were included. Comparing McCannet study with ours, we had a significantly higher incidence. Author will like to mention that it is difficult to provide any direct comparison of this study with any meta analysis performed in the western world. We have to take into account the rural southern Punjab population with their general health conditions, hygiene level, psychological considerations, poverty, literacy rate, socio-economic factors and spiritual/cultural values and beliefs. These factors can have a great influence on post-operative practices which may lead to a less than favorable outcomes and a higher incidence of post-operative complications. These factors are clear limitation when we compare our cohort with international meta analysis.

Another recent study published by Abell RG et al,¹⁰ comparing incidence of endophthalmitis post

intravitreal injections performed between operation theatre and outpatient rooms. A statistically higher incidence of endophthalmitis was noticed in procedures performed in outpatient clinics. Although incidence quoted i.e. 0.12% (4 in 3,376 IVI) is significantly less than our study. Author again will like to highlight a cohort size almost ten times larger than what we had as the critical limiting factor. According to recommendation of this study procedure should be carried out in sterile operating room environment.

Author is of the view that systemic disease control is of vital importance in preventing post procedural complications. Both of our patients who developed endophthalmitis despite following strict procedural protocols had poorly controlled diabetes with raised HbA1C levels. Endophthalmitis though a rare but no doubted vision limiting condition can be prevented with improved systemic status, hygiene level and better understanding of prescribed post-operative medications.^{11,12} Author also finds it interesting to conduct a similar study comparing outpatient and operating room incidence for endophthalmitis. By following international reported incidence the rate of endophthalmitis in clinic settings can presumably be significantly high. This however, is author's personal observation and can only be confirmed with a randomized, prospective study. A direct comparison between our study and incidence reported by Brencher et al and McCannet^{3,6} will require a minimum of 5000 procedures. This will incur significant increase in the cost and human resources and is beyond author's institutional capacity.

Endophthalmitis results from direct inoculation of pathogen at the time of procedure or immediately afterwards.^{11,12} Hypothetically this can be minimized by following international documented standards. This includes reducing the load of pathogen in conjunctival sac by using povidone iodine and giving it optimum time to work.^{11,13} This also includes the use of sterile operating facility, sterile instruments, surgical drape, following standard technique for drug administration and use of post operative topical antibiotics.⁶ Author find it very interesting to have a higher incidence despite of following all the standard, documented protocols.¹³ Nevertheless, in our society there might be some other factors which play their role in final outcome and needs to be identified. Author supports the international recommended standards devised for this procedure. One important recommendation to be made from our results is use of preoperative topical antibiotic drops for atleast a period of three days. This hypothetically will play a significant role in achieving optimum sterility of conjunctival sac and hence will minimize the incidence of endophthalmitis. Author will also recommend for a prospective study comparing mentioned groups to prove his hypothesis. We have to take into account the fact that there are published

studies against the use of preoperative topical antibiotics. The main concern, being increased in the resistance against pathogens post antibiotic use.¹⁴ Difference however as reported by Moss JM and Roger DL is not statistically different and hence no recommendations can be made on these bases.^{12,15}

Taking into account other associated factors leading to endophthalmitis are respiratory droplets and needle contamination. Risk from respiratory droplets however, in this study is not considered to be significant.¹⁶ Surgical masks was used by the surgeon during all procedure with sterile drapes being placed on patient minimizing this particular risk factor. Moreover, vitreous tap failed to grow any pathogen associated with airborne contamination.

Rate of needle contamination has been reported from 0.36% to 18%.^{17,18} Author will like to point out the fact that in our study injections were transported in non sterile condition as this is the common practice in the country. Lack of local pharmacies, equipped to prepare the injection under sterile condition lead to a transport source 350 km north of the city. This incurs a significant time delay which can greatly effect the sterility of the product. Another important consideration is that bevacizumab syringes are recapped following preparation. This again is against internationally recommended standard for maintaining sterility and contamination free product.^{19,20} This study's main limitation is it's sample size. Author will like to recommend further studies especially focused on country's rural population with larger sample size. Author will also like to recommend for a national metanalysis based on local published studies and audits.

CONCLUSION

In this study we have found a higher incidence of endophthalmitis in our rural population as compared to the standard internationally accepted figures. Author will like to register his reservation on our current national practices and recommends a robust change in order to reduce the incidence of endophthalmitis. Author will also like to recommend for a national metanalysis based on local published studies and audits.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Elman MJ, Qin H, Aiello LP, et al; Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmol* 2012;119:2312-2318.
2. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve month outcomes of a phase III study. *Ophthalmol* 2011;118:2041-2049.
3. Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 medicare free-for-service part B claims file. *Am J Ophthalmol* 2011;151:887-895.
4. Michels S, Becker M, Wachtlin J, Binder S. The intravitreal injection: variations in regulations, cost and reimbursement in Europe, *Spektrum der Augenheilkunde* 2012;26:2-6.
5. Endophthalmitis Vitrectomy study Group. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. *Arch Ophthalmol* 1995; 113:1479-1496.
6. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Retina* 2011; 31:654-661.
7. Rosenfeld PJ, Brown DM, Heier JS, et al. MARINA study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419-1431.
8. Brown DM, Kaiser PK, Michels M, et al. ANCHOR study Group. Anibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432-1444.
9. Green-Simms AE, Ekdawi NS, Bakri SJ. Survey of intravitreal injection techniques among retinal specialists in the United States. *Am J Ophthalmol* 2011;151:329-332.
10. Abell RG, Kerr NM, Allen P, Vote BJ. Intravitreal injections: is there benefit for a theatre setting? *Br J Ophthalmol* 2012;96:1474-1478.
11. Safar A, Dellimore MC. The effect of povidone iodine flush versus drops on conjunctival colonization before intravitreal injections. *Int Ophthalmol* 2007;27:307-312.
12. Moss JM, Sanislo SR, Ta CN. A prospective randomized evaluation of topical gatifloxacin on conjunctival flora in patients undergo intravitreal injections. *Ophthalmol* 2009;116:1498-1501.
13. Alabiad CR, Miller D, SeiffmanJC, Davis JL. Antimicrobial resistance profiles of ocular and nasal flora in patients undergo intravitreal injections. *Am J Ophthalmol* 2011;152:999-1004.
14. Kim SJ, Toma HS. Antimicrobial resistance and ophthalmic antibiotics: 1-year results of a longitudinal controlled study of patients

- undergoing intravitreal injections. Arch Ophthalmol 2011;129:1180-1188.
15. Rogers DL, Chheda I, Ford C, et al. the effect of surgical preparation technique on the bacterial load of surgical needles and suture material used during strabismus surgery. J AAPOS 2011;15:230-233.
 16. de Caro JJ, Ta CN, Ho HK, et al. Bacterial contamination of ocular surface and needles in patients undergoing intravitreal injections. Retina 2008;28:877-883.
 17. Nentwich m, Yactayo-Miranda Y, Weimann S, et al. Bacterial contamination of needle points after intravitreal injection. Eur J Ophthalmol 2009;19: 268-271.
 18. Stewart JM, Srivastava SK, Fung AE, et al. Bacterial contamination of needles used for intravitreal injections; a prospective, multicenter study. OculImmunol Inflamm 2011;19:32-38.
 19. Speaker MG, Milch FA, Shah MK, Eisner W, Kreiswirth BN. Role of external bacterial flora in the pathogenesis of acute postoperative endophthalmitis. Ophthalmol 1991;98(5)639-650.
 20. Nentwich M, Ta CN, Kreutzer TC, et al. Incidence of postoperative endophthalmitis from 1990 to 2009 using povidone-iodine but no intracameral antibiotics at a single academic institution. J Cataract Refractive Surg 2015;41(1)58-66.

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Anti- Phospholipid Antibodies in Multiple Blood Transfusion Dependent β -Thalassemia Major Patients at Hyderabad

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ABSTRACT

Objective: The study aimed to observe the anti-phospholipid antibodies in multiple blood transfusion dependent β -thalassemia patients at the Hyderabad.

Study Design: Observational / cross sectional study.

Place and Duration of Study: This study was conducted at pathology and pediatric department, Liaquat University of Medical & Health Sciences, Jamshoro, from June 2013 to May 2015.

Material and Method: A total of 121 patients were enrolled. Blood samples were collected in citrated tube. APTT was performed on Sysmex (CA 500) while Lupus anticoagulant and Anticardiolipin antibodies were performed on commercial kits.

Results: Of 121 patients 81(66.9%) patients were positive for anti-phospholipid antibody while 40(33.1%) were negative. Lupus anticoagulant were present in 69 (57%) and were not detected in 52 (43%). Cardiolipin antibodies were found positive in 45 (37.2%) while negative in 76 (62.8%) cases.

Conclusion: Anti-phospholipid is common in patients with beta thalassemia major. APLs are considered as a common acquired autoimmune hyper coagulation state for thrombotic risk factor.

Key words: Anti-phospholipid antibodies, anticardiolipin antibodies, Lupus anticoagulant, β -Thalassemia

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INTRODUCTION

Beta- (β) thalassemia is an inherited blood disorder caused by a defect in the synthesis of β -globin chain.¹ Prevalence of beta thalassemia has been reported 16% in Cyprus, up to 14% in Thailand, India, Pakistan, Bangladesh, China and 0.9% & 0.1 in African blacks and Europe respectively.³ Transfusion of red blood cells and iron chelation therapy has immensely improved the quality of life of thalassemia major patients⁴ however; these patients may develop complications including thrombosis pulmonary hypertension and thrombo embolic events.⁵ The estimation of risk in patients of thalassaemia regarding hemostatic anomalies is thought to be resulting from hepatic dysfunction, chronic platelet activation, red cell membrane alteration and activation of intrinsic coagulation system. However further studies are required to clearly understand the risk factors.^{6,7} Studies have reported the presence anti-

phospholipid antibodies such as (APA), lupus anticoagulant (LA) and anti-cardiolipin antibody (ACA) in beta thalassemia major.⁸ Antiphospholipid syndrome (APS) is an autoimmune disease in which antibodies such as lupus anticoagulant (LA), anticardiolipin antibodies (ACL) and anti- β 2-glycoprotein-1 (anti- β 2-GP1) are present and hence causing arterial and venous thromboembolism. Patients with repeated pregnancy morbidity and/or thromboembolic complications are distinguished by the presence of these antibodies. They are also associated with fetal loss, thrombocytopenia and neurological manifestations and has influence on multiple pathways including coagulation and complement pathways.^{9,10}

APLs with its associated clinical features got increasingly significant recognition from the past decade in various pediatric diseases. In the neonatal period APLs may be present as a result of vertical transmission resulting in disturbance of intricate balance between coagulation and anti-coagulation factor including reduced concentration of naturally occurring anticoagulant proteins and increased levels of factor VIII and von Willebrand factor with less active fibrinolysis that leads to the prothrombotic state. Numerous congenital and acquired risk factors such as coagulation inhibitors, genetic mutations like polymorphism of methylene tetrahydrofolate reductase

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(MTHFR) gene, maternal eclampsia, traumatic delivery, hyperchromocytinemia, infections, dehydration, complex inherited heart diseases and catheter placement in the newborn may lead to neonatal thrombosis¹⁰⁻¹². The hypercoagulable state in beta thalassemia major patients is due the presence of reduced naturally occurring anticoagulation proteins such as The natural coagulation inhibitors protein C, protein S and anti thrombin.¹³ Thrombocytopenia is a frequent finding in patients with APS, and balancing the need for anticoagulation when faced with significant thrombocytopenia can be a considerable challenge for clinicians managing such patients. This study will help us to identify the presence of anti-phospholipid antibodies in beta thalassemia patients so the new for approach for screening of such patients and treatment could prevent from the coagulation abnormalities.

MATERIALS AND METHODS

This Cross sectional study was conducted at Department of Pathology and Pediatric, Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro and thalassemia centers from June 2013 to 2015. A total of 121 subjects were selected for this study after an informed consent from the patient or next of kin and fulfilling the inclusion criteria. IRB approval was reserved for this study from institutional ethics committee. Two blood samples were collected from each individual, Ethylene diamine tetra acetic acid (EDTA) and citrate 3.8%. Full blood count (FBC) and activated partial thromboplastin time (aPTT) was performed on sysmex XE2100 and sysmex CA 500 automated coagulation analyzer respectively. Anti-phospholipid antibody :Lupus anticoagulant and anticardiolipin antibodies were determined by commercially available kits. Statistical Package for Social Science (SPSS) software version 22.0 was used for data analysis. Descriptive statistics was applied for qualitative variables such as gender anticardiolipin antibody, lupus anticoagulant and antiphospholipid antibodies. Effect modifier was controlled through stratification of age, gender and number of transfusions by applying chi square test, $p \leq 0.05$ was considered as significant.

RESULTS

A total of 121 patients of beta thalassemia major with mean age 9.21 ± 2.5 ; (range 3-13 years) of them most of the patients were the age group of 11-13 (57%). Sixty two were male (51.2%) while 59 (48.2) (male /female: 1.05:1). Lupus anticoagulant, cardiolipin antibody and anti-phospholipid antibodies were positive in 69(57%), 45(37.2%) and 81(66.9%) patients respectively. Antibodies were negative LA 52(43%), cardiolipin antibody 76 (62.8%) and anti-phospholipid antibodies

40(33.1%) (Table1). Minimum number of transfusion were 20 and maximum were 370 and mean transfusion were 132.17 ± 62.173 (Table 2). Patients age and gender with anti-phospholipid antibodies were found to be non-significant i.e. (0.063), (0.082) while transfusion were found to be highly significant i.e. (0.001) as shown in table 5.

Table No.1: Frequency of lupus anticoagulant, cardiolipin antibody and anti phospholipid antibodies

Types of antibodies test	Positive	Negative
Lupus anticoagulant (n=121)	69(57%)	52(43%)
cardiolipin antibody (n=121)	45(37.2%)	76(62.8%)
anti-phospholipid antibodies (n=121)	81(66.9%)	40(33.1%)

Table No. 2. Anti-phospholipid antibodies status and number of transfusion

Number of Transfusion	Negative	Positive	Total
4-100	35	15	50
101-200	5	53	58
201-370	0	13	13

Table No.3: Anti-phospholipid antibodies status with various age groups

Age Groups	Negative	Positive	Total
3-6	4	7	11
7-10	19	22	41
11-13	17	52	69

Table No.4: Anti-phospholipid antibodies status in male and female

Gender	Negative	Positive	Total
Female	24	35	59
Male	16	46	62

Table No.5: Statistical significance in antiphospholipid antibody and various age groups, gender and no, of transfusions

	Age group	Gender	No, of Transfusions
p-value	0.06	0.08	0.0001

DISCUSSION

It is recommended to test the LA after discontinuation of antithrombotic therapy as screening for LA is performed using two phospholipid dependent coagulation tests.¹⁴⁻¹⁸ Patients who are on oral anticoagulants show prolonged clotting time, mixing and confirmatory tests. Hence may lead to false positive results.⁹ However ACL and anti $\beta 2$ -GP1 can be detected by using enzyme-linked immunosorbent assay (ELISA) techniques. Standardization of these assays is

not well established and variations may exist among batches.⁹ This study revealed 57% incidence of LA in patients of thalassemia major.¹⁹

Anticardiolipin antibodies were positive in 37.2% of the thalassemia major patients. There was a 2 GP1 ACA in 13% of the cases of α -thalassemia. LA positive patients manifested higher numbers of transfusions and mean age as compared to LA negative patients but still the comparison was not proven significant statistically. A correlation of LA with multiple transfusions were observed.⁸ Our study also showed no evidence of thrombosis in the patient having LA. One international study has mentioned the same findings. Two studies have reported the incident of intracranial bleeding and cerebral infarction associated with LA.⁸

The present study is of value for the blood transfusion dependent thalassemia patients as it will improve the health in future. The main limitation of the present study is small sample size, particular race and ethnicity of particular geographical area; hence results should be interpreted cautiously for other settings.

CONCLUSION

The present study shows increase frequency of lupus anti-coagulant and anti cardiolipin antibodies in multiple blood transfusion dependent β -thalassemias major demonstrating the presence of in comparison to normal individuals. The blood transfusions requirements were higher in patients with positive antiphospholipid antibody as compared with negative.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Triplett DA. New diagnostic strategies for lupus anticoagulants and antiphospholipid antibodies. *Pathophysiol Haemost Thromb* 1994;24(3):155-64.
2. Weatherall DJ. Phenotype-genotype relationships in monogenic disease: lessons from the thalassaemias. *Nat Rev Genet* 2001;245-255.
3. Lao TT. Obstetric care for women with thalassemia. *Best Practice & Research Clinical Obstetrics & Gynaecol* 2016.
4. Borgna-Pignatti C. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica* 2004;89 (10):1187-93.
5. Taher AT. Thalassemia and hypercoagulability. *Blood Rev* 2008;283-92.
6. Cappellini MD. Coagulation in the pathophysiology of hemolytic anemias. *ASH Education Program Book* 2007;74-78.
7. Pereira SP, Peter GL, Roger W. The management of abnormalities of hemostasis in acute liver failure. *Seminars in liver disease*. Thieme Medical Publishers Inc 1996;16(04):196.
8. Sharma S. Lupus anticoagulant and anticardiolipin antibodies in polytransfused beta thalassemia major. *Hematol* 2006;287-290.
9. Lim W. Antiphospholipid antibody syndrome." *ASH Education Program Book* 2009;233-9.
10. Avcin T. Antiphospholipid syndrome in children. *Current opinion in rheumatology* 2008;595-600.
11. D'Ippolito S. Obstetric antiphospholipid syndrome: a recent classification for an old defined disorder. *Autoimmunity reviews* 2014;901-908.
12. Avramović M, Todor A. Antiphospholipid Antibody Syndrome in Childhood. *Pediatric Rheumatology*. Springer Singapore 2017;377-92.
13. Ataga KI, Mann DC, Eliezer AR. β -Thalassaemia and sickle cell anaemia as paradigms of hypercoagulability. *Bri J Haematol* 2007;3-13.
14. Bertoni AM. Systemic lupus erythematosus in a multiethnic US cohort: Clinical features, course, and outcome in patients with late-onset disease. *Arthritis & Rheumatism* 2006;1580-7.
15. Akter R. Rat Bite Fever Resembling Rheumatoid Arthritis in a 46 Year Old Female. *J Rheumatol* 2016; 43 (6):365.
16. Zocco MA. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. *J Hepatol* 2009;682-9.
17. Cervera R. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis & Rheumatism* 2002;1019-27.
18. Miyakis S. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *Journal of Thrombosis and Haemostasis* 2006;295-306.
19. Pullarkat V. Detection of lupus anticoagulant identifies patients with autoimmune haemolyticanaemia at increased risk for venous thromboembolism. *Bri J Haematol* 2002;1166-9.

Array of Unnatural Deaths: A Study of Medico Legal Autopsies at District Head Quarter Hospital Lakki Marwat

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ABSTRACT

Objective: To determine the modalities and manners of unnatural deaths among all cases brought to the district headquarter hospital Lakki Marwat for autopsy.

Study Design: Observational / descriptive study

Place and Duration of Study: This study was conducted at the District Headquarter Hospital, Lakki Marwat, Khyber Pakhtunkhwa from January 2013 to December 2014.

Materials and Methods: A total of 126 dead bodies received during two years for postmortem examination through autopsy. This study was based on a data of unnatural deaths. The data were collected on structured checklist whereas, data analysis was done using SPSS version 20 and presented in terms of frequencies and percentages.

Results: Out of 126 dead bodies, 116 (92.1%) were males and 10 (7.9%) females. Out of total, 3 (2.4%) were also found decomposed. The dead bodies received for autopsy were in the age range from 5 to 72 years. Regarding manner of death 95 (75.4%) were homicidal, 22 (17.5%) accidental, 7 (5.5%) suicidal and 2 (1.6%) cases remained undetermined. Furthermore the types of modalities included; death due to fire arm injuries are 93 (73.8%), road traffic accidents 19 (15.1%), blunt weapon and hanging each 4 (3.2%), bomb blast 3 (2.4%) strangulation 1 (0.8%) and the cause of death in 2 (1.6%) cases remained undetermined which were labeled as negative autopsy.

Conclusion: A high proportion male were referred for forensic examination as compare to female where, most of them were from young age. Homicide was noted as the major type of manner of death followed by accident. Fire arm injury was reported as the major modality of death followed by road traffic accident.

Key Words: Autopsy; Homicide; Suicide; Accidents; Wounds; Gunshot; Cause of Death

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INTRODUCTION

To ascertain the cause and manner of death is always the demand of judicial system in order to provide justice to community¹. Such medicolegal investigations are carried out through an autopsy study which has no substitute. The information provided through medicolegal autopsy carries immense value in cases of any foul play by any person². The information gathered from crime scene investigation, circumstantial evidence or external examination cannot answer the question for cause of death which necessitates the performance of proper autopsy³.

Medicolegal autopsy is the detailed systemic external and internal scrutiny of dead body supported by laboratory examination carried out by authorized medical officer in the pursuance of law to ascertain the underlying and possible contributing cause and manner of death¹. A competent legal authority can ask for investigation through autopsy in case a person reportedly committed suicide or a case of homicidal death or death caused by an accident or death under any suspicious circumstances⁴. Law also has provision to investigate the deaths occurring in prison, police custody or any other similar conditions⁵.

It is required to determine the cause of death as natural or unnatural which is caused either by an accident or by hostile action of a member of community¹. Manner of death can be natural and unnatural. The natural deaths are caused by a disease which may include environmental insult or chronic over usage of drug while, unnatural deaths include; suicide (self murder where the lethal action of some one's is intentionally inflicted), homicide (death caused by the act of other person), accidental (death occurred without intention to cause harm). Hence, undetermined is used when reasonable classification cannot be made⁶.

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Despite of its undoubted value for improving the death certificate in term of determination the cause of death, it is considered fallible in revealing the true cause of death⁷. It contributes to conclusion in many cases but in sometimes it has less finding for the reason that ante mortem trauma being obscured or destroyed by decomposition or even cause of death is equally difficult to prove⁸. This, results in negative autopsy despite of adopting all standard procedure by medico legal doctor, the rate of negative autopsy can be minimized by improving in skill and other facilities⁹.

The global estimate of homicides indicates that there were 475,000 cases reported in 2012, where majority victims (82%) were male¹⁰. Literatures from Bangalore and Dhaka reveal accident was the main manner of death followed by suicide and homicide^{11,12}. In Pakistan homicides were the most common manner of death followed by accidents and suicides.^{13,14} Gunshot wounds were reported as the leading cause of death in homicides in Pakistan^{15,16,17}. This study aims to determine the modalities and manners of unnatural deaths in district headquarter hospital (DHQ) Lakki Marwat.

MATERIALS AND METHODS

This was a cross sectional study based on post mortem reports (PMR) at district headquarters hospital (DHQ) Lakki Marwat. The data pertains to two years, started from January 2013 to December 2014. After taking permission from in-charge, a total of 126 post mortem reports were reviewed during the study period. All the cases regardless of gender and age were selected in the study, only those cases with incomplete data on the final decision about autopsy awaited were excluded. The data were scrutinized on the bases of gender, age, type of weapons used, nature of assault and outcome of autopsy examination in terms of modalities and manner of death. Data were analyzed using SPSS version 20 and results were presented in terms of frequencies and percentages.

RESULTS

A total of 126 Post Mortem Reports (PMRs) were evaluated, 73(57.9%) cases were reported in 2013 and 53(42.1%) in 2014. Out of total 116 (92.1%) were being males and 10 (7.9%) were females. The mean age of the victims was 31.7±13.6 (ranged from 3 -72 years). Most of the cases 71 (56.3%) were between 20-39 years (Table 1).

Frequency of various types of modalities were: deaths due to fire arm injuries were 93(73.8%), road traffic accidents 19(15.1%), blunt weapon and hanging each 4(3.2%), bomb blast 3(2.4%), strangulation 1(0.8%) and 2(1.6%) of unknown causes were examined (Table 2). 2(1.6%) cases were labeled as negative autopsy and 3(2.4%) cases received as decomposed bodies (Table 2).

Table No.1: Age and Gender wise distribution of unnatural deaths

Age categories	Sex		Total
	Female	Male	
	F (%)	F (%)	F (%)
< 20 years	1(5.6%)	17(94.4%)	18(14.3%)
20 – 39 years	6(8.5%)	65(91.5%)	71(56.3%)
40 – 59 years	3(10.0%)	27(90.0%)	30(23.8%)
>59years	0(.0%)	07(100.0%)	07(5.6%)
Total	10(7.9%)	116(92.1%)	126

Table No.2: Modalities of unnatural deaths- Gender wise

Type of Modalities	Male	Female	Total	Percent
Fire Arm Injuries	85	8	93	73.8
Road Traffic Accidents	18	1	19	15.1
Blunt Weapon	4	0	4	3.2
Hanging	3	1	4	3.2
Bomb Blast	3	0	3	2.4
Strangulation	1	0	1	0.8
Unknown	2	0	2	1.6
Total	116	10	126	100

The frequency of manner of death was as follow: homicides 95(75.4%), accidental 22 (17.5%), suicides 7(5.5%) and 2(1.6%) cases remained undetermined (Fig 1). The homicidal deaths were further grouped as 90 (94.7%) cases of fire arm injuries, 4 (4.2%) as blunt weapon and one case (1.1%) of strangulation.

DISCUSSION

Autopsy is a vital tool for forensic investigation of death which is caused either by natural or unnatural causes. Legal aspects of human deaths have always been part of the human experience, which can be evaluated from different medico-legal approaches, the intimal screening for manner and cause of unnatural remain the core component of this investigations. To attain the objective of present study, secondary data of autopsies were used. The result reveals that male were the common victim especially in the young age (20 to 39 years). This finding is in consistence with studies conducted in India¹⁸. Homicidal assault was noted as major type of manner of death in our study followed by accident and suicide, this is relevant to a study reported from Karachi and Faisalabad that homicide was the most common manner of death followed by accident and suicide^{13,14}.

Out of the reported homicidal cases 90 (94.7%) were due to fire arm injuries which correlates with a study stating that fire-arm injury was the commonest causes of homicidal death in Dera Ismail Khan¹⁶. The same finding is also reported from a study in district Faisalabad and Peshawar that fire arm injuries are the leading cause of homicidal deaths^{14, 15}. A study from India about fatal fire injuries reported that homicide was the most common manner of death in fatal fire arm

injuries¹⁹. Similar studies performed in Bangalore and Dhaka with a dislike reports from our result that accident is a major manner of death followed by suicide and homicide^{11, 12}.

According to the frequency of various modalities of death in this study, the higher no of deaths were found due to gunshot wounds followed by road traffic accidents, which matches with the results of a study conducted at Karachi¹³.

Negative autopsies in present study accounted 1.6%, which is approximately similar 1.5% to a study conducted in Peshawar²⁰, however results of studies from Peshawar 4% and Faisalabad 9.2% shown an increases in proportion^{21, 9}. While the rate in Dhaka, Bangladesh is reported 5.9%²².

CONCLUSION

Male were the common victim mostly from young age. The common manner of death was homicide followed accident, while the fire arm injury was the main modality of death in the present sample. A thorough multi-sectorial study is needed to investigate overall aspects of medicolegal autopsies, incorporating all factors.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Saukko P, Pollak S. Autopsy; procedure and standards. In: James JP, Byard RW, Corey TS, Henderson C, editors. Encyclopedia of forensic and legal medicine. Elsevier Academic press; 2005. p.166-68.
2. Wood MJ, Guha AK. Declining clinical autopsy rates versus increasing medicolegal autopsies rates in Halifax, Nova Scotia. Archives of Pathology Laboratory Med 2001;125(7):924-30
3. Lunetta P, Lounamaa A, Shyrock S. Surveillance of injury-related deaths, medicolegal autopsy rates and trends in Finland. Injury Prevention 2007; 13(4):282-4.
4. The Code of Criminal Procedure, Act No V of 1898, Section 174; Police to inquire and report on suicide page 91, available from; <http://pakistancode.gov.pk/english/UY2FqaJw1-apaUY2Fqa-apea-sg-jjjjjjjjjjjjj> [accessed on 12/1/2017]
5. The Code of Criminal Procedure, Act No V of 1898, Section 176; Inquiry by magistrate into cause of death page 91-2, available from; <http://pakistancode.gov.pk/english/UY2FqaJw1-apaUY2Fqa-apea-sg-jjjjjjjjjjjjj> [accessed on 12/1/2017]
6. Adams VI, Flomenbaum MA, Hirsch CS. Trauma and disease. In: Spitz WU, Spitz DJ, Fisher RS, editors. Spitz and Fisher's medicolegal investigation of death: Guidelines for application of pathology to crime investigation. Charles C Thomas Publishers; 2006. p.436-9.
7. Saukko P, Knight B. Knight's forensic pathology. 3rd ed. London: Hodder Arnold; 2004. p.45
8. Clark J. War crimes; pathological investigation. In: James JP, Byard RW, Corey TS, Henderson C. editors. Encyclopedia of forensic and legal medicine. Elsevier Academic Press; 2005. p. 369.
9. Qasim AP, Tariq SA, Makhdoom PA, et al. Profile of negative autopsy cases at Punjab Medical College, Faisalabad. JUMDC 2015;6(1):1-6.
10. Butchart A, Mikton C, Dahlberg L, Krug EG. Global status report on violence prevention 2014. Injury prevention 2015;21:3 214
11. Anjanamma TC, Vijaya NM, Vijayanath V, Praveen Athani. A Study of Unnatural death at MVJ Medical College and Research Hospital. Ind J Forensic Comm Med 2016;3(2):138-141.
12. Al-Azad MAS1, Ahmad M, Rahman MZ, Ali M, Islam SMJ. Determination of manners of death: an analysis of 3012 post mortem cases. JAFMC Bangladesh 2013;9(2):15-25.
13. Mirza FH, Hassan Q, Naz R, Khan M. Spectrum of Medico-legal Deaths in Metropolis of Karachi: An Autopsy Based Study. Pak J Med Dent 2013;2 (4):224-6.
14. Qasim AP, Tariq SA, Naeem M. Profile of Unnatural Deaths; in Faisalabad. Medical Forum Monthly 2014; 25(5):51-4
15. Hussain Z, Shah MM, Afridi HK, Arif M. Homicidal deaths by firearms in Peshawar: an autopsy study. J Ayub Med Coll Abbottabad 2006;18(1).
16. Humayun M, Khan D, Zaman FU, Khan J, Khan O, Parveen Z, et al. Analysis of homicidal deaths in district D.I. Khan: An Autopsy Study. J Ayub Med Coll Abbottabad 2009;21(1).
17. Ullah A, Raja A, Yasmin, Hamid A, Khan J. Pattern of causes of death in homicidal cases on autopsy in Pakistan. Gomal J Med Sci 2014;12: 218-21.
18. Patel DJ. Analysis of Homicidal Deaths in and Around Bastar Region of Chhattisgarh. Ind Acad Forensic Med 2012;34(2).
19. Sachan R, Kumar A, Verma A. Frequency of Firearm Injuries, Deaths and Related Factors in Kanpur, India; an Original Study with Review of Literature. Int J Med Toxicol Forensic Med. 2013; 3(3): 88-95.
20. Khan MY, Jan A, Munawwar AZ, et al. Frequency of negative autopsy and their demographic evaluation at Khyber medical college, Peshawar. J Postgrad Med Inst 2007;21(2).
21. Qadeer R, Haq RU, Haq AU. Prevalence of Negative Autopsy in Peshawar, KPK (An Autopsy based study), Ophthalmology Update 2016;14(1): 79-81.
22. Das TC, Swapon MR. Study on Negative autopsy rate at forensic medicine department of Dhaka medical college. Dinajpur Med Col J 2008; 1(1): 21-23.

Association Between Chewing Tobacco and Lesions of Oral Precancer

Hafiz Muhammad Rafique Tagar¹, Saima Aqil², Dost Muhammad Kalhoro³, Muhammad Abdul Hafeez⁴ and Farhan Jaleel⁵

ABSTRACT

Objective: To evaluate the association between different addictive habits and oral premalignant conditions/lesions.

Study Design: Cross sectional Study

Place and Duration of Study: This study was conducted at the Department of Biochemistry in collaboration with Clinical Oncology department of Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Centre (JPMC), Karachi in 2015.

Materials and Methods: A total of 34 patients visiting the outpatient clinic of clinical oncology department with different addictive chewing habits were included in this study. Initial assessment and diagnosis was made by history and clinical examination which was subsequently confirmed histopathologically. The socio-demographic profile of the patients, type of habit and nature of lesion all were recorded. The collected data was then evaluated for its statistical significance on SPSS version 19.

Results: Out of 34 patients, 55.8% (n=19) were female while 44.2% (n=15) were males. The mean age was 39.1 years and 47% of the patients were in the 21-40 year age group. Gutka chewing was the most prevalent lifestyle habit (41.2%) followed by chaliya (29.4%), naswar (14.7%), and pan (11.7%). Leukoplakia was the most frequent precancerous lesion to be observed (58.8%) followed by oral erythroplakia (29.4%).

Conclusion: The habit of Gutka chewing showed a statistically significant association to the development of oral precancerous lesions and conditions.

Key Words: Oral precancerous lesions, Lifestyle habits, Gutka, Chaliya, Naswar, pan

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INTRODUCTION

The lesions of oral cavity constitute the major public problem in South Asian countries including Pakistan. The public of these areas have habits of chewing Gutka, pan and betel quid (Quid is defined as a substance or group of substances remaining in contact with the oral mucosa containing one or both of the two basic ingredients i.e. tobacco and areca nut). Chaliya/areca nut, smoking and naswar (snuff).^{1,12} These are the common addictive habits of public in this region.

Research has found that these habits are risk factors for producing oral lesions¹. A change in colour of the normal reddish oral mucosa to white constitutes one of the most frequently encountered oral abnormalities². A variety of malignant and premalignant lesions of oral cavity appear white, like leukoplakia, oral submucous fibrosis, oral lichen planus, erythroplakia and erythroleukoplakia¹. The initiation of these precancerous conditions may depend upon extrinsic local factors. The more frequently blamed factor is tobacco used in different ways i.e. smoking and chewing that causes local irritation⁴. Pindborg and Renstrup¹³ found that, smoking, chewing tobacco alone or included in pan are the causative factors for leukoplakia. They further reported that habit of keeping naswar (snuff) in the vestibule of mouth produces oral precancerous lesions⁵. Caniff³ reported that there is general agreement in the literature that the areca nut chewing is another significant causative factor for oral lesions⁶. Tilakaratne pointed out in his study that eating spicy food and chewing chaliya/areca nut are the causative factors of oral lesions^{7,8}. In our study we have examined the patients having oral mucosal lesions with deleterious chewing habits of Gutka, chaliya/ areca nut, pan, smoking tobacco, taking spicy food and using naswar and evaluated the association of these risk factors in causing oral precancerous lesions.

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MATERIALS AND METHODS

The study was carried out on 34 patients of precancerous lesions (i.e. leukoplakia, erythroplakia and oral sub mucous fibrosis) of oral mucosa, at the department of Biochemistry, Basic Medical Sciences Institute (BMSI), in collaboration with Clinical Oncology ward of JPMC, Karachi in the last one year. The criteria of oral examination were included on the colour of oral mucosa and site of occurrence. The patients were asked about the habits of taking gutka, chaliya/areca nut, pan, spicy food, smoking, naswar and all the findings were noted in a specially designed proforma. The diagnosis of lesions was made clinically which was later confirmed by histopathological examination. Patients were categorized according to the type of lesion and using deleterious chewing habits of gutka, chaliya/areca nut, pan, spicy food, smoking, and naswar. The data was analyzed by using the SPSS (Statistical Package for Social Sciences) version 19. The results were tested for risk factors and statistical significance was evaluated by applying students-t-test and chi-square test.

RESULTS

The study involved 34 patients with suspected precancerous lesions out of which 15 (44.1%) were male and 19 (55.9%) were female. The youngest patient seen in this study was 14 years old and the oldest one was 70 years old. The mean age of study subjects being 43.97 years. The mean age for male patients was 47.28 years and female mean age was 40.66 years (Table. Figure. 1). The lesions were provisionally labeled by clinical examination and histologically confirmed. Out of 34 Patients, 20 were diagnosed histologically as Leukoplakia, 10 patients of erythroplakia and 04

patients were of oral submucous fibrosis (Table 2, Figure 2).

Table No. 1: Distribution of study subjects According to age and gender (n=34)

Age Group (years)	Male	Female	Total
Under 25	2	1	3
25-34	3	5	8
35-44	2	5	7
45-54	3	4	7
55 & above	5	4	9
Total	15	19	34
Mean ages	47.28	40.66	43.97



Figure No. 1: Showing age wise distribution of precancerous conditions

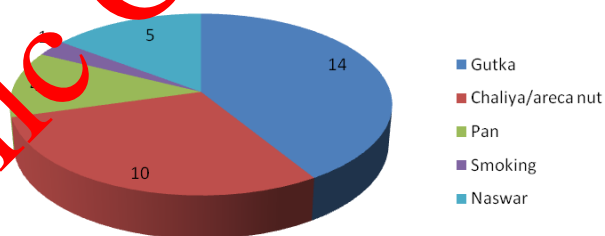


Figure No.2: Showing predisposing factors of precancerous lesions

Table No.2: Distribution of Precancerous Lesions In Relation To Predisposing Factors

Precancerous Lesions	Gutka	Chaliya/areca nut	Pan	Smoking	Naswar	Total
Leukoplakia	08	06	02	01	03	20
Erythroplakia	04	03	02	-	02	10
Oral Submucous Fibrosis	02	01	-	-	-	4
Total	14	10	04	01	05	34

All of these 34 patients were asked about their deleterious chewing habits like gutka, chaliya/ areca nut, pan, spicy food, smoking and naswar. It was observed that most of the subjects were having deleterious chewing habits of Gutka (41.2%) followed by chaliya/areca nut (29.4%), naswar (14.7%), and pan (11.7%). Some of the patients had mixed habits of using more than one of the risk substances. These predisposing factors were statistically analyzed and results showed that gutka chewing was more predominant and statistically significant risk factor with

P value <0.05 where as the association of other factors to oral premalignant lesions or conditions was not as such significant (Table. 2).

DISCUSSION

A variety of oral precancerous lesions have been identified to exist in conjunction with oral habits of chewing the deleterious addictive substances^{9,10}. In our study all the patients were habitual of chewing gutka, chaliya/areca nut, pan, spicy food, smoking or naswar in different forms and frequencies either in a single or

joined form^{1,4,11}. The gutka and chaliya/areca nut chewing habits were statistically found significant. Interpretation of data from a single institution has clear limitations. The data reflects the specific patient population reporting to this hospital and not the community as a whole. In various studies regarding the addictive habits of smoking, gutka, pan, chaliya/areca nut, spicy food, naswar etc were found in positively association with oral precancerous conditions^{8,11}. In the study of Gupta⁵, leukoplakia was seen more frequently in smokers than non smokers and reducing tobacco consumption regressed the lesion while in the study of Silverman and Griffith¹⁴ disappearance of oral leukoplakia had occasionally been reported in patients who continued to smoke. In same study the pan-chewers lesion consisted of a thick brownish black encrustation on the buccal mucosa at the site of placement of areca nut/betel quid, their study shows that the pan-chewers lesion deserve the designation of leukoplakia^{11,15,16}.

The chewing of betel quid (gutka) is practiced in several different ways in various countries, while the major components are comparatively consistent^{17,18}. In Pakistan and Southeast Asia, tobacco is usually used as an ingredient for areca nut products especially in gutka, chaliya, pan therefore it is difficult to know the individual risk effect of tobacco or areca/betel quid^{19,9,10}. A higher relative risk of oral cancer for areca/betel quid chewing with tobacco was notably higher^{20,21} than that for betel quid chewing without tobacco, and the evidence for leukoplakia as well as oral submucous fibrosis was also in the same direction^{5,7,8}.

In our study it was found that gutka, chaliya/areca nut and pan consumers were on a significant risk for the development of oral cancer which is in consistent with Khan¹¹ and Akram¹ (Table No. 2). In the study of Yang²² many oral lesions still did not have significant statistical power to clarify the effect of areca/betel quid from tobacco. In the study of Shah and Sharma²⁰ 2.6% were quid chewers, 20.8% of quid chewers had tobacco as an ingredient, 13.1% used pan masala with tobacco. For oral lesions in this study the ratio of gutka and chaliya/areca nut users was high which was comparable to our study.

In our study the gutka and chaliya/areca nut chewers were found more significant as compared with study the of Y-H Yang²² who showed in their study that chaliya/areca nut quid chewing was a significant risk factor for developing oral precancerous lesions²³. But Mahar¹⁷ found in his study that the quid chewers with tobacco and quid chewers without tobacco were affected by oral precancerous lesions which are inconsistent with the present study. Pan was found significant in the study of Sarawathi²¹. Other so many workers have found that the chewing/smoking of Tobacco and areca nuts/betel quid usage were

positively associated for producing oral mucosal lesions^{24,25}. In the study of Hashibel⁶ the above factors were found significant in producing oral leukoplakia.

This study demonstrated a significant positive association between oral precancerous lesions and addictive chewing habits especially of gutka, chaliya/areca nut and pan^{25,9,10}. As pan is a mixture of different substances i.e. betel leaf, areca nut, tobacco, slacked lime and different other seasonings therefore the individual roles of each of these ingredients in causing oral precancerous lesions need further investigation.

CONCLUSION

The habit of gutka, chaliya/areca nut and pan chewing has showed a statistically significant association to the development of oral precancerous lesions. Therefore, it is recommended that the peoples aged ≥ 40 years who are habitual cigarette smokers, areca nut, gutka, chaliya and betel quid chewers should undergo oral mucosa screening regularly so that potential of oral precancer can be identified as early as possible. Synergistic effects endured patients with all the above habits had an over 40-fold higher risk of developing oral cavity cancer than patients who abstained.

The public should be aware of such high risk factors causing the oral precancerous lesions induced by different life styles/social addictive habits.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Akram S, Mirza T, Mirza M A, Qureshi M. Emerging patterns in clinico-pathological spectrum of Oral Cancers. Pak J Med Sci 2013;29(3).
2. Bramley PA, Simith CJ. Oral Cancer and Pre cancer establishing a diagnosis. Br Dent J 1990; 168-103.
3. Canniff JP, Harvey W, Harris M. Oral Sub mucosa fibrosis and management. Br Dent J 1986;160: 429-434.
4. Collins FM. Tobacco cessation and the impact of tobacco use on oral health. RDH. Oklahoma: Penn well dental group; 2010: 1-12.
5. Gupta PC, Mehta FS Daftary DK, Pindborg JJ, Bhonsle RB, Jalanawalk PN, et al. "Incidence rates of oral cancer and natural history in a 10 years follow up study of Indian Villages. common Dent Oral Epidemiol 1980;8:287-333.
6. Hashibe M, Sankaranarayanan R, Thomas G, Kurnvilla B, Mathew B, et al. Alcohol drinking, body mass index and the risk of oral leukoplakia in a Indian population Int J Cancer 2002;88(1): 129-134.

7. Joshi M, Patil R. Estimation and Comparative study of Serum Total Sialic Acid Levels as Tumor Markers in oral cancer and precancer. *J Can Reas and Therap* 2010;(63):263-266.
8. Jyoti S, Afzal M, Siddiue YS. Genotoxic Effects of Pann Masala and Gutica. *WORLD. J Zool* 2011; 6(3):301-306.
9. Kumar M, Riaz A, Dwivedi P, SH Thippeswamy, Khare A, Verma R. Seduced by tobacco, killed by cancer. *Inter Arch Integ Med* 2015; 2:217-222.
10. Roy SK, Chakraborty SN, Rahaman MA, Ghose G. Pattern of Smoking and Chewing Tobacco Use in a Slum of Durgapur: An Industrial City. *J Med Dent Sci* 2015;14:88-92.
11. Khan MA, Saleem S, Shahid SM, Hameed A, Qureshi NR, Abbasi Z, et al. Prevalence of oral squamous cell carcinoma (OSCC) in relation to different chewing habits in Karachi, Pakistan. *Pak J Biochem Mol Biol* 2012; 45(2):59-63.
12. Narang D, Shishodiya S, Sur, Khan NF. White blood cells count: As a pathological diagnostic marker for oral pre-cancerous lesions and conditions: A randomized blind trial. *J Carcino Mutag* 2014; 5:1-3.
13. Pindborg JJ, Murti PR, Bhonsle RB, Gupta PC, Daftari DK, Mahta FS. Oral submucous fibrosis as pre cancerous condition. *Scand J Dent Res* 1984; 92:224-229.
14. Silverman S, Ciriffith M. Smoking characteristics of patients with oral carcinoma. *J AM Dent Assoc* 1972;85:637.
15. Khadim MI. White lesions of oral musoca. *Pak Oral and Dent J* 1987;7:25-33.
16. Murti PR, Bhonsle RB, Pind Borg JJ, Daftari DK, Gupta PC, Mehta FS. Malignant transformation in oral submucous fibrosis over a 17 years period common. *Dent Oral Epidermal* 1984;12:340-341.
17. Mahar R, Lee AJ, Warnakulasuriyaka Lewis JA, Johnoson NW. Role of areca nut in the causation of oral sub mucosa fibrosis. A case control study in Pakistan. *J Oral Pathol Med* 1994;23:65 – 69.
18. Mehta FS, Gupta PC, Daftary DK, Pind borg JJ. Choksisk. An epidemiological study of oral cancer and pre cancerous conditions among 101, 761 villagers in Maharashtra India. *Int J Cancer* 1972; 24: 73-78.
19. R Rajendran, Shafers. A text book of Oral Pathology. 5th ed. Elsevier: India; 2006.
20. Shah N, Sharma PP. Role of Chewing and Smoking habits in etiology of oral submucosa fibrosis (OSF) a case control study *J Oral Pathol Med* 1998;27:475-479.
21. Saraswathi TR, Ranganathan K, Shanmugams, et al. Prevalence of Oral lesion in relation to habits: Cross-Sectional Study in South India. *Ind J Dent Res* 2006;17(3):121-125.
22. Yang YH, Lien YC, HS PS, et al. The effects of chewing areca // betelquid with and without cigarette smoking on oral submucous fibrosis and oral mucosal lesions oral disease 2005;11:88-94.
23. Tseng CH, et al. Nut Chewing Is Associated With Hypertension In Taiwanese Type 2 Diabetic Patients. *Hypertens Res* 2008;31: 417-423.
24. Sujatha D, Hebbar PB, Pai A. Prevalence and Correlation of Oral Lesions among Tobacco Smokers, Tobacco Chewers, Areca Nut and Alcohol Users. *Asian Pac J Cancer Preven* 2014; 13:1633-37.
25. Bassiony MA, Aqil M, Khalili M, Radosevich JA, Elsabaa HM. Tobacco Consumption and Oral, Pharyngeal and Lung Cancers. *Open Cancer J* 2015; 8:1-11.

Clinical Presentation and Histopathological Assessment of Acalculous Cholecystitis

Shahnawaz Abro¹, Shahida¹ and Adnan Ahmed²

ABSTRACT

Objective: To determine the clinical pattern and histopathological assessment in patients with acalculous cholecystitis.

Study Design: Descriptive case series study

Place and Duration of Study: This study was conducted at the all units of General Surgery, LUMHS, Jamshoro from January 2016 to July 2016.

Materials and Methods: Patients after diagnosis of acalculous cholecystitis through ultrasound were incorporated in the study. Patients were selected from OPD of general surgery and admitted for the cholecystectomy. Surgeries were carried out by senior general surgeons with more than 5 year experience. After surgeries all the specimen of the removal gall bladder, were sent to the laboratory from all the cases for the histopathological assessment.

Results: This study contains 49 cases with diagnosis of acalculous cholecystitis, mean age was 43.12±4.23 years. Females were found most common 59.19%. Right upper quadrant pain was the most common in 92% of the cases, following by epigastrium pain, fatty food intolerance, nausea and vomiting and others as well as feeling fatigue and abdominal discomfort were found with percentage of 51.02%, 12.24%, 30.61% and 20.40% respectively. Chronic cholecystitis was the most common histological finding in 57.14% patients, acute cholecystitis was found in 15.32%, Xanthogranulomatous cholecystitis was in 10.20%, gangrenous cholecystitis was in 4.08%, while malignancy was found only in 1 case and 2 cases were without pathology.

Conclusion: Female gender is more associated with acalculous cholecystitis; most common clinical presentation was right upper quadrant pain and most prevalent histopathological finding was the chronic cholecystitis and carcinoma was very low only in one case.

Key Words: Acalculous cholecystitis, clinical pattern, histopathology

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INTRODUCTION

Acute acalculous cholecystitis (AC) is the situation which typically happens through severe clinical status, and also relatively rare and difficult to diagnose.¹ AC is the type of pathology in which GB wall becomes thickened.² Cholecystitis presents in >10% of people increases with the age. The commonest causes of the GB pathologies are the DM, estrogen, pregnancy, liver cirrhosis, hemolytic diseases and the obesity.² Though estimate 2 - 15% of acute cholecystitis may occur without the events of gallstone, and without calculus these are named as, acalculous cholecystitis, and this condition is diagnosed through increasing frequency in critical cases and is also stated worldwide.^{1,3,4}

Many clinical observations occur but are nonspecific to acalculous cholecystitis: pain at right upper-quadrant,

temperature elevation, leukocytosis, and some hepatic abnormal tests "aminotransferases, ALT, and the bilirubin".^{3,4} Several situations predispose to its presence. It has not been likely to reliably determine the prevalence of risk factors of AC, but several studies have listed their occurrence frequency in their cases populations.

Etiology of AC is multifactorial and likely outcomes from bile stasis or ischemia or both. Bile stasis may be caused due to fasting, obstruction, postsurgical/procedural irritation or ileus "TPN", those may lead to bile inspissation which is directly toxic to GB epithelium.^{1,5} Ischemia to organ may occur from several risks related with systemic inflammation and could have deleterious effects directly to all the walls of GB layers.^{6,7} It is observed that current practice is not to send cholecystectomy specimen, in really all cases, for histopathology; solely relying upon gross examination of the tissues to avoid additional financial burden on patients' family.⁸ Therefore aim of this study to determine the histopathological evaluation in patient with acalculous cholecystitis.

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MATERIALS AND METHODS

This descriptive case series study had done at LUMHS in the all units of general surgery Jamshoro. Study duration was 7 months from January 2016 to July 2016. Patients after diagnosis of calculus cholecystitis through ultrasound were incorporated in the study. Patients were selected from OPD of general surgery and admitted for the cholecystectomy. After admission all the required laboratory investigation were carried out. Ultrasound was repeated in all the cases after admission. Complete clinical examination was carried out. After complete preoperative workup cases prepared for the cholecystectomies. Surgeries were carried out by senior general surgeons with more than 5 year experience. After surgeries all the specimen of the removal gall bladder, were sent to the laboratory from all the cases for the histopathological assessment. All the information regarding patients clinical presentation and histopathological findings were recorded in the proforma. For results analysis data was entered in the SPSS program version 20.

RESULTS

This study was contains 49 cases with diagnosis of acalculous cholecystitis, mean age was 43.12 ± 4.23 years. Male were found in most common 59.19%, while female were 40.81%. History of disease duration less than 5 years in 71.42% and 28.58% patients has disease more than 5 years. Table:1.

Right upper quadrant pain was the most common in 92% of the cases, following by epigastrium pain, fatty food intolerance, nausea and vomiting and others as well as feeling fatigue and abdominal discomfort were found with percentage of 51.02%, 12.24%, 30.61% and 20.40% respectively. Figure 1.

Table No. 1: Basic characteristics n=49

Basic variables	Frequency/%
Age (mean$\pm$SD)	43.12 $\pm$ 4.23 years
Gender	
Male	29/59.19%
Female	20/40.81%
Disease duration	
Less than 5 years	35/71.42%
More than 5 years	14/28.58%

Table No.2: Histopathological pattern n=49

Histopathology	Frequency (%)
Chronic cholecystitis	26(57.14%)
Acute cholecystitis	08(15.32%)
Xanthogranulomatous	05(10.20%)
Gangrenous cholecystitis	02(4.08%)
Malignancy	01(2.04%)
Normal	02(4.08%)
Others	06(12.24%)

Chronic cholecystitis was the most common histological finding in 57.14% patients, acute cholecystitis was found in 15.32%, Xanthogranulomatous cholecystitis was in 10.20%, gangrenous cholecystitis was in 4.08%, while malignancy was found only in 1 case and 2 cases were without pathology. Table 2.

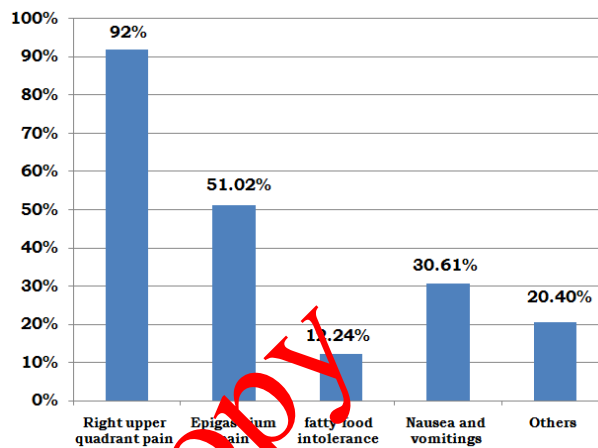


Figure No.1: Clinical pattern n= 49

DISCUSSION

This study was contains 49 cases with diagnosis of acalculous cholecystitis, mean age was 43.12 ± 4.23 years. Male were found in most common 59.19%, while female were 40.81%. History of disease duration less than 5 years in 71.42% and 28.58% patients has disease more than 5 years. Comparable findings were found in the study of Siddiqui FG et al⁹ reported that 193 were females and 27 were males with ratio f1:7. Meanage was 32.3 ± 5.3 years with range 19 - 80 years. On other hand Soomro AG et al⁸ reported that 79 were males and 442 were females and mean age was 47 years with range of 7-75 years. While Gelani et al¹⁰ also reported comparable mean age as well as 42.7 years.

In this study commonest clinical presentation was right upper quadrant pain in 92% of the cases, following by epigastrium pain, fatty food intolerance, nausea and vomiting and others as well as feeling fatigue and abdominal discomfort were found with percentage of 51.02%, 12.24%, 30.61% and 20.40% respectively. In the comparison of our study Ghimire P et al¹¹ reported that the main presentation was the epigastrium pain in 70.11% patients, and dyspepsia in 62.84% patients, nausea was in 56.96% and anorexia was in 44.57% of the cases. Pain at right hypochondrium, radiating to epigastrium and scapula, presents the condition onset. Elevated temperature, vomiting and nausea may occur in 70% of the cases.¹² Abscesses formation; GB gangrene should raise suspicions in occurrence of elevated temperature, leukocytosis and peristalsis decreases.¹² Subsequently several of these symptoms are often observed in the cases having severe conditions, who needed sedation, clinical consideration may impaired, therefore impeding rapid diagnosis.¹²

Some other studies^{13,14} reported such elevated temperature, vomiting and nausea, altered mental status, dyspepsia and the occurrence of jaundice may occur, but these very nonspecific presentations in patients with a calculus cholecystitis.

In our study chronic cholecystitis was the most common histological finding in 57.14% patients and acute cholecystitis was found in 15.32%. Similarly Talreja V et al¹⁵ found matching results and reported that chronic cholecystitis was the most common and noted in the 756 cases and acute was in the 61 cases. On other hand, Kumar H et al¹⁶ demonstrated that from histopathological assessment commonest finding was chronic cholecystitis in 66.75% cases. We found xanthogranulomatous cholecystitis in 10.20%, gangrenous cholecystitis was in 4.08% and 2 cases were without pathology. Similarly Kumar H et al¹⁶ stated that gangrenous cholecystitis in the 2.25% cases, xanthogranulomatous cholecystitis only in the 0.50% cases, empyema in 1%, and adenocarcinoma in 1.25% and 1% were normal gallbladders. Talreja V, et al¹⁵ mentioned other histological results as anthogranulomatous cholecystitis in the 12 patients and gall bladder carcinoma was in the 11(1.14%) patients. Similarly we found in this study malignancy of gall bladder specimen only in 1 case. Mukhopadhyay S et al¹⁷ reported that intestinal metaplasia was in the 9.8% cases and dysplasia was found in the 5% of the patients. Chronic inflammation containing GB may develop the dysplasia, and consequent progression of the GB carcinoma.

CONCLUSION

Female gender is more associated with acalculous cholecystitis; most common clinical presentation was right upper quadrant pain and most prevalent histopathological finding was the chronic cholecystitis and carcinoma was very low only in one case. More research is required to more confirmed assessment of acalculous gallbladder carcinoma.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

- Oliveira Júnior SA, Lemos TE, de Medeiros Junior AC, Freire AD, de Carvalho Garcia C, e Silva RD, et al. Acute Acalculous Cholecystitis in Critically ill Patients: Risk Factors, Diagnosis and Treatment Strategies. JOP 2016;08;17(6):580-86.
- Maya MCA, Freitas RG, Pitombo MB, Ronay A. Colecistite aguda: diagnóstico e tratamento. Revista Hospital Universitário Pedro Ernesto 2009;8:52-60.
- Carvalho D, Azevedo C, Coelho R, Ferreira A, Figueiredo P, Santos L, et al. Colecistite aguda alitiásica. Acta Med Port 2011; 24:631-634.
- Vakkala M, Laurila J, Saarnio JJ, Koivukangas V, Syrjäla H, Karttunen T, Soini Y, et al. Cellular turnover and expression of hypoxic-inducible factor in acute acalculous and calculous cholecystitis. Critical Care 2007;11:116.
- McChesney JA, Northup PG, Bickston SJ. Acute acalculous cho-lecystitis associated with systemic sepsis and visceral arterial hypoperfusion: a case series and review of pathophysiology. Dig Dis Sci 2003;48:1960 –67
- Kaminski DL, Amir G, Deshpande YG, et al. Studies on the etiology of acute acalculous cholecystitis: the effect of lipopoly-saccharide on human gallbladder mucosal cells. Prostaglandins 1994;47:319 –30
- Kaminski DL, Feinstein WK, Deshpande YG. The production of experimental cholecystitis by endotoxin. Prostaglandins 1994; 47:233-45.
- Soomro AG, Jarwar M, Ali SA, Nizamani NB, Memon AS. Frequency of Carcinoma in Gall Bladder Specimens sent for Histopathology in a University Hospital. JUMHS 2013;12(01):55-59.
- Siddiqui FG, Memon AA, Abro AH, Sasoli NA, Ahmad L. Routine histopathology of gallbladder after elective cholecystectomy for gallstones: waste of resource or a justified act?. BMC Surg 2013; 8;13(1):26.
- Gilani SI, Ali I, Raza W, Hassan A, Qureshi I. Histopathological evaluation of cholecystectomy specimens: an experience from Holy Family Hospital, Rawalpindi. Pak J Gastrol 2008; 22(1); 15-19.
- Ghimire P, Yogi N, Shrestha BB. Incidence of incidental carcinoma gall bladder in cases of routine cholecystectomy. Kathmandu Univ Med J 2011; 34(2)3-6
- Maya MCA, Freitas RG, Pitombo MB, Ronay A. Colecistite aguda: diagnóstico e tratamento. Revista Hospital Universitário Pedro Ernesto 2009;8:52-60.
- Khan FY, El-Hiday AH. Acute acalculous cholecystitis complicating an imported case of mixed malaria caused by Plasmodium falciparum and Plasmodium vivax. Int J Infect Dis 2010; 30;14:217-9..
- Siqueira VS, Alvim Ambrósio AV, Cunha PF, Furtado VM, Souza TO, Teixeira Almeida MT, et al. Colecistite alitiásica aguda: revisão de literatura. Rev Med Minas Gerais 2012; 22:59-62.
- Talreja V, Ali A, Khawaja R, Rani K, Samnani SS, Farid FN. Surgically resected gall bladder: is histopathology needed for all? Surg Res Pract 2016; 30;1-4
- Kumar H, Kini H, Tiwari A. Histological evaluation of 400 cholecystectomy specimens. J Pathol Nepal 2015;5(10):834-40.
- Mukhopadhyay S, Landas SK. Putative precursors of gallbladder dysplasia – a review of 400 routinely resected specimens. Arch pathol Lab Med 2005; 129:386-90.

Comparison of Medical and Surgical Management Options for Incomplete Abortion

Fouzia Shaikh, Sabreena Abbas, Nabila Hassan, Sabreena Talpur and Sajida Yousfani

ABSTRACT

Objective: To compare the maternal outcome in medical versus surgical management of incomplete abortion.

Study Design: Comparative cross-sectional study

Materials and Methods: This study was conducted at the Department of Obstetrics and Gynaecology Unit II Liaquat University Hospital Hyderabad from 1st August 2015 to 31st July 2016.

Materials and Methods: Non-probability purposive sampling of 100 patients was done. During the study period, a total 100 cases of incomplete abortion were enrolled in the study with gestational age <12 weeks and vaginal bleeding with ultrasound showing retained products of conception for comparison analysis. Half of them were given Misoprostol 200 µg twice daily for 5 days, and out of rest, 25 underwent manual vacuum aspiration and 25 underwent conventional evacuation under anesthesia. Maternal outcome was noted and compared in both groups using chi square test.

Results: The mean age of women in both study groups was 28.09±5.60 years. Majority of women were multiparous with mean parity 2.90±2.25. Mostly the women were at gestational age of 10 weeks. Maternal complications were less in medically treated group (22%) as compared to surgically treated group (46%) with P-value 0.011.

Patients who underwent Manual vacuum aspiration had lesser infection rates than those who underwent evacuation under anaesthesia (P-value=0.022).

Conclusion: Medical treatment is the safest method to offer to a woman with retained products of conception with least side effects and no hospital stay. Manual vacuum aspiration is a safe alternate to evacuation under anaesthesia where medical treatment fails or is contraindicated.

Key Words: Incomplete abortion; medical treatment, surgical treatment, manual vacuum aspiration; evacuation under anaesthesia.

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INTRODUCTION

Miscarriage (abortion) is defined as the spontaneous loss of a pregnancy prior to the age of viability of fetus¹. Each year throughout the world, approximately 210 million women became pregnant and out of them some 80 million pregnancies end in still birth, or spontaneous or induced abortion². In countries where abortion is legal it is usually very safe in contrast to the countries where abortion is restricted and large numbers are performed under unsafe conditions³. In United States, the overall mortality rate from abortion is 1.1/100,000 of legally induced abortions. Approximately 1.2 million legal abortions are performed annually in the United States⁴. Data from developed countries suggest that about 15 % of pregnancies end in miscarriage.

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Distinguishing between an incomplete spontaneous abortion and induced abortion is significant as there is high-risk of complications as uterine perforation, infection, infertility. Incomplete miscarriage is a major public health problem in developing countries¹.

Management of miscarriage includes expectant, medical and surgical. Expectant management of miscarriage is safe and likely to be cost-effective. In medical treatment the misoprostol is commonly used worldwide⁵. Medical treatment using an antiprogesterin, mifepristone (RU486), followed by a prostaglandin (misoprostol or gemeprost), can also be used for evacuation of uterine cavity. Medical approach is easy, safe and given as outpatient basis^{6,7}. Of the Surgical techniques used in the first trimester. Manual vacuum aspiration is commonly applied to uterine evacuation using a hand-held syringe as the source of vacuum⁸.

Vacuum technique is quicker, produces less blood loss, and has a lower rate of perforation hospitalization for post abortal infection than sharp curettage. Vacuum aspiration should whenever possible; replace dilatation & curettage^{9,10}. Other surgical treatment option is dilatation & curettage. It is less safe and more painful than aspiration, so reserved for patients in whom other options fail or not available⁹.

Considering the prevalence of this problem and multiple methods available for managing a case of incomplete abortion, this study was planned. The objective of this study is to compare the maternal outcome in medical versus surgical management of incomplete abortion. By conducting this study, we may be able to appreciate the first line option for all women with incomplete abortion in our setup and reduce the associated maternal morbidity and mortality.

MATERIALS AND METHODS

The patients fulfilling the inclusion criteria (gestational age < to 12 weeks with vaginal bleeding, ultrasound showing retained products of conception) admitted either from outpatient department or through emergency were enrolled in the study after well-informed verbal consent. Hemodynamically unstable patients, those beyond first trimester, with bleeding disorders or other comorbidities were excluded from the study. Patients were randomly assigned to two equal groups. Group I patients were given Tab Misoprostol 200µmg orally twice a day for 5 days to evacuate the uterus and Group II patient received surgical management. Half of them underwent Manual vacuum aspiration and the rest underwent evacuation under anesthesia. Relevant obstetric history and examination carried out. Maternal outcome was measured in terms of uterine infection, perforation and failure of procedure in terms of incomplete evacuation diagnosed on ultrasound on day 7 of treatment. Data was collected on a pre-designed proforma and analysed on computer software SPSS version 19. Chi square test was used to compare the outcome between groups with P value < 0.05 taken as significant.

RESULTS

It was observed that among the Group I cases (Medical treatment group), the mean±SD age was 28.4±4.56 years. In Group II (surgical treatment group) mean±SD age 27.78±6.52 years. Considering parity, in group I majority were multiparous with 19 (38%) cases and the mean±SD parity in this group was 3.0±2.30. Among group II cases also, majority were multiparous with 22 (44%) cases and the mean±SD parity in this group was 2.80±2.21.

Regarding gestational age, in group I the most frequently presented gestational age was 10 weeks presented by 21 (42%) cases. Amongst group II also the most frequently presented gestational age was 10 weeks presented by 17 (34%) cases. Among medical treatment group 39 (78%) cases did not develop any complication, 2 (4%) cases developed infection and 9 (18%) cases had incomplete evacuation. Among surgical treatment group 27 (54%) did not develop any complication, 6 (12%) cases developed infection, 5 (10%) cases had perforation and 12 (24%) cases had incomplete evacuation. Cases treated by manual

vacuum aspiration were less likely to develop infection than cases treated by dilatation and curettage and the difference was statistically significant (Chi square = 9.61, P-value = 0.022). Among medical treatment group 38 (76%) cases were successfully treated for incomplete abortion whereas among surgical treatment group 37 (74%) cases of incomplete abortion were successfully treated. There was not statistically significant difference in success rate between both treatment modalities (Chi square = 0.53, P-value = 0.817).

Table No.1: Complications Among Procedures in Surgical Treatment Group (n=50)

Complication	MVA (n=25)	D&C (n=25)
None	16 (64%)	11 (44%)
Infection	01 (04%)	05 (20%)
Perforation	0 (0%)	05 (20%)
Incomplete Evacuation	08 (32%)	04 (16%)

Chi Square = 9.61, P-value = 0.022

MVA = Manual Vacuum Aspiration

D&C = Dilatation and Curettage

Table No.2: Comparison of Outcome Between Both Groups (n=100)

Treatment Outcome	Medical Treatment Group (n=50)	Surgical Treatment Group (n=50)
Successful	38 (76%)	37 (74%)
Unsuccessful	12 (24%)	13 (26%)

Chi Square = 0.53, P-value = 0.817

DISCUSSION

Surgical techniques for first trimester pregnancy abortion have been practiced since ancient times. Progress in methods, development of improved procedures and inventions of better equipment have been done in the greater benefit of women as well as for ease of the clinicians. The most widely practiced surgical techniques for first trimester abortion in this modern world are dilatation and curettage (D&C) and vacuum aspiration—of which manual vacuum aspiration (MVA) is more likely to be used among resource limited developing countries like ours¹¹.

Progression in medical technology has offered women a safer, cheaper and simpler alternative namely 'medical abortion'¹². Since more than a decade This treatment is gaining acceptance by clinicians and patients¹³. Although misoprostol could be given alone to induce a miscarriage, some studies have reported that its effectiveness is still low in addition to a higher rate of side effects¹⁴. While mifepristone and misoprostol is registered in the WHO Model List of Essential Medicines¹⁵ and is recommended to be used for early pregnancy terminations¹⁶, this is not the case in Pakistan where mifepristone has yet to be registered,

leaving clinicians with misoprostol alone instead of a better option of these two drugs combined.

In the present study the mean $\pm$ SD age was 28.09 $\pm$ 5.60 years. Similar observations were made by Sochet T et al¹⁷ and Zhang J et al¹⁸. In a study carried by Woldetsadik MA et al¹⁹ the reported mean age of study population was 23.0 $\pm$ 4.4 years, which is quite lower than that encountered in the present study.

In the study 34% subjects were nulliparous. Similar observations were made in another study from Pakistan by Farooq F et al²⁰. However, contrast reports have also been published. Zhang J et al¹⁸ reported lower proportions of nulliparous cases i.e. 22%, whereas Woldetsadik MA et al¹⁹ reported quite higher proportion of nulliparous cases i.e. 67.3%. This difference in the proportion of nulliparous cases seems to be highly correlated with the age of the women because there is a considerable difference in mean age of the subjects between these studies.

The mean gestational age was 9.93 $\pm$ 1.52 weeks. Graziosi GCM et al²¹ reported similar findings. In contrast, Bagratee JS et al²² have reported a higher mean gestational age i.e. 10.6 $\pm$ 1.3 weeks, whereas Woldetsadik MA et al¹⁹ reported lower mean gestational age i.e. 7.4 $\pm$ 1.2 weeks. This difference in gestational age also seems to be correlated with the age of the subjects in a directly proportional manner.

In the present study the safety of medical abortion was compared with surgical abortion. Among medical abortion group only 4% cases developed infection in comparison of surgical abortion group in which 22% cases developed complications i.e. 12% developed infection and 10% developed perforation. Hence, medical abortion was found to be the far safer method than surgical abortion in the present study. However, unlike the present study, medical abortion is likely to have similar or higher complication than surgical abortion. Trinder J et al²³ reported non-significantly different complications between two methods, whereas Woldetsadik MA et al¹⁹ reported a higher complication rate in medical abortion group than surgical abortion group i.e. 11.6% and 6.3% respectively. Most of the studies available in the literature on management of first trimester abortion have been conducted on large scale with careful selection of subjects, heavy funding, supported by a government or an NGO, and/or carried out by skilled and designated medical personnel. On the other hand, the present study was carried out in a tertiary care hospital of a developing country with limited resources. The cases were dealt as per hospital protocol by different teams who may have different skill levels in performing the relevant surgical procedures and in use of particular tools. Also, the sterilization levels may not be up to the mark sometimes. These all factors may have added up and caused this higher complication rate. 20% complications among surgically treated group were

developed in cases who underwent D&C and only 2% in those who underwent MVA. Similar results were reported by Farooq F et al²⁰. In their study more complications were developed in D&C group than in MVA group with very high statistically significant difference ($p < 0.0001$).

In the present study, the difference of success rate between medical abortion and surgical abortion was statistically non-significant ($p = 0.817$). Moodliar S et al²⁴ reported insignificantly lower success rate in medically treated group, as also reported by Zhang J et al¹⁸ Woldetsadik MA et al¹⁹. However, Graziosi GCM et al²¹ reported significantly low success rate in medically treated group (53%) than in surgically treated group (96%).

CONCLUSION

Medical treatment is found to be a safer mode of treatment than surgical treatment in terms of complications. Both medical and surgical methods for the treatment of incomplete abortion were similarly efficient in terms of success rate. Among surgically treated cases, manual vacuum aspiration was safer option than D&C in terms of complications.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Clip chase J. Jones, D. Randomised trial of expectant verses surgical management of spontaneous miscarriage Br J Obstet Gynaecol 1997;104:840-1.
2. Jones EF, Forrest JD. Under-reporting of abortion in surveys of U.S woman:1979 to 1988. Demography 1992;29(1):13-6.
3. Ahman E, Shah I. Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated morbidity in 2000. 4th ed. Geneva: world health organization; 2004.
4. Koonin LM, Smith JC, Ramicle M, Green CA. Abortion surveillance united states, 1993 and 1994. MMWR August 1997;46(SS-4);37-98.
5. Ankum WM, wieringa-de W. management of spontaneous miscarriage in the first trimester: an example of putting informed sheard decision making into practice. Br Med J 2001;322: 1343-46.
6. McIntosh PE. Woman's preference for altisbutes of first- trimester miscarriage management. A Steted Preference discrete-choice experiment. Value Health 2009;12(4):551-9.
7. Diop A, Raghavan S, Rakstova JP, comendant R, Blumenthal PD, Winikeoff B. Routes of administration for misoprostol in the treatment of incomplete abortion: a randominzed clinical trial. Contraception 2009;79-81.

8. Shwekerla B, kalumuna R, kipingili R, Mashalea N, Westheimer E, Clark W, et al. Is intrapartum asphyxia preventable? BJOG 2007;144(11): 32-5.
9. Neilson JP, Hickey M, Vazquea JC. Medical treatment for early fetal death. Cochrane Database of systemic review 2006.
10. Von Hertzen H, Honkanen H, Piaggio G, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, et al. WHO Research Group on Post-Ovulatory Methods for fertility Regulation. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion: Efficacy. Bri J Obstet Gynaecol 2003;110 (9):808-818.
11. Borgatta L, Stubblefield PG. Surgical techniques for first trimester abortion. Lib Women's Med. 2008;10:3843-5.
12. Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists. The management of early pregnancy loss: clinical green top guidelines. London: RCOG 2000.
13. Robledo C, Zhang J, Troendle J, Barnhart K, Creinin MD, Westhoff C, et al. Clinical indicators for success of misoprostol treatment after early pregnancy failure. In J Gynaecol Obstet 2007; 99(1):46-51.
14. Tong WT, Low WY, Wong YL, Choong SP, Jegasothy R. Exploring pregnancy termination experiences and needs among Malaysian women: a qualitative study. BMC Public Health 2012;12: 743-9.
15. WHO: The 17th WHO Model List of Essential Medicine, Geneva: WHO; 2012. Available at: http://www.who.int/selection_medicines/list/en/
16. WHO: Frequently asked questions about medical abortion: conclusions of an International Consensus Conference on Medical Abortion in Early First Trimester Bellagio, Italy. Geneva: WHO; 2006.
17. Sochet T, Diop A, Gaye A, Nayama M, Sall AB, Bukola F. Sublingual misoprostol versus standard surgical care for treatment of incomplete abortion in five sub-Saharan African countries. BMC Pregnancy and Childbirth 2012;12:127-131.
18. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM, et al. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med. 2005;353(8):761-9.
19. Woldetsadik MA, Sendekie YT, White MT, Zegeye DT. Client preferences and acceptability for medical abortion and MVA as early pregnancy termination method in Northwest Ethiopia. Rep Health 2011;8:19-25.
20. Farooq F, Javed L, Mumtaz A, Naveed N. Comparison of manual vacuum aspiration, and dilatation and curettage in the treatment of early pregnancy failure. J Ayub Med Coll Abbottabad. 2011;23(3):28-31.
21. Graziosi GCM, Mor BWJ, Reuwer PJH, Drogtop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Human Rep. 2004;19(8):1894-9.
22. Bagratee JS, Khullar V, Regan L, Moodley J, Kagoro H. A randomized controlled trial comparing medical and expectant management of first trimester miscarriage. Human Rep. 2004; 19(2):266-71.
23. Trinder J, Brocklehurst P, Porter R, Read M, Vyas S, Smith L. Management of miscarriage: expectant, medical, or surgical? Results of randomized controlled trial (miscarriage treatment (MIST) trial). Br J Med 2006;1136-45.
24. Moodliar S, Bagratee JS, Moodley J. Medical vs. surgical evacuation of first-trimester spontaneous abortion. Int J Gynaecol Obstet 2005;91(1):21-6.

C-Reactive Protein Elevation in Patients With Acute Pancreatitis

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ABSTRACT

Objective: To find out the frequency of CRP elevation in patients having severe acute pancreatitis at tertiary care Hospital.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Surgery Department of LUMHS from September 2015 to March 2016.

Materials and Methods: Total 60 selected for the study and informed consents were taken. All the patients of acute pancreatitis were selected for study while patients with other severe co-morbidities and other infections were not selected. C-reactive was noted in all the cases by blood test from diagnostic laboratory. Patients who had other co morbidities were excluded from the study. All the information was gathered on self-designed proforma regarding age, gender, clinical features, c reactive protein etc.

Results: Total 61 patients were included in the study. Mean age was 32 ± 2.04 . 13(20.1%) patients belonged to age group of <30 years while 18(30%) patients were from 30-40 years of age group. 45(75%) patients were females while 15(25%) were males. According to the cause of acute pancreatitis cholelithiasis was the most common in 33.34% of the cases, alcohol consumption was in 16.6%. 45(75%) patients with cholelithiasis had raised c reactive protein while 15(25%) had normal c reactive protein. CRP is the good non-invasive diagnostic tool for acute pancreatitis.

Conclusion: We concluded that CRP elevations is the good and noninvasive diagnostic tool for pancreas inflammation with good efficacy

Key Words: C-Reactive Protein, Pancreatitis.

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INTRODUCTION

Acute pancreatitis is the commonest diseases of GI tract, prominent to incredible, physical and the financial burden.^{1,2} In 2009 in US acute pancreatitis is the commonest gastroenterological diagnosis with 2.6 billion dollars cost.² Despite the fact that the illness procedure might be constrained to pancreatic tissue, it additionally can include peripancreatic tissues or more reserved organ locations. Acute pancreatitis may happen as a segregated assault or might be recurrent. It has an assortment of causes and can run in seriousness from gentle to extreme and life threatening. A few patients may require prolonged hospital stay, while others might be fundamentally sick with numerous organ dysfunctions requiring ICU observing. Mild acute pancreatitis having very less rate of mortality as well as < 1%,³ While the mortality is significantly associated with severe acute pancreatitis estimate 10

to 30% containing on the occurrence of non-infected versus infected necrosis.⁴ In United States, up to 210,000 cases for each year are admitted in the hospitals due to acute pancreatitis. Hallmark symptom of the acute pancreatitis is an onset of acute pain of upper abdomen, with nausea and the vomiting frequently. Frequent locations of the pain are umbilical region and epigastrium regions. Pain may originate to back side, trunk, flanks, and lower part of the abdomen. CRP is a generally utilized diagnostic tool for emergency, particularly in febrile and equivocal infective cases. It was distinguished in 1930 and was in this manner arranged into an "acute phase protein". CRP may be significant in the evaluation and diagnosis of the acute. C receptive protein reactions and progression rate in the acute pancreatitis reflect distinctive severities. CRP large concentrations more than 10mg/dL sustained in the severe attack, and give the cautions of following strict local inflammations in cases whose early disease is comparatively mild and clinical course is at first generous. ESR can also predict the severity of the acute pancreatitis with a somewhat substandard implementation to CRP. Consolidated ESR and CRP at twenty four hours can perfectly predict the severity of acute pancreatitis⁵. For pancreatitis, CRP is an evaluation tool to assess the pancreatic severity. Truly we can't recognize the bacteremia from the non-bacteremia illness through CRP level, and doctors must

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take the definite history of fever onset to enhance the accurate prediction of the bacteremia before the blood culture findings came out⁶. Acute-phase reactant CRP is presently the serum variable of the choice to early, perfect and cost effective assessment of the severity of in routine clinical practice of acute pancreatitis. Very few studies on this aspect are conducted in our setup so we aimed to find out the association between c reactive protein elevations in patients with acute pancreatitis.

MATERIALS AND METHODS

This cross-sectional study was conducted in surgery department of LUMHS from 2015 to 2016. Total 60 patients were included in the study after taking informed consent. In this study all the patients with diagnosis of acute pancreatitis were selected. Acute pancreatitis was confirmed by CT scan and C reactive protein had assessed through taking 2CC venous blood and referred to the Hospital diagnostic laboratory. All the patients with history of any severe co morbidities and any other inflammatory disease were not selected. All the cases were diagnosed according to the presenting sign and symptoms and according to the serum amylase level and lipase levels. After those patients in whom diagnosis had confirmed, through serum CRP elevation after 2nd day of admission and all and by abdominal contrast enhanced CT scan after 72 hours of admission. All the information was gathered on self-designed proforma regarding age, gender, clinical features, c reactive protein etc and in SPSS analyzed.

RESULTS

Total 60 were studied. Mean age was 32.2.04. 13(20.1%) patients belonged to age group of <30 years while 18(30%) patients were from 30-40 years of age group. 45(75%) patients were males while 15(25%) were females. Table 1

According to the cause of acute pancreatitis cholelithiasis was the most common in 33.34% of the cases, alcohol consumption was in 16.6% patients while 40% cases were with multiple causes and 10% were unknown fig:1.

In this study, 45(75%) patients with cholecystitis had raised c reactive protein while 15(25%) had normal c reactive protein. Figure 2

Table 1:Age and gender distribution of the patients n=60

Age and gender	Number	Percentages
Agegroups		
< 30 years	12	(20%)
30-40 years	18	(30%)
>40 years	30	(50%)
Gender		
Males	45	(75%)
Females	15	(25%)

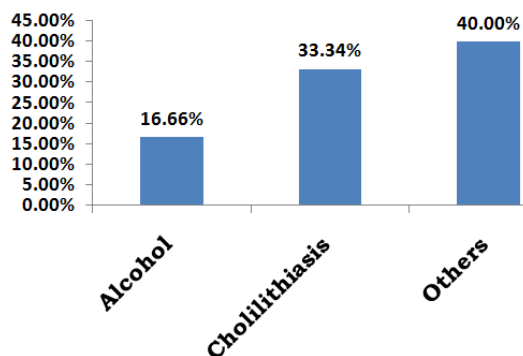


Figure No.1: Causes of acute pancreatitis n=60

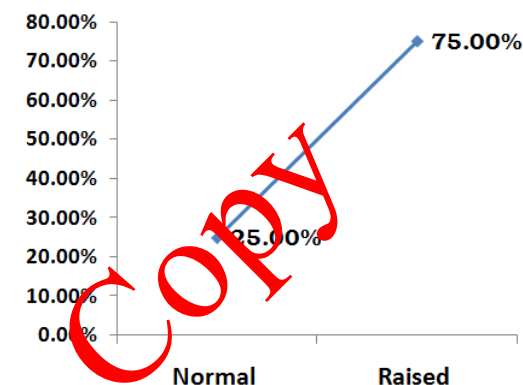


Figure No.2: Frequency of CRP elevation in patients with acute pancreatitis n=60

DISCUSSION

Acute pancreatitis is the condition in which sudden inflammation that goes on for a brief timeframe. It might run from mild to severe, discomfort life-threatening disease. Mostly cases having acute pancreatitis may completely manage after taking right and timely treatment. In cases having severe acute pancreatitis in resulting may bleed in the gland severely tissue damage formation of the cysts and infection. It is an acute pancreatic inflammation presenting clinically with the acute abdomen.⁷ Disease severity associated with macroscopic hemorrhage and fat necrosis in and around the pancreas.⁷

In our study in 75% cases with severe acute pancreatitis CRP elevation was found in 75% of the cases. Similarly Alfenjo et al⁸ reported out of 157 patients of acute pancreatitis whose serum CRP level were determined. Out of 157, 132 patients had high CRP level less than or equal to 200mg/L obtained at 72 hrs of symptoms onset is valuable to interdict with the big degree of the probability, the presence of necrosis. On other hand Vermeire S et al⁹ also found the relationship between the CRP level and pancreatic necrosis and reported that out of 78 patients most of patients had high CRP level cut off of 110mg/L. In the favor of our study Tariq Saeed et al.¹⁰ demonstrated that estimation of the severity state in patients having Acute pancreatitis constitute a significant part of diagnosis and complex treatment so in this diseases early diagnosis and severity can prevent complications and CRP level can

early predict the severity of diseases. Barauskas G et al¹¹ reported that CRP significantly elevated in early pancreatic necrotic stage, and CRP is the commonest prognostic tool for necrosis of the pancreatitis with high sensitivity and specificity and the NPV is 110 mg/l. Del et al.¹² suggested that the early diagnosis is mandatory for successful treatment and in acute pancreatitis most widely used scoring frameworks are frequently bulky and hard to use in clinical practice on account of their multi factorial nature. Therefore the quantity of uni-factorial prognostic directions has been utilized in the clinical practice routinely, in which CRP is the one of estimation. Sharma S et al¹³ reported that 12 were having severe condition and CRP level was between 96-192 mg/L, in 7 cases with mild presentation CRP elevated level was from 24-48 mg/L and only one case had CRP level was normal i.e. below 6 mg/L. Elevated CRP appears to give a notice of serious inflammation in cases whose underlying sickness is generally mild and whose clinical course is obviously benign. Present study in the favor that pancreatic accumulations which create in such cases have their inceptions at an early stage of attack. CRP reaction is comparable in extent to that in patients with all the more clearly extreme pancreatitis.

Similar results are seen in the study conducted by Chun-Chia Chen on Pro-inflammatory cytokines in the initial evaluation of acute pancreatitis prognosis cytokines in acute pancreatitis shows results showed that concentrations of the interleukin-1- β , interleukin-6, interleukin-8, and CRP in 1 to 7 days were significantly greater in cases having severe pancreatitis as compare to those having mild pancreatitis.¹⁴ In our study 45(75%) patients were males while 15(25%) were females. similar results are seen in the study conducted by Mahmood T et al whose results also shows that males had more pancreatitis.¹⁵ This again could be attributed to alcohol which was the main etiologic agent and which is more common in male population of low socioeconomic status. Shah SSH et al¹⁶ reported that out of 50 cases, 76% were women and 24% were men, with a ratio of 3:1, and age range between 18 to 70 years with the mean of 42 years. The gender difference may due to small sample sizes of both studies. In our study cholelithiasis was the most common in 33.34% of the cases, alcohol consumption was in 16.6% patients while 40% cases were with multiple causes and 10% were unknown, similar results are seen in the study conducted by Mahmood T.¹⁵ On other hand in the favor of findings Barauskas G et al¹¹ reported that Etiologic factor for necrotic pancreatitis in 52.9% of patients was gallstones.

CONCLUSION

We concluded that CRP elevations are the good and noninvasive diagnostic tool for pancreas inflammation with good efficacy. More big sample size studies are required to achieve more conformation.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *AJG* 2013;1108(9):1400-15.
2. Fagenholz PJ, Fernandez-del Castillo C, Harris NS, et al. Direct medical costs of acute pancreatitis hospitalizations in the United States. *Pancreas* 2007;35:302-7
3. Russo MW, Wei JT, Thiny MT, Gangarosa LM. Digestive and liver diseases statistics, 2004. *Gastroenterol* 2004;126:1448-53.
4. Dervenis C, Johnson CD, Bassi C, Bradley E, Imrie CW. Diagnosis, objective assessment of severity, and management of acute pancreatitis. Santorini consensus conference. *Int J Pancreatol* 1999;25:195-210.
5. Smith E. C-reactive protein in the emergency department. *Emerg Med* 2006; 23(3): 241.
6. Lee CC, Hong MY, Lee NY, Chen PL, Chang CM, Ko WC. Pitfalls in using serum C-reactive protein to predict bacteremia in febrile adults in the ED. *Am J Emerg Med* 2012; 30 (4): 562-569.
7. Su YJ. The value of C reactive protein in emergency medicine. *J Acute Dis* 2014;1;3(1):1-5
8. Alfonso V, Gomez F, Lopez A, Moreno-Osset. Value of C Reactive protein level in the detection of necrosis in acute pancreatitis. *Gastroenterol Hepatol* 2003;26(5):288-93.
9. Vermeire S, Assche GV, Rutgeerts P. C reactive protein as a marker for inflammatory bowel diseases. *Inflamm Bowel Dis* 2004;10(5):661-665.
10. Tariq S, Shahid M, Muhammad T. C-reactive protein as a severity marker in Acute Pancreatitis. *JRMC* 2011;15(2):88-89.
11. Barauskas G, Švagždys S, Maleckas A. C-reactive protein in early prediction of pancreatic necrosis. *alcohol* 2004;17:29-6.
12. Del Prete M, Castiglia D, Meli M. Prognostic value of C Reactive Protein in Acute Pancreatitis. *Chir Ital* 2001;53(1): 33-8.
13. Sharma S. Early Prediction Of Severity Of Acute Pancreatitis Role Of C Reactive Protein. *IJCR* 2014;6(8):7181-83
14. Chen CC, Wang SS, Lee FY, Chang FY, Lee SD. Proinflammatory cytokines in early assessment of the prognosis of acute pancreatitis. *AJG* 1999 Jan 1;94(1):213-8.
15. Mahmood T, Naseem K, Rasheed Z. An Audit Of Management Of Acute Pancreatitis. *JUMDC* 2016;7;1;6.
16. Shah SSH, Ansari MA, Ali S. Early prediction of severity and outcome of acute severe pancreatitis. *Pak J Med Sci* 2009;25(4): 619-62.

Cystic Duct Anomalies Encountered During Laparoscopic Cholecystectomy

Huda Ashfaq Ali, Sohail Ahmed Memon, Ambreen Muneer, Shiraz Shaikh, Ghulam Akbar Khaskeli and Tahmida Almani

ABSTRACT

Objective: To determine frequency of cystic duct anomalies and its common types in patients during laparoscopic cholecystectomy.

Study design: Descriptive / cross sectional study.

Place and duration of study: This study was conducted at Liaquat University of Medical and Health Sciences, Jamshoro and in Rajputana Hospital, Hyderabad from July 2014 to December 2014.

Materials and Methods: After all relevant investigations, patient with diagnosis of cholelithiasis was submitted for laparoscopic cholecystectomy. Final outcome of cases operated in terms of cystic duct (C.D) anomalies were entered on proforma provided to all operating surgeons having >5 years of experience.

Results: A total of 301 patients were included in this study. The mean age of the patients was 40.58 ± 16.82 years (range is 31-60 years). Most of the patients were < 46 years 175(58.1%) only. Out of 301 numbers of cases 116(38.6%) patients were male and 185(61.4%) were females. Cystic duct anomalies were noted in 38 (12.6%) cases only. In the present study the most common and higher incidence rate of anomalies like Spiral cystic duct were observed. Statistically the Incidence was found to be higher than in the previous studies.

Conclusion: In this study the most common & higher incidence rate of anomalies like Spiral cystic duct were observed. Statistically the Incidence was found to be higher previous studies. Identification and careful dissection especially with anomalies prevent the damage to biliary tree during laparoscopic cholecystectomy.

Key Words: Bile duct injury, Laparoscopic cholecystectomy, Cystic duct, Spiral cystic duct

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INTRODUCTION

Cholecystectomy is one of very common operation being performed in Pakistan. Laparoscopic cholecystectomy (LC) is now considered as the gold standard surgical option for treatment of cholelithiasis and nowadays it is also being widely accepted by our society¹. Variations have been observed in the anatomy of gallbladder, intrahepatic as well extra hepatic ductal system and vasculature supplying them and liver. It is important for the surgeon to know these variations, because failure to recognize these anomalies may lead to inadvertent ductal ligation, biliary injuries, leaks and stricture after laparoscopic cholecystectomy². In biliary surgery though ductal injury is an uncommon complication but with increasing use of LC, there has been an associated rise in the incidence of biliary ductal injury³. Therefore a surgeon should know and be aware of variations in anatomy in order to avoid significant ductal injury during biliary surgery.⁴

The incidence and variety of biliary anomalies have been reported to be as high as 47% of the population, based on operative, cholangiography, and autopsy studies. Within a 3-cm critical zone along the cyst-hepatic angle, 85% of all aberrant bile ducts are found⁵. Incidence of cystic duct anomalies in study is (4.33%)². Incidental finding have been reported in the literature as case reports, unique anomalies of cystic duct (CD)⁶. Anomalies found in literature are spiral cystic duct (7.9%)⁷, low insertion of the cystic duct (9%)^{4,8} and aberrant right hepatic duct draining into common bile duct (CBD) and common hepatic duct (4.6-8.4%)³. However, drainage of aberrant right duct into cystic duct is rare and only four cases reported³. Most of these cases were reported from United State of America (USA) and from United Kingdom (UK). Little is known about its rate of occurrence and varieties in our population.

Therefore, this study is planned to assess types of anatomical variations of the cystic duct morphology during laparoscopic cholecystectomy, in our society, in order to help the future surgeons to avoid serious complications during laparoscopic cholecystectomy.

MATERIALS AND METHODS

Study was conducted in department of surgery of Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro and in Rajputana Hospital, Hyderabad. It is a descriptive cross sectional study.

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Non-Probability Consecutive sampling technique applied where every patient meet the inclusion criteria will be recruited. All cases of elective laparoscopic cholecystectomy after confirmation of diagnosis of cholelithiasis by history, clinical examination and investigations were included in study. Investigation for confirmation of diagnosis includes ultrasound abdomen, LFTs and if needed CT scan upper abdomen or MRCP is also performed. All patients with acute cholecystitis, empyema of gall bladder, acute pancreatitis, obstructive jaundice and carcinoma of gall bladder were excluded from the study. This was conducted from July 2014 to December 2014 after ethical committee approval. Data was collected using structured proforma including all variables like age, gender, cystic duct anomaly and its common types which will be filled by principle investigator and by all operating surgeons having > 5 years experience.

Data was entered and analyzed by SPSS version 20. Descriptive statistics was calculated. Where mean and standard deviation was calculated for age of patient respectively. We arrest frequency and percentages of ages was calculated for gender distribution, cystic duct anomalies (yes/no) and its outcome variables: spiral cystic duct (yes/no), low insertion of cystic duct (yes/no), aberrant hepatic duct (yes/no). To see the effect modifier of outcome variables was controlled through stratification like age & gender. Chi square test was applied when frequency found to be less than 5. Fisher exact test was applied and p value <0.05 will be taken as significance.

RESULTS

A total of 301 admitted in the department of general meeting the inclusion and exclusion criteria were included in the study. The mean age was 40.58 ± 16.82 (range 31-60 years). Most of the patients were lie < 46 years 175(58.1%). Median age was 46.2 years. Out of 301 number of cases 116(38.6%) patients were male and 185(61.4%) were females.

Table No.1: Types of Cystic Duct Anomaly according to their 38 number of Patient's

Types of Cystic Duct Anomaly	Frequency (f)	%ages
Spiral cystic duct	20	52.6%
Low insertion of cystic duct	13	34.2%
Aberrant right hepatic duct joining cystic duct	05	13.1%

In this study among 301 cases, Cystic duct anomalies were noted in 38 (12.6%) cases. In the present study the most common and higher incidence rate of anomalies like Spiral cystic duct were observed. Statistically the Incidence was found to be higher than in the previous studies. (Table 1)

When we compare age and gender with cystic duct anomalies we found both of the variable were statistically significant with p-value less than 0.05.(Table 2,3)

Table No.2: Comparison of Cystic Duct anomaly with gender distribution (N=301)

Gender	Cystic Duct Anomaly		Total	P Value
	Yes	No		
Male	08 (2.7%)	108 (35.9%)	116 (38.5%)	0.018* Significant
Female	30 (10%)	155 (51.5%)	185 (61.5%)	
Total	38 (12.6%)	263 (87.4%)	301 (100%)	

Table No.3: Comparison of Cystic Duct anomaly with Age Group distribution (N=301)

Gender	Cystic Duct Anomaly		Total	P Value
	Yes	No		
Age<46 Years	29 (9.6%)	146 (48.5%)	175 (61.5%)	0.000* Significant
Age>46 Years	9 (3%)	117 (38.9%)	126 (41.9%)	
Total	38 (12.6%)	263 (87.4%)	301 (100%)	

DISCUSSION

Cholelithiasis and cholecystitis commonly affecting our population especially the female patients. Laparoscopic cholecystectomy and also open cholecystectomy are the two surgical options for symptomatic gallstones with a cure rate of up to 95%.⁹ In the present times laparoscopic cholecystectomy has become a very common procedure for patients with cholelithiasis producing symptoms. The success and safety of laparoscopic cholecystectomy depends upon the basic knowledge of normal anatomy and common variants of extra-hepatic biliary system and cystic duct.¹⁰ A thorough knowledge of the Extra-hepatic biliary apparatus could go a long way to minimize post-operative complications. As early as 1803 a study by Luschka showed the presence of accessory hepatic ducts. In a prospective study(1996) on 513 cholangiograms by Kullman E et al, anatomical aberrations of bile ducts were found in 98(19%) cases. In 8.4% cases the aberrant bile ducts opened into cystic duct.¹¹ Lamah M, et al(1999) also found anatomical variation by intra-operative cholangiography in twelve cases out of 2080 cases and commonest anomaly(n=5) was accessory bile duct followed by abnormal termination of cystic duct (n= 3).¹² Hence anomalies of the cystic duct was viewed with extra interest.

In this study the average age of patients was 40.58(16.82) years. Minimum age was 31 years and maximum age was 60 years. There were 185 (61.4%) females and 116 (38.6%) males. A study from Sindh

Pakistan studied 300 cases of cholelithiasis reported the similar gender and age distribution¹³ Another study from Iraq reported Patients' age ranged from 20-69 years, with a higher frequency during the third and fourth decade. Females constituted 84% of the patients¹⁴.

In our study 38 (12.6%) cases have cystic duct anomalies out of 301 cases. Out of thirty eight case spiral cystic duct anomaly was common and found in 20 (50.6 %) cases. While aberrant right hepatic duct joining cystic duct was found only in 5 (13.1 %) cases and low insertion of cystic duct was found in 13 (34.2%) cases. The incidence and variety of biliary anomalies have been reported to be as high as 47% of the population, based on operative, cholangiography, and autopsy studies. Incidence of cystic duct anomalies in study is (4.33%).² Incidental finding have been reported in the literature as case reports, unique anomalies of cystic duct (CD)⁶ like spiral cystic duct, low lateral insertion and narrow-winding of the cystic duct reported with incidence of (7.9%)⁷ and (9%)^{4,8} respectively. Aberrant right hepatic duct draining into common bile duct (CBD) & in common hepatic duct with incidence of 4.6-8.4%, however, drainage into cystic duct is rare and only four cases reported.[3] A local study reported anatomical variation in 14% cases, among total anomalies of 14 cases, the Moynihan's hump (6%) ,accessory cystic artery (6%) , Double cystic duct (1%) and Long cystic duct (1%) were the total encountered variations¹⁵ In another local study the operative findings revealed variations in 61 (20.33%) patients mainly involving cystic artery (10.67%), cystic duct (4.33%), right hepatic artery (2.67%) and gallbladder (2%).¹⁰ Other studies reported incidence of accessory cystic duct from 1 to 30%.^{14,17}

Anatomic variation of the extra hepatic biliary tree has been the subject of numerous investigations, the reported incidence of congenital anomalies varying from 1.6 to 47.2%. In this study anatomical variation was noted in 12.6% (n=38) cases. Biliary tract has more anomalies in 1cm - 13cm of the space in the cystic duct region than in any other part of the body.^{5,18} Careful exploration of Calot's triangle and exact identification of extra hepatic biliary tree and cystic duct anomalies such as spiral cystic duct, low insertion of cystic duct and aberrant right hepatic duct joining cystic duct is important to avoid biliary injuries during laparoscopic cholecystectomy.^{19,20}

CONCLUSION

In the present study the most common & higher incidence rate of anomalies like Spiral cystic duct were observed. Statistically the Incidence was found to be higher than in the previous studies. Identification and careful dissection especially with anomalies prevent the damage to biliary tree during laparoscopic cholecystectomy.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Taimur M, Hasan A, Samiullah, Masood R, Imran M. Vascular variation in calot's triangle seen on laparoscopic cholecystectomy. Pak Armed Force Med J 2011;1(4).
2. Talpur AH, Laghari AA, Yousfani SA, Malik AM, Memon AI, Khan SA. Anatomical variations and congenital anomalies of Extra Hepatic Biliary System encountered during Laparoscopic Cholecystectomy Pak Med Assoc 2010;60.
3. Sofi AA, Alaradi OH, Alboujoud M, Nawras A. Aberrant right hepatic duct draining into the cystic duct: clinical outcomes and management. Gastro Res Prac 2011;458915.
4. Wu YH, Liu Z, Min Z, Ai Z, Sun Q, Bangoura G, et al. Anatomical variation of cystic duct: two case reports. World J Gastroenterol 2008;14(1): 155-57.
5. Fujikawa T, Takeda H, Matsue S, Nakamura Y, Nishimura S. Anomalous duplicated cystic duct as a surgical hazard: report of a case. Jpn J Surg 1998; 28:313-15.
6. Kadon J, Sakoda K, Tabata M, Mizouchi J, Osako M, Shibuya H, et al. Cystic duct directly joining the main pancreatic duct. J Hepatobiliary Pancreat Surg 2005;12(5):419-21.
7. Elakkary E, Ching K, Jacobs MJ. Spiral Cystic Duct: beware, casereport. JSLs 2006;10(4): 514-16.
8. Jung CW, Min BW, Song TJ, Son GS, Lee HS, Kim SJ, et al. Mirizzi syndrome in an anomalous cystic duct: a case report. World J Gastroenterol 2007;13(41):5527-9.
9. Harris HW. Biliary System. In: Norton JA, editor. Surgery, Basic Science and Clinical Evidence. 1st ed. New York: Springer;2000.p.561.
10. Lamah M, Dickson GH. Congenital abnormalities of the extra Hepatic biliary duct: A personal audit. Surg Radiol Anat 1999;21:325-7.
11. Kullman E, Borch K, Lindstrom E, Svanvik J, Anderberg B. Value of routine intraoperative cholangiography in detecting aberrant bile ducts and bile duct injuries during laparoscopic cholecystectomy. Bri J Surg 1996;83(2):171-5.
12. Lamah M, Dickson GH. Congenital abnormalities of the extra hepatic biliary duct: A personal audit. Surg Radiol Anat 1999;21:325-7.
13. Talpur KA, Laghari AA, Yousfani SA, Malik AM, Memon AI, Khan SA. Anatomical variations and

- congenital anomalies of extra hepatic biliary system encountered during laparoscopic cholecystectomy. J Pak Med Assoc 2010; 60(2): 89-93.
14. Hashimoto M, Ishikawa T, Lizuka T, Matsuda M, Watanabe G. Right hepatic duct emptying into the cystic duct: Report of a Case. Surg Endosc 2002;16: 359.
 15. Khan A.H, Zaheer M. Frequency of Extra Hepatic Biliary Tree Anomalies Seen During Cholecystectomy. Ann Pak Inst Med Sci 2008; 4(4):198-200.
 16. Huston TL, Dakin GF. Double cystic duct. Can J Surg 2008;51(1) :E9-E10.
 17. Losanoff JE, Jones JW, Richman BW, Rangnekar NJ. Hepatic cystic duct: A rare anomaly of the extra hepatic biliary system. Clin Anat 2002;15: 314-15.
 18. Walia HS, Abraham TK, Baraka A. Gallbladder Interposition: A rare anomaly of the extra hepatic ducts. Int Surg 1986;71:117-212
 19. Dişibeyaz S, Öztaş E, Akpınar MY, Kuzu UB, Coşkun O, Kayacetin E. A rarely seen biliary variation: Right posterior and right anterior hepatic ducts were opening to the cystic duct. Acta gastroenterologica Belgica 2016;79(2):275.
 20. Suna N, Dişibeyaz S, Kuzu UB, Yüksel M, Yıldız H, Kayaçetin E. Aberrant right posterior hepatic duct opening into the cystic duct: a very rarely seen biliary anatomic variation. Endoscopy 2014;46 (S 01):E657.

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Diagnosis of Neonatal Meningitis with early Onset Sepsis in Pakistan Institute of Medical Sciences Islamabad

Neonatal
Meningitis with
early Onset
Sepsis

Misbah Anjum¹, Chetan Das² and Devi Dass²

ABSTRACT

Objective: To see frequency of neonatal Meningitis in early onset of neonatal sepsis.

Study Design: Descriptive study

Place and Duration of Study: This study was conducted at the Children's Hospital NICU and Neonatal Nursery of MCH Centre PIMS, Islamabad from February 2015 to August 2015

Materials and Methods: Total of 90 septic neonates were screened who fulfilled the inclusion criteria. All the information recorded in the proforma and data was entered in software SPSS version 18. The descriptive analysis were carried out and reported as mean with standard deviation for age. The level of significance was selected as 5% (p-value 0.05). The results are presented as tables and graphs.

Results: Total of 90 septic neonates were enrolled in this study. The mean (standard deviation) age of all septic neonates was 36.3 ($\pm$ 20.2) hours and half of the neonates with sepsis 51 (56.7%) were preterm. The male to female ratio was 1.9 to 1 and intrapartum maternal high fever was present in only 4 (4.4%). Poor feeding which was present in 51 (57.0%) neonates with sepsis and irritability was significantly associated with septic neonates with meningitis (p-value 0.001).

Conclusion: We concluded in this study that there is low incidence of neonatal meningitis among neonates with early onset sepsis, but it is quite important to have lumbar puncture in all neonates with early onset sepsis because these 3.3 percent cases of meningitis would have been otherwise missed.

Key Words: Neonatal, meningitis, early onset, sepsis, Lumbar puncture

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INTRODUCTION

Septic neonates are defined on clinical grounds as those not doing well, with lethargy, irritability, poor feeding, temperature instability, respiratory distress, apnea, abdominal distension, vomiting or poor perfusion. Laboratory investigations shows Leukopenia <5000 white blood cell (WBC) per mm³ or leukocytosis $>20,000$ WBC per mm³ or positive C-reactive protein and/ or Positive blood culture.

Early onset neonatal sepsis is defined as presentation of neonates with sepsis in the first 72 hours of life. Late onset neonatal sepsis is defined as presentation of neonates with sepsis after 72 hours of life. Neonatal meningitis is defined as: Positive cerebrospinal fluid (CSF) culture (Gold Standard) or Negative CSF culture but raised CSF WBC count >25 WBC per mm³ of an atraumatic tap with Red Blood cells (RBC) count <1000 RBC per mm³.²

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MATERIALS AND METHODS

All neonates with suspected sepsis admitted at the Neonatal Intensive Care Unit (NICU), The Children's Hospital, Islamabad and Neonatal Nursery of Mother and Child Health (MCH) Centre, Pakistan Institute of Medical Sciences (PIMS), Islamabad were screened and fulfilled inclusion criteria were enrolled in the study. The study was conducted from February 2015 to August 2015. The sample size for the study was estimated by using Statcalc program of EpiInfo software. By selecting the population size as 100, (estimated admissions of suspected early onset neonatal sepsis at our setting in six months) and expected frequencies as 6% with worse expected as 3%. With the confidence level selected as 95%, the estimated sample size was 71. A convenience, non-probability, sampling technique was chosen. Inclusion criteria for enrollment were age less than 72 hours, both gender, diagnosed to have sepsis as defined above and informed consent given. The neonates who has age more than 72 hours, major congenital abnormalities such as meningomyelocele, hydrocephalous, consent refused by parents and traumatic lumbar puncture were excluded from study. Parents/caretakers were informed about the nature of the study and about the association of neonatal sepsis with meningitis and consequences of delayed or missed diagnosis of meningitis. The approval from hospital ethical committee was taken.

All parents/caretakers were interviewed and detailed information regarding the maternal and neonatal risk factors was collected. General physical and systemic examination was carried out. Afterwards, a lumbar puncture was performed by keeping aseptic measures in each neonate. Samples were taken and sent for the laboratory investigations at the time of enrollment. All the information regarding history, examination and laboratory investigations was filled on a proforma, especially designed for this study. The management of neonatal sepsis was then started in all neonates.

Data Analysis: All the information recorded in the Proforma was entered by using the software SPSS version 13. Student t test and Chi-square tests were carried out. The Chi-square test values were estimated and p-values were obtained and reported. The level of significance was selected as 5% (p-value 0.05). The results are presented as tables and graphs.

RESULTS

During the study period of six months, a total of 90 septic neonates, who fulfilled the inclusion criteria were enrolled in this study. The age in hours at the time of enrollment of all the enrolled neonates with sepsis are shown in Table 1. The mean (standard deviation) age of all septic neonates was 36.3 ($\pm$ 20.2) hours. The youngest neonate was only one hour old, while the oldest one was 71 hours of age. The peak age of enrollment was between 21 to 50 hours of age, as 62% (n = 56) of neonates with sepsis were aged between 21 and 50 hours.

Out of 90 neonates with sepsis, majority of neonates were male 59 (65.6%), whereas only 31 (34.4%) were females. The male to female ratio was 1.9 to 1.

The frequencies and percentages of various reported maternal risk factors are presented in Table 2. The preterm, defined as less than 37 weeks of gestational age, was identified as the most common risk factor as more than half of the neonates with sepsis 51 (56.7%) were preterm.

The history of intrapartum maternal high fever was present in only 04 (4.4%) neonates, while 18 (20.0%) neonates with sepsis had positive history of premature rupture of membrane.

Amongst the neonatal risk factors, birth weight less than 2.5 Kg was the most frequently reported risk factors among the neonates with sepsis, as 64 (71.1%) neonates had birth weight less than 2.5 Kg.

Low APGAR score, defined as less than 5 at 5 minutes, was reported in 09 (10.0%) neonates with sepsis, whereas chorioamnionitis was present in only 2 (2.2%) neonates with sepsis.

Leukopenia was present in 09 (10.0%) of neonates with sepsis, while leukocytosis was present in 19 (21.1%) neonates with sepsis. Out of 90 neonates with sepsis, 45 (50.0%) had positive C-reactive protein. Out of 90

neonates with sepsis, more than half of neonates with sepsis, 52 (57.8%) had positive blood culture, while 38 (42.2%) neonates had negative blood culture.

Amongst the 52 neonates who had positive blood culture, the most common micro-organism was Coagulase Negative Staphylococcus, which was found in 27 (51.9%) neonates with sepsis. However, cultures positive for coagulase negative staphylococci were regarded as contaminants. In remaining 25 blood culture positive cases, other micro-organisms were present and the most common organism was Enterobacter reported in 12 (48%) neonates with sepsis. Other organisms grown were Klebsiella, E-Coli and Staph Aureus present in 9 (36%), 3 (12%) and 1 (4%) respectively (Figure 1).

The frequency of meningitis among all the neonates with sepsis enrolled in this study. Out of 90 neonates with sepsis, only 3 (3.3%) neonates were declared to have neonatal meningitis. CSF culture was negative in all three neonates and these neonates were diagnosed to have neonatal meningitis on the basis of abnormal CSF pleocytosis.

The neonates diagnosed to have meningitis were slightly younger than neonates with no meningitis as the mean (standard deviation) age of all septic neonates with meningitis was 29.3 ($\pm$ 16.7) hours and among septic neonates without meningitis it was 36.6 ($\pm$ 20.5) hours. However, this difference was not statistically significant (p-value = 0.55).

All septic neonates with meningitis were male, while among septic neonates without meningitis, 56 (64.4%) were boys and this difference was not statistically significant (p-value = 0.20) (Table 2).

The presence of various risk factors were also compared between septic neonates with meningitis and without meningitis and shown in Table 3. No statistical significant differences were found in the presence of various risk factors between the septic neonates with meningitis and without meningitis. All septic neonates with meningitis had positive blood cultures. Out of three septic neonates with meningitis, one had Enterobacter, other had Klebsiella and the third one had E-Coli.

Table No.1: Frequency of maternal risk factors among neonates (n =90)

	No. of neonates	%age
Intrapartum maternal high fever		
Yes	04	4.4%
No	86	95.6%
PROM > 24 hours		
Yes	18	20%
No	72	80%
Preterm (< 37 weeks)		
Yes	51	56.7%
No	39	43.3%

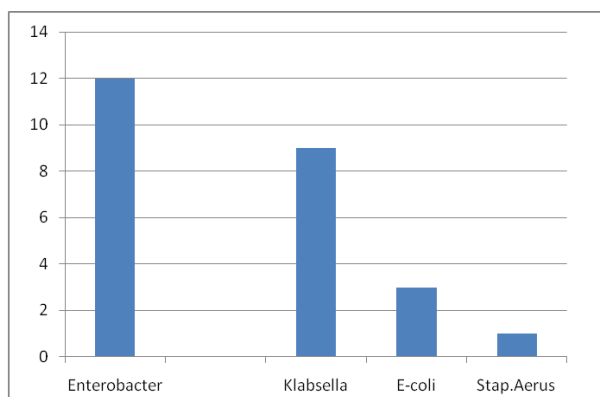


Figure No.1: Frequency of presence of various organisms among the blood culture positive septic neonates (n = 25)

Table 2: Comparison of demographic characteristics of septic neonates with meningitis versus septic neonates without meningitis (n = 90)

Demographic features	With meningitis (n = 3)	Without meningitis (n = 87)	p-value
Age (in hours)			
Mean (SD)	29.3(± 16.7)	36.6 (± 20.4)	0.55
Gender			
Male	3(100%)	56(64.4%)	0.20
Female	0 (0%)	31(35.6%)	---

Table No.3: Comparison of presence of risk factors among septic neonates with meningitis versus septic neonates without meningitis (n = 90)

Septic Neonates Risk factors	With meningitis (n = 3)	Without meningitis (n = 87)	p-value
Intrapartum maternal high fever	0 (0.0%)	4 (4.6%)	0.70
PROM > 24 hours	1 (33.3%)	17 (19.5%)	0.55
Preterm (< 37 Weeks)	1 (33.3%)	50 (57.5%)	0.40
Low APGAR	0 (%)	9 (10.3%)	0.71
Birth weight < 2.5 Kg	02 (66.7%)	62 (71.3%)	0.86
Chorioamnionitis	0 (0%)	2 (2.3%)	0.79
Abdominal distension	1 (33.3%)	15 (17.2%)	0.47

DISCUSSION

Early onset neonatal sepsis is usually caused by micro-organisms such as Group B Streptococcus, E-Coli, Klebsiella, Listeria or other Gram-negative organisms. These micro-organisms are usually acquired from the

maternal genitourinary tract. The timing of clinical infection depends on the density of colonization of the mother, rate and density of colonization of the newborn, strain and hence the invasiveness of the micro-organism, and presence or absence of various obstetric risk factors.^{3, 4, 5}

Incidence of neonatal meningitis in early onset sepsis in this study is comparable with other studies. A recent study by Shiva and colleagues in Iran enrolled 380 suspected cases of neonatal sepsis. Out of 380, 248 neonates were younger than 72 hours of life. Among neonates younger than 72 hours, meningitis was diagnosed in 17 (6.9 percent) neonates. In India, Chacko and Sohi examined 36 neonates with early onset sepsis and found that meningitis was present in 3 (8.3 percent) of neonates.^{6, 7, 8}

A hospital based study in Nairobi, Kenya, reported a much higher rate of meningitis among neonates with sepsis 15 (17.9 percent) septic neonates had neonatal meningitis.⁹

On the other hand, several studies have reported extremely low yields from routine lumbar puncture. Walsh-Sukys and colleagues evaluated 861 neonates for sepsis within the first 72 hours of life and found only 2 (0.2 percent) cases of meningitis. Hence, the authors suggested that lumbar punctures should be reserved for infants with central nervous system signs or bacteremia.^{10, 11, 12}

Similarly, another study from Nigeria, examined 562 neonates and lumbar punctures were performed in all neonates less than 72 hours of age and no case of meningitis is found in neonates less than 72 hours of age. The authors suggested that meningitis is very rare in the first 72 hours of life and therefore, the expected yield of routine lumbar punctures in early onset sepsis does not justify the risks associated with the procedure. They subscribed to the view expressed in several earlier studies that routine lumbar puncture should be eliminated from early onset sepsis evaluation and reserved for bacteremic infants, or infants with neurological signs.¹³

There are several reasons for variation like sample size, medico-legal perspective in different health settings from less than 1 percent to around 18 percent of incidence of neonatal meningitis among septic neonates. In communities with heightened awareness of medico-legal implications, there is a trend to be very stringent in the work-up of a possible septic neonate, resulting in a low yield of positive lumbar puncture. If the selection criteria for a septic work-up would have been similar in different settings then the incidence of meningitis would not have shown such diversity in different surveys. However, early recognition of neonatal meningitis is of prime concern because of the increased morbidity and mortality associated with delayed or missed diagnosis. Because neonates have a limited repertoire of responses to any stressful

condition, sepsis with or without meningitis is often invoked as a possible diagnosis in any sick infant. In current study, out of 90 neonates with sepsis, blood culture was positive in 25 neonates with sepsis. The most common micro-organism is *Enterobacter*, which is reported in 12 (48 percent) septic neonates with positive blood cultures. Other micro-organisms cultured are *Klebsiella*, *E-Coli* and *Staph Aureus* present in 9 (36 percent), 3 (12 percent) and 1 (4 percent) septic neonates with positive blood cultures respectively. These results are comparable with other studies in this region.

In India, a study reported approximately 42 percent blood culture positive cases of early onset sepsis. In their sample, they reported *Pseudomonas* (60 percent) as the most common micro-organism. Other micro-organisms, *Klebsiella*, *Staph. Aureus*, *S. Viridin* and *E-Coli* were present in 13 percent, 13 percent, 7 percent and 7 percent respectively among the septic neonates with positive blood cultures⁸.

A study from Iran reviewed 136 neonates with sepsis and found *Pseudomonas* as the most common micro-organism, as 42 percent blood cultures were positive for this organism. Other most common organisms were *Klebsiella* and coagulase negative *Staphylococci*, as 32 percent and 15 percent respectively among the septic neonates with positive blood cultures. Other 10 percent were due to micro-organisms such as *E. Coli*, *Enterococci*, *Micrococci*, *Citrobacter*, *Staph. Aureus* and *Streptococcus group B* 13. In another study in Iran researchers reviewed 242 neonates with sepsis. The researchers found that *Staph Aureus* and *Klebsiella* were the leading etiologic micro-organisms for neonatal sepsis¹⁴.

From Libya, Misallati and colleagues retrospectively reviewed 36 cases of blood culture proven neonatal septicemia. Out of 36, 11 (31 percent) neonates were less than 72 hours of age at the time of presentation, and therefore diagnosed to have early onset sepsis. Among the neonates with early onset sepsis, *Enterobacter* (36 percent) was the most common micro-organism cultured in those neonates. Other common micro-organisms were *Salmonella*, *Klebsiella* and *Pseudomonas*. *E-Coli* were present in only one neonate with early onset sepsis¹⁵.

Not a single case of Group B *Streptococcus* is found in our study. This is consistent with other studies which reported a significantly low rate of early onset Group B streptococcus sepsis and meningitis. This reduction is further evidence of the effectiveness of maternal intrapartum antibiotic prophylaxis in preterm neonates. There is a positive correlation between positive blood culture and neonatal meningitis. Johnson and colleagues also reported an association of positive blood culture with the presence of meningitis in neonates^{13,14,15,16}.

Results of this study are quite similar with other studies, out of 25 cases of blood culture positive sepsis, 3 (12

percent) have neonatal meningitis. Hence, all septic neonates with meningitis have positive blood cultures. Out of three septic neonates with meningitis, one has *Enterobacter*, other has *Klebsiella*, while third one has *E-Coli*. Our results are comparable with an Indian study where researchers examined 36 neonates with early onset sepsis and found that meningitis was present in 3 cases. Similar to our study, in their study too, all meningitis cases have positive blood cultures. Therefore, some experts have pointed out that in early onset sepsis, lumbar puncture is indicated in the presence of a positive blood culture or if the clinical picture is consistent with septicemia⁹.

However, it is difficult to rely on blood culture to perform lumbar puncture because the blood culture results are usually available after 48 hours. Furthermore, blood cultures are negative in 15 to 55 percent cases of neonatal meningitis. If lumbar punctures are performed only in neonates with positive blood culture, a number of neonates with meningitis will be missed^{17,18}.

In this study, the comparison of neonates with meningitis and without meningitis regarding their demographic features such as age and gender show no statistical difference. Moreover, there is no statistical difference regarding the maternal and neonatal risk factors between neonates with meningitis and with no meningitis. However, out of three neonates with meningitis, two have weight less than 2.5 Kg in our study. Some researchers suggest that in low birth weight babies with respiratory distress, a lumbar puncture is not necessary. On the other hand, Stoll and colleagues have shown their concern that meningitis may be under diagnosed in very low birth weight neonates due to failure to perform lumbar puncture in these neonates.^{19, 20}

Our results show that apart from irritability, there are no statistical differences regarding presence of various symptoms between the septic neonates with meningitis and without meningitis. The septic neonates with meningitis are statistically more likely to have irritability than septic neonates without meningitis. However, in our study cases, the septic neonates with meningitis also have various specific as well as non-specific symptoms for neonatal meningitis such as poor feeding, seizures, lethargy and abdominal distension but no statistical differences are seen between septic neonates with meningitis and without meningitis. Likewise, several studies have shown that neonates with meningitis have shown neurological manifestations including seizures, lethargy, stupor, irritability. However, neurological symptoms are more common in late onset sepsis; consideration of meningitis remains prudent whenever a neonate demonstrates even slight lethargy or irritability. Therefore, on the basis of symptoms in neonates with early onset sepsis, it is difficult to distinguish to

perform a lumbar puncture to rule out meningitis and hence, lumbar puncture should be carried out in all neonates with early onset sepsis, regardless of their symptoms.^{7,16}

CONCLUSION

Although a low incidence of neonatal meningitis with early onset sepsis, but it is quite important to have lumbar puncture in all neonates with early onset sepsis because these 3.3 percent cases of meningitis would have been otherwise missed. All neonates with early onset sepsis diagnosed to have meningitis have positive blood cultures. Apart from, irritability, there are no statistical differences regarding the fetal and maternal risk factors and symptoms between septic neonates with meningitis and with no meningitis. Hence, we suggest that the lumbar puncture should be a part of routine septic work up in all neonates less than 72 hours of age with suspected sepsis.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Simonsen KA, Ann L, Anderson-Berry B, Shirley F, Delair A, Dele Davies H. Early-Onset Neonatal Sepsis. *Clin Microbiol Rev* 2014; 27(1): 21–47.
2. Singh M, Narang A, Bhakoo ON. Predictive perinatal score in the diagnosis of neonatal sepsis. *J Trop Pediatr* 1994; 40:365–8.
3. Ajayi OA, Mokuolu OA. Evaluation of neonates with risk for infection/suspected sepsis: is routine lumbar puncture necessary in the first 72 hours of life? *Trop Med Int Health* 1997; 2:284–8.
4. Hamer DH, Darmstadt GL, John BC, Anita KM, Zaidi SM. Etiology of Bacteremia in Young Infants in Six Countries *Pediatr Infect Dis J* 2015;34(1): e1–e8.
5. Birju A Shah, James F. Radbury. Neonatal sepsis Virulence 2014; 5(1): 170–178.
6. Chacko B, Sohi A. Early Onset Neonatal Sepsis. *Indian J Pediatr* 2005; 72:23–6.
7. Shiva F, Mosaffa N, Khabbaz R, Padyab M. Lumbar puncture in neonates under and over 72 hours of age. *JCPSP* 2006; 16:525–8.
8. Eldadah M, Frenkel LD, Hiatt M, Hegyi T. Evaluation of routine lumbar punctures in newborn infants with respiratory distress syndrome. *Pediatr Infect Dis J* 1987;6:243–6.
9. Walsh-Sukys M, Shenker N, Boxerbaum B, Fanaroff AA. Lumbar puncture in the newborn sepsis evaluation: Another Anachronism? *Pediatric Research* 1992;31:228A.
10. Laving AM, Musoke RN, Wasunna AO, Revathi G. Neonatal bacterial meningitis at the newborn unit of Kenyatta National Hospital. *East Afr Med J* 2003; 80:456– 62.
11. Hendricks-Munoz KD, Shapiro DL. The role of the lumbar puncture in the admission sepsis evaluation of the premature infant. *J Perinatol* 1990; 10:60–4.
12. Weiss MG, Ionides SP, Anderson CL. Meningitis in premature infants with respiratory distress: role of admission lumbar puncture. *J Pediatr* 1991; 19: 973– 5.
13. Rad EM, Montazmani A, N. Neonatal Sepsis due to Klebsiella: Frequency, Outcome and Antibiotic Sensitivity. *Iran J Publ Health* 2004; 33:43–8.
14. Ghadamli P. A review of bacterial pathogens of neonatal sepsis at hospitals of ShahidBeheshti University during the period between1992-1997. *J Qazvin Univ Med Sci* 1998; 2:53–7.
15. Misallati A, El-Bargathy S, Shembesh N. Blood-culture-proven neonatal septicemia: a review of 36 cases. *East Mediterr Health* 2000;2-3:483–6.
16. Johnson CE, Whitwell JK, Pethe K, Saxena K, Super DM. Term Newborns WhoAre at Risk for Sepsis: Are Lumbar Punctures Necessary? *Pediatrics* 1997; 99:e10.
17. Heath PT, NikYouseff NK, Baker CJ. Neonatal meningitis. *Arch Dis Child Fetal Neonatal Ed* 2003; 88:73–8.
18. MacMahon P, Jewes L, de Louvois J. Routine lumbar punctures in the newborn—are they justified? *Eur J Pediatr* 1990;149:797–9.
19. Kaftan H, Kinney JS. Early onset neonatal bacterial infections *Semin Perinatol* 1998; 22:15–24.
20. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. *Pediatrics* 2004;113: 1181–6.

Epidemiological Profile of Agriculture Pesticide Poisoning: An Experience at a Tertiary Care Hospital of Sindh

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ABSTRACT

Objective: To study the current trends of Epidemiological Profile of Pesticide Poisoning Cases reporting at a tertiary care hospital of Sindh.

Study Design: Prospective observational study

Place and Duration of Study: This study was conducted at the Chandka Medical College Hospital from January 2015 to May 2016.

Materials and Methods: A sample of 60 agriculture pesticide poisoning cases was studied in accordance to the inclusion and exclusion criteria. Biodata and physical examination were noted in the proforma. The patient data was kept confidential. Written informed consent was mandatory. SPSS 22.0 (IBM, Incorporation, USA) was available for the data analysis at 95% Confidence interval ($P \leq 0.05$).

Results: Mean $\pm$ SD age noted was 43.5 ± 9.6 years; majority belonged to the 4th decade of life ($p=0.0001$). Of 60 subjects, 51 (85%) were male and 9 (15%) were female ($p=0.0001$). Male to female ratio was 5.6:1. Pinpoint pupil, hypotension, unconsciousness, sweating, cyanosis, and bradypnea were noted in the majority of study subjects. Medicolegal aspects of poisoning show 51.6% were accidental, 21.6% were suicidal and 16.6% were homicidal cases.

Conclusion: The findings of present study show accidental agricultural pesticide poisoning as most common followed by suicidal and homicidal poisoning. Legal restrictions of safe use of pesticides should be implemented urgently and strictly.

Key Words: Agriculture Pesticides, Accidental Poisoning, Villagers

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INTRODUCTION

A poison is a substance capable of causing the body damage, dysfunction or death of a living organism when administered or absorbed into body. A poison usually interferes with the functions of enzyme systems. Entry into body may produce local or general toxic effects. Poisons are known since ancient times. Pesticides are a class of compounds used to kill pests, which may be mites, ticks, rodents, insects, nematodes, herbs and weeds, etc. Agriculture pesticides are

commonly used substances for the protection of agriculture crops and horticulture. They are also used for domestic purpose.^{1,2} Agriculture pesticides are now easily available; hence the problem of intentional or accidental poisoning is on the rise particularly in the developing countries. Pesticide poisoning now accounts for 3 million cases yearly, with approximately 200,000 deaths. Now >90% of cases are reported from the developing countries, such as the Pakistan.^{3,4} In Developing countries, Agriculture pesticide poisoning has risen to serious level which may be called as a "Social calamity".^{4,5} Modern facilities of agriculture pesticides have revolutionized the agriculture crop production, but had appeared as easily available poisonous substances for suicidal and homicidal purpose. This led to an increased frequency of poisoning cases.^{6,7} Death toll has increased due to agriculture pesticide poisoning despite of advanced medical treatment and awareness. A number of agriculture pesticides are available, which are handy for misuse or accidental calamity. Some of persons use for the purpose of suicide as these poisons causes a peaceful death. The agriculture pesticide poisoning now equals to the deaths in road traffic accidents, however, this type of death is being neglected.^{6,8} Acute agriculture poisoning may be intentional or accidental;

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the former exceeds the later one.⁹ Agriculture poisoning is now a calamity because of easy availability by a particular class of society. Deaths by the agriculture pesticides now account more than road traffic accidents for the villagers. This is because of improper handling of lethal pesticides, although they are liable to be handled as per rules and regulations, but the implementation of laws is neglected seriously, leading to severe misuse often for the poisoning purpose. Agricultural Organophosphorus compounds are freely available poisonous substances. These have helped greatly in the green revolution as a boon but at the cost of risk of death due to poisoning.¹⁰ WHO estimates show approximately 1 million accidental poisoning cases and 2 million suicidal poisoning cases per annum throughout the World.¹¹ The agriculture pesticide poisoning have assumed an alarming situation in developing countries like Pakistan, because of lack of implementation of law handling these pesticides. This has been attributed to various causes but easy availability, indiscriminate handling, lack of rules and regulations implementation, lack of knowledge and handling by un- educated farmers.¹² In Pakistan, the surveillance of poisoning substance is lacking seriously, this has resulted in mishandling and misuse of agricultural pesticides for other purposes. Now days the agriculture pesticides are most suitable poisons for suicide and homicide because of their easy access. The present study is being reported on the current trends of Epidemiological Profile of Pesticide Poisoning Cases at a tertiary care hospital of Sindh.

MATERIALS AND METHODS

The present prospective observational study was conducted at the Chandka Medical College Hospital from January 2015 to May 2016. Our hospital is 500 bed tertiary care hospital which caters surrounding rural population comprising of farmers (which are busy in the agriculture land and crop production. Adult villager subjects, diagnosed as cases of agriculture pesticide poisoning, was the inclusion criteria. Subjects of other poisoning, urban poisoning cases and subjects with severe co morbid systemic disease such as the Diabetes mellitus, chronic kidney disease (CKD) and heart failure, etc were excluded. The diagnosis of poisoning for pesticide poisoning was established by clinical history and physical examination. Conscious patients were interviewed, while attendants of unconscious patients were enquired about the type and cause of poisoning.

Approval was provided by the Institutional ethical committee. A sample of 60 agriculture pesticide poisoning cases was studied. Case selection was in accordance to the inclusion and exclusion criteria. A pre structured, pre-designed proforma was used for the collection of data. Patients presenting at the emergency department and admitted in the wards were approached

as per Helsinki's declaration of human research ethics. Biodata and physical examination was noted in the proforma. The patient data was kept confidential. Only authorized doctors engaged in the research project were allowed of access to the patient's data. Written informed consent for was signed by patients or legal guardians.

The data was typed on the Excel sheet. Compiled data once completed was ready for statistical analysis. SPSS 22.0 (IBM, Incorporation, USA) was available for the data analysis. The Continuous variables were presented as mean $\pm$ S.D after analysis by Student t-test. Contrary to this, the categorical variables were analyzed by Chi-square test and results were presented as frequency and %. All data variables were analysed at 95% Confidence interval ($P \leq 0.05$).

RESULTS

Total sixty subjects presenting at the emergency department and admitted in the intensive care unit were studied. The demography of study subjects is summarized in the table 1. Mean $\pm$ SD age noted was 43.5 $\pm$ 9.6 years. majority belonged to the 4th decade of life ($p=0.0001$) although young age was also noted as shown in table 1.

Table No.1: Demography characteristics of study subjects (n=60)

	No	%	P-value
Age Groups			≤ 0.01
• 20-29.9 years	12	20.0	
• 30- 39.9 years	16	26.6	
• 40-49.9 years	21	35.0	
• >50 years	11	18.3	
Male	51	85.0	
Female	09	15.0	
Villagers	60	100	

Table No.2: Clinical findings of study subjects (n=60)

	No	%
Pinpoint pupil	51	85.0
Hypotension	50	83.3
Bradycardia	21	35.0
Conscious	11	18.3
Unconscious	51	85.0
Fasciculation	50	83.3
Salivation	41	68.3
Sweating	56	93.3
Cyanosis	39	65.0
Bradypnea	43	71.6
Total	60	100%

Male to female ratio was 5.6:1, this shows male dominance. Of 60 subjects, 51 (85%) were male and 9 (15%) were female ($\chi^2 = 45.8$, $p=0.0001$). All of 60 subjects were villagers. Clinical findings of study subjects of organophosphate poisoning are summarized

in the table 2. Pinpoint pupil, hypotension, unconsciousness, sweating, cyanosis, and bradypnea were noted in the majority of study subjects. Types of agriculture agents used are shown in table 3 and graph 1. In 11.6% cases, the nature of poison was not known. Medicolegal aspects of poisoning show 51.6% were accidental, 31.6 were suicidal and 16.6% were homicidal cases.

Table No.3: Agriculture Pesticide (n=60)

	No	%
Chlorpyrifos	11	18.3
Methyl Parathion	09	15.0
Propanophos	12	20.0
Trichlorophos	17	28.8
Acephate	04	6.60
Not known	07	11.6
Total	60	100%

Table No.4: Medicolegal Aspects of Agriculture Pesticide Poisoning (n=60)

	No	%
Accidental	31	51.6
Suicidal	19	31.6
Homicidal	10	16.6
Total	60	100%

DISCUSSION

The present study is a first prospective study reporting on the agriculture pesticides poisoning in villagers of Sindh population. Agriculture pesticide poisoning is becoming a public health problem in the rural societies, this is because of illiteracy, lack of training of spreading agriculture agents on the crops and lack of public awareness about the agriculture pesticides that how much dangerous substances they are handling with. More than this is the misuse of agriculture pesticides for the suicidal and homicidal purpose by the villagers. The situation has now reached to an alarming level where the mortality and morbidity are proposed to increase at the most. Agriculture pesticides have already taken lives of bread earners of village families due to accidental poisoning. Accidental poisoning was most common encountered type noted in the present small scale study. Mean $\pm$ SD age noted was 43.5 ± 9.6 years; majority belonged to the 4th decade of life ($p=0.0001$) although young age was also noted (table 1). The findings are in agreement with previous studies.¹³⁻¹⁵ Male to female ratio was 5.6:1, this shows male dominance. Of 60 subjects, 51 (85%) were male and 9 (15%) were female ($\chi^2= 45.8$, $p=0.0001$). The male dominance is in agreement with previous studies.^{9, 13-15} This is a fact because the male partners of village families are the workers engaged most of the time in the agriculture lands. Pinpoint pupil, hypotension, unconsciousness, sweating, cyanosis, and bradypnea were noted in the majority of study subjects.

Our clinical findings are in agreement with previous studies.^{16,17} Types of agriculture agents used are shown in table 3. In 11.6% cases, the nature of poison was not known; this is due to the illiteracy of villagers which is highly prevalent. Medicolegal aspects of poisoning show 51.6% were accidental, 31.6 were suicidal and 16.6% were homicidal cases. Our findings are in keeping with previous studies.¹⁸⁻²⁰

Most common poisoning cases were due to the agriculture organophosphates, the finding is discordant to a previous study by Gargi et al.²¹ The Gargi et al.²¹ reported that aluminum phosphide as most common followed by organophosphates. The findings are inconsistent to present and previous studies.^{16,17} A previous study⁹ has reported 75.4% male were suffering from poisoning compared to only 24.6% in female; this finding is in agreement with the 85% male observed in the present study (table 1). The World Health Organization²² has warned on the restricted use of agriculture pesticide sale, but implementation of these regulations is a dream in developing countries like Pakistan. If the sale of agriculture pesticides is restricted according to rules, then the suicidal and homicidal deaths may be prevented to some extent, this is in agreement with previous studies.^{23,24} Legislation of pesticide sale and purchase has been effective in some countries and they reported a decrease in the suicidal and homicidal deaths.²³⁻²⁵

Training the farmers on the use of agriculture pesticides may reduce the accidental poisoning too. Public education programs should be planned in order to reduce the menace of the agricultural poisoning. Public health poisoning centers should also be established at the rural health center for early initiation of preventive and therapeutic measure to prevent the mortality.²⁵ Establishing Poisoning emergency centers at the Public health dispensaries will be a good step in changing the current scenario of agriculture pesticide poisoning. Primary health care centers should be provided with facilities of handling the poisoning cases as has been in the China,¹⁴ similar facilities should be provided in the Pakistan.

As our primary economy depends on agriculture, hence establishing poisoning centers at the rural areas will be contribute greatly towards managing the agriculture pesticides poisoning at the door step of villagers. Periodic training and refreshal courses for the young doctors will also be a useful who are working at the basic health units. This will strengthen the public health sector and will benefit the rural community.

CONCLUSION

The findings of present study show accidental agricultural pesticide poisoning as most common followed by suicidal and homicidal poisoning. The accidental poisoning may be prevented if the farmers are trained by the public health authorities. Suicidal and homicidal poisoning cases may be decreased by

implementation of legislation for agriculture pesticide sale and purchase in the country. Legal restrictions of safe use of pesticides should be implemented urgently and strictly.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

- Ahmed A, Ali L, Shehbaz L, Nasir S, Rizvi SRH, Aman MZ, Ali Z. Prevalence and characteristics of organophosphate poisoning at a tertiary care centre in Karachi, Pakistan. *Pak J Surg* 2016;32(4): 269-273.
- Maqbool F, Satti AI, Jeelani RA, Baqai HZ. Organophosphate Poisoning – clinical Profile. *J Rawal Med Coll (JRMC)* 2015; 19(1):15-19.
- Sangalad PN, Huddar MG. Pesticide poisoning among agriculturists of Dharwad District: A Study. *Recent Research Sci Technol* 2010; 2: 109-11.
- Kumar SV, Fareedullah M, Sudhakar Y, Venkateswarlu B, Kumar EA. Current review on organophosphorus poisoning. *Arch Appl Sci Res* 2010;2: 199-215.
- Khan NU, Pérez-Núñez R, Shamim N, Khan UR, Naseer N, Feroze A, et al. Intentional and unintentional poisoning in Pakistan: a pilot study using the Emergency Departments surveillance project. *BMC Emergency Med* 2015;15(Suppl 2): S2.
- Bhattacharyya K. serum creatine phosphokinase: A proable marker of severity in OP poisoning. *Toxicol Int'l* 2011; 18.
- Chen Y. Organophosphate-induced brain damage: Mechanisms, neuropsychiatric and neurological consequences and potential therapeutic strategies. *Neurotoxicol* 2012; 33: 391-400.
- Sangeetha K, Mohandas R, Deepavarshini P, Shiv GK. Clinical utility of creatine kinase and lactate dehydrogenase as severity markers of Organophosphorus compound poisoning. *Euro J Pharm Med Res* 2017;4(1), 597-601.
- Khodabandeh F, Emamhadi MA, Mostafazadeh B. Epidemiological Assessment of Acute Poisoning Death–One Year Survey. *Intl J Med Toxicol Forens Med* 2012; 2(3):103-109.
- Prakash MV, Ram OV, Shah HD. Acute organophosphorus poisoning and clinical admission score association among patients admitted in emergency ward of a tertiary teaching hospital of Medical College. *J Pharmaceut Biomed Sci* 2012; 17 (17):1-5.
- Javed A, Waqar F, Ahmed S, Rahman AS, Jamal Q, Hussain T. Different patterns of ECG in organophosphate poisoning and effect on mortality. *Pak Heart J* 2016; 49(03): 121-5.
- Lakhair MA, Shaikh MA, Kumar S, Zafarullah, Bano R, Maheshwari BK. Frequency of various clinical and electrocardiac manifestation in patients with acute organophosphorous compound (OPC) poisoning. *J Liaquat Uni Med Health Sci* 2012; 11(1):34-8.
- Paul UK, Bhattacharyya AK. ECG manifestations in acute organophosphorus poisoning. *J Indian Med Assoc* 2012; 110(2):98.
- Balouch GH, Yousfani AH, Jaffery MH, Devrajani BR, Shah SZA, Baloch ZAQ. Electrocardiographical manifestations of acute organophosphate poisoning. *World Appl Sci J* 2012;16(8):1118-22.
- Joshi P, Manoria P, Joseph D, Gandhi Z. Acute myocardial infarction: can it be a complication of acute organophosphorus compound poisoning? *J Postgrad Med* 2013; 55(1):2-4.
- Shahid M, Khan MZ, Afzal B, Khan ST, Nakeer R. Deliberate self-harm patients visiting public and private emergency departments of Karachi. *J Pak Psychiatr Soc* 2014; 11(1):28-30.
- Jafar A, Khan MJ, Khan MTH, Khan MTM, Fatima S. Poisons implicated in homicidal, suicidal and accidental cases in North-West Pakistan. *J Ayub Med Coll Abbottabad* 2016; 28(2):308-11.
- Santheti B K, Singh U P. The pattern of poisoning in Khammam. *J Ind Acad Forensic Med* 2011; 33(4):145-8.
- Gupta BD, Vagehela PC. Profile of fatal poisoning in and around Jamnagar. *J Ind Acad Forensic Med* 2005; 27(3):145-8.
- Palimar V, Kumar GP. Poisoning Deaths in children. *J Ind Acad Forensic Med* 2009; 31(3): 218-21.
- Gargi J, Rai H, Chanana A, Raj G, Sharma G, Bagga IJS. Current trends in Poisoning- A hospital profile. *J Punjab Acad Forensic Med Toxicol* 2005; 27(3):145-8.
- Wadia RS. Treatment of organophosphate poisoning. *Indian J Crit Care Med* 2003, 7:85-87.
- Shahid M. Deliberate self-harm prevention in Pakistan. *J Coll Physicians Surg Pak* 2013; 23(2): 101-2.
- Faiz MS, Mughal S, Memon AQ. Acute and late complications of organophosphate poisoning. *J Coll Physicians Surg Pak* 2011; 21(5):288-90.
- Khan TM, Mehr MT, Ullah H. Drugs-facilitated Street and travel related crimes: a new public health issue. *Gomal J Med Sci* 2015; 12(4): 11-5.

Exclusive Breast Feeding and Reasons of its Failure in Infants Less Than 6 Months of Age

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ABSTRACT

Objective: To know the frequency of exclusive breast feeding and the reasons given by the mothers for not practicing 'exclusive breast feeding'.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Children Outdoor of Bahawal Victoria Hospital, Bahawalpur from July to September 2016.

Methods and Materials: 200 mothers visiting the Children Outdoor with infant less than six months of age were interviewed.

Results: 200 mothers were interviewed. 89.5% of them were housewives while 10.5% were working ladies. 43.5% mothers were having monthly family income less than 10000, 46% with 10000-49000 and 10.5% with 50000 rupees or more. 18% infants were given colostrum as first feed while the 14.5% infants were put on breast milk within one hour of birth. 26.5% infants were exclusively breast fed while 73.5% were belonging to the group of 'not exclusively breast fed'. The three most common reasons included 'mother milk is insufficient (51.2%)', 'mother feels baby is weak (14.3%)' and 'she is a working lady (11.6%)'.

Conclusion: The exclusive breast feeding practices are poor and three common reasons are maternal perception of having insufficient milk, mothers feeling baby is weak/ill and mothers are working ladies.

Key Words: First feed; colostrum; exclusive breast feeding; insufficient milk

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INTRODUCTION

The breast milk is the best and most safe form of food for infants¹. The World Health Organization (WHO) has defined exclusive breastfeeding 'as the infant below six months of age should receive only breast milk [no other fluids including water or solids except oral rehydration solution, or vitamins or medicines]². Breastfeeding provides nutrients for healthy growth and development in infants and improves immunity. The exclusive breastfeeding for the first 6 months gives protection against infections especially gastrointestinal and iron deficiency anemia. It causes delayed recommencement of menses (thus avoiding unplanned pregnancies) and more speedy loss of maternal postpartum weight loss³. Breast feeding also stimulates sensory cognitive and development. It also decreases

incidence of atopic dermatitis in infants. It also decreases infant mortality^{4,5}. The exclusive breastfeeding is the most cost-effective intervention in reducing infant mortality especially in developing countries. Globally, less than 40% of infants of age less than six months are exclusively breastfed and the poor breastfeeding practices are responsible for 800 000 deaths each year in children under five years of age⁶. In Pakistan exclusive breast feeding is practiced in about 38% infants⁷ which is much below the global target of 65.6% for year 2025⁸. The exclusive breast feeding rate varies, not only, across the countries^{9,10,11} but also varies from place to place in Pakistan^{12,13,14}.

The objective of the study was to know the frequency of exclusive breast feeding and the reasons given by the mothers of not practicing 'exclusive breast feeding'.

MATERIALS AND METHODS

This is a cross sectional study that was conducted at the Children Outdoor of Bahawal Victoria Hospital, Bahawalpur from July to October, 2016. The mothers visiting the Children Outdoor with infants less than six months of age were included. The verbal informed consent was taken from the mothers before including them in the study. Infants who remained admitted in the hospital for more than first five days of life due to some serious illness causing interference in breast feeding, infants with congenital malformations interfering in the

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breast feeding, infants with neurological disorders, infants not accompanying with their mothers or if the mother is having some chronic illness or having HIV were excluded.

The interview from the mother was taken in her understandable language by one of the researchers. The mother was asked about her age, her educational status, her employment status, monthly family income, age and sex of infant, whether colostrum given to the infant after birth as first feed or not, was infant put on breast within one hour of life, anything other than breast milk given in the last 24 hours given and reasons if infant was not on exclusive breast feeding by using a prepared formula. Exclusive breast feeding was labeled if the infant did not take any liquid including water or any semisolid in the last 24 hours before the interview. The data were entered and analyzed by SPSS version 10 and were presented as proportions or percentages.

RESULTS

There were 200 mothers who were interviewed, 26 (13%) were of age group less than 20 years, 99 (49.5%) were of 20-30 years, 60 (30%) of 30-40 years and 15 (7.5%) were of age group more than 40 years. 52 (26%) mothers were either illiterate/primary failed, 74 (37%) primary passed, 45 (22.5%) were having secondary school certificate, 15 (7.5%) were having higher secondary school certificate, 11 (5.5%) were graduate and 3 (1.5%) were postgraduate. 179 (89.5%) mothers were housewives while 21 (10.5%) were working ladies. 87 (43.5%) mothers were having monthly family income less than 10000, 92 (46%) with 10000-49000 and 21 (10.5%) with 50000 rupees or more. There were 111 (55.5%) male while 89 (44.5%) female infants. 45 (22.5%) infants were below the age of 2 months, 77 (38.5%) between the age of 2-4 months and 78 (39%) were ≥ 4 months but less than six months of age. There were only 36 (18%) infants who were given colostrum as first feed while 29 (14.5%) infants were put on breast milk within one hour of birth.

Table No.I: The reasons given by the mothers of not practicing 'exclusive breast feeding' Total cases: 147

Reason	Number of cases	Percentage
Mother milk is insufficient	87	59.2%
Mother feels baby is weak/ill	21	14.3%
Mother is a working lady	17	11.6%
Mother feels she is physically weak/ill	11	7.5%
Mother feel that her milk causes illness in the baby	8	5.4%
Twin pregnancy	1	0.7%
She is pregnant	2	1.3%

There were 53 (26.5%) infants who were exclusively breast fed in the last 24 hours while 147 (73.5%) were belonging to group of 'not exclusively breast fed'. The reasons given by the mothers of not practicing 'exclusive breast feeding' recommendation are shown in table-I. The three most common reasons included 'mother milk is insufficient (59.2%)', 'mother feels baby is weak (14.3%)' and 'she is a working lady (11.6%)'.

DISCUSSION

There were 13% mothers belonged to age group less than 20 years, 49.5% to 20-30 years, 30% to 30-40 years and 7.5% to age group more than 40 years in this study. The study done at Gilgit¹⁴ showed mean age of mothers was 24.3 years $\pm$ 4.8.

There were 26% mothers who were illiterate/primary failed, 37% primary passed, 22.5% were having secondary school certificate, 7.5% were having higher secondary school certificate, 5.5% were graduate and 1.5% were postgraduate in this study. The study done at Gilgit¹⁴ showed that 27% mothers were uneducated while only 14% were having matriculation while the study done at Islamabad¹⁵ showed that 43.5% mothers were uneducated. The study done at Nowshera¹⁶ showed a high rate of illiteracy (71.8%) among the mothers.

This study showed that 89.5% mothers were housewives. The study done at Islamabad¹⁵ showed that 91% mothers were housewives. This study showed that 43.5% mothers were having monthly family income less than 10000, 46% with 10000-49000 and 10.5% with 50000 rupees or more. The study done at Islamabad¹⁵ showed that the monthly income was 16542 $\pm$ 12761 (mean $\pm$ SD) rupees.

There were 55.5% male while 44.5% were female infants in this study. The study done at Gilgit¹⁴ showed that 61% infants while the study done at Islamabad¹⁵ showed that 59.7% were male. There were only 18% infants who were given colostrums as first feed in this study. The study done at Lahore¹⁷ showed that first feed was colostrum in 41.8%.

14.5% infants were put on breast milk within one hour of birth. The study done at Islamabad¹⁵ showed only 0.6% babies the breast feeding was started within <1 hour after birth. This study showed that there were 26.5% infants who were exclusively breast fed in the last 24 hours. Other studies done in Pakistan^{12,13,14} showed exclusive breast feeding in 19%-64.8% infants while the international studies^{9,10,11} showed exclusive breast feeding in 13.8% -81.1% cases.

The three most common reasons given by the mothers of not practicing 'exclusive breast feeding' included 'mother milk is insufficient' (59.2%), 'mother feels baby is weak' (14.3%) and 'she is a working lady' (11.6%). The study done at Islamabad¹⁵ showed the reasons of non exclusive breastfeeding were deficient

milk production in 93.2%, working lady in 4.2%, ill health of infant in 0.65% and the mother ill health in 1.9% cases. The study done in interior Sindh¹³ showed the reasons of non exclusive breastfeeding were working ladies in 40%, to make acquainted baby to bottle feeding in 22.5%, inadequate milk (presumed by mothers) in 17.5%, true inadequate milk in 7.5%, family pressure in 3.75%, prematurity in 3.75%, and delivery by Cesarean in 2.5% and next pregnancy in 1.25% cases. The study done in Nowshera¹⁶ showed that maternal perception of having insufficient milk (45.9%), working ladies (18.4%), ill mothers (13.1%), illness in infants (17%), pregnancy of mothers (3.61%), infants whose mothers were died (0.98 %) and twin infants (0.98%) were the causes. The international studies^{10,11} showed that employment in mother is associated with exclusive breast feeding.

CONCLUSION

The exclusive breast feeding practices are poor and three common reasons are maternal perception of having insufficient milk, mothers feeling baby is weak/ill and mothers are working ladies.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Ssemukasa EL, Kearney J. Six months of exclusive breastfeeding recommendation: how applicable is the universal exclusive breastfeeding recommendation policy? *Afr J Food Agric Nutr Dev* 2014;14(4):9071-84.
2. World Health Organization. Indicators for Assessing Infant and Young Child Feeding Practices Part-1. Definitions. Geneva: World Health Organization; 2008.
3. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* 2002;(1):CD001851.
4. Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dezakovich I, Shapiro S, et al. Promotion of breastfeeding intervention trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA* 2001; 285 (4): 413–20.
5. Kramer MS, Kakuma R. The optimal duration of exclusive breastfeeding: a systematic review. *World Health Organization. Geneva: World Health Organization; 2001.*
6. Health in 2015: from MDGs, Millennium Development Goals to SDGs, Sustainable Development Goals Geneva: World Health Organization; 2015.
7. UNICEF. The State of the World's Children 2016. New York: UNICE; 2016
8. World Health Organization. Global Nutrition Targets 2025: Breastfeeding policy brief. Geneva: World Health Organization; 2014.
9. Al-Sahab B, Lanes A, Feldman M, Tamim H. Prevalence and predictors of 6-month exclusive breastfeeding among Canadian women: a national survey. *BMC Pediatr* 2010;10:20.
10. Setegn T, Belachew T, Gerbaba M, Deribe K, Deribew A, Biadgilign S. Factors associated with exclusive breastfeeding practices among mothers in Goba district, south east Ethiopia: a cross-sectional study. *Int Breastfeed J* 2012;7(1):17.
11. Liben ML, Gemechu YB, Adugnew M, Asrade A, Adamie B, Gebremedhin E, et al. Factors associated with exclusive breastfeeding practices among mothers in Goba town, afar regional state, northeast Ethiopia: a community based cross-sectional study. *Int Breastfeed J* 2016;11:4.
12. Ayub T, Khawar N. Prevalence of exclusive breastfeeding in infants suffering from diarrhoeal disease. *J Med Sci* 2005;13(2):143-7.
13. Jamro B, Jamro S, Bhatti R, Kumari R. Experience of exclusive breast feeding in tertiary care hospitals. *Med Channel* 2011;17(3):72-5.
14. Aslam S, Sultan S, Akram F. Exclusive breast feeding. *Professional Med J* 2010; 17(2):286-90.
15. Yaqub A, Gul S. Reasons for failure of exclusive breastfeeding in children less than six months of age. *J Ayub Med Coll Abbottabad* 2013;25(1): 165-7.
16. Nawaz R, Rehman SU, Nawaz S, Mohammad T. Factors causing non-breastfeeding in children under six months of age in district Nowshera, Pakistan. *J Ayub Med Coll Abbottabad* 2009; 21(4):93-5.
17. Iqbal SMJ, Afzal MF, Azhar IA, Sultan MA. First feed in newborn: are we following WHO recommendations? *Ann King Edward Med Uni* 2010;16(4):229-32.

Frequency of Depression among Patients with Diabetes Mellitus at PMCH Nawabshah

Depression
among
Diabetics

Jeando Khan Daidano¹, Noor Nabi Siyal¹, Mukhtiar Ahmed Abro¹, Rafique Ahmed Memon¹
and Noor Ahmed Channar²

ABSTRACT

Objective: We will assess depressive symptoms with diabetes on diabetes self care treatment non adherence, functioning and health care.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Department of Medicine, PMCH Nawabshah from Jan 2016 to dec 2016.

Materials and Methods: 120 patients both males and females were selected for this study. We administered a Questionnaire to 120 patients with type 1 and type 2 Diabetes, depressive symptoms, diabetes control, self care. Assess the impact of depressive symptoms on adherence to diabetes self care HbA1c levels functional impairment and health care.

Results: 120 cases were selected, 79 were males 41 were females, 25 pts were of type 1, 95 were of type 2. Depression was diagnosed using the structural clinical interview using Beck's Depression Inventory.

Conclusion: Findings demonstrate association of depression with diabetes clinical consideration, treatment non adherence, proper drug treatment of diabetes, depression, self care and counseling mortality can be reduced with incidence of depression.

Key Words: Depression, Diabetes Mellitus, Complications, Glycemic control, Treatment, Quality of life.

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INTRODUCTION

Diabetes mellitus is chronic illness present in 2 to 5 percent population. Diabetes Mellitus is common problem, 180 million people affected with this disease world wide.¹

This count can be doubled in 2030². There are two types of Diabetes Mellitus, type 1 and type 2. Insulin therapy for type 1, oral anti diabetic drugs for type 2 and for uncontrolled type 2 Diabetes Mellitus insulin therapy is recommended.

Depression is more in diabetic than in general population with poor quality of life,³ patients with diabetes mellitus are 1.4 to 3 times to suffer from comorbid depression as compared to non diabetic.⁴

Uncontrolled diabetes Mellitus with Increase in blood glucose level incidence of complications are increased.⁵ Depression in Diabetes Mellitus is due to non adherence to treatment and self care.⁶

Risk factors for Depression in Diabetes mellitus are younger age, female, unmarried or divorce and widow,

lower socioeconomic level, poor glucose control low social support, low education level, complications of Diabetes mellitus, any medical comorbidity and past history of depression.⁷ Risk of type 2 Diabetes Mellitus with Depressed Patients is reported to be as high as 1.6.⁸

Depressive symptoms are more in type 2 diabetic patients as compared to type 1 patients.⁹

Depression is more noted in Diabetes Mellitus with complications as compared without complications in both type 1 and type 2 Diabetes Mellitus.¹⁰

With relationship between depression and diabetes depression may be risk factor for the onset of diabetes.¹¹ Increased risk of diabetes type 2 patients with depression is due to increased counterregulatory hormone release, disturbance in glucose transport function and raised immuno inflammatory activation.¹² Insulin resistance and beta cell dysfunction result due to above physiological mechanism and development of type 2 diabetes mellitus. Poor glycemic control associated with depression in diabetes both type 1 and type 2 patients.¹³

High HbA1c level associate with depression in diabetes.¹⁴ Depressive symptoms are associated with poor adherence to self care particularly medications, diet and exercise.¹⁵ In a review of treatment adherence among patients with depression in diabetes, it was observed relationship between depression and treatment nonadherence.¹⁶ Comorbid depression among patients

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with diabetes associated with less physical activity, unhealthy diet, and lower adherence to oral drugs, hypoglycemic, antihypertensives, and lipid lowering¹⁷ Unsatisfactory metabolic control associated with psychiatric comorbidity, depression in diabetes associated with inadequate metabolic control in those patients with poor glycemic control despite good medical treatment. As a consequence poor disease control morbidity and mortality is increased¹⁸

MATERIALS AND METHODS

This cross sectional study was carried out in the Department of Medicine PMCH Nawabshah from Jan 2015 to Dec 2016, this study was conducted to observe depression in diabetes with other complications of diabetes in a population poor adherence to treatment and quality of life. Informed consent was taken from the patients questionnaire was

Given to all patients data collected according to Questionnaire.

Depression was assessed using structural clinical interview using Beck's Depression Inventory on separate questionnaire.

Level of depression according BDI

Total score Level of Depression

1-10 These ups and downs are considered normal

11-16 Mild mood disturbance

17-20 Border line clinical Depression

21-30 Moderate Depression

31-40 Severe Depression

Over 40 extreme Depression

Inclusion criteria:

Males and females

age 12ys to 60ys

depressed patients

DM type 1 and 2

Exclusion Criteria:

Age below 12 ys and above 60 ys

Severe Psychotic illness

Severe medical illness

In order to get correct information Questionnaire was translated into Urdu and Sindhi languages

RESULTS

120 cases were selected for this study 79 were males 41 were females 90 patients belonged to Rural areas 30 belonged to Arabian areas.

➤ Age no of patients

➤ 12-24ys 20

➤ 25-40ys 31

➤ 40-60ys 69

Depression as per education

Illiterate 56

Primary 19

Middle 15

Metric 9

Intermediate 7

Graduation 6

Masters 8

Depression as per marital status

Married 83

Single 8

Widow 19

Divorced 10

Depression as per occupation

Farmer 64

House wife 26

Unemployed 10

Service 7

Business 5

Laborer 8

Depression Socioeconomic status

Lower 80

Middle 39

Upper 1

Investigations

➤ RBS no of patients

➤ 140-185 60

➤ 185-300 40

➤ 300-500 20

HbA1c Level

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	6.5	58	48.3	48.3	48.3
	7.5	32	26.7	26.7	75.0
	8.5	30	25.0	25.0	100.0
	Total	120	100.0	100.0	

Becks Depression Scale status

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	19.00	1	.8	.8	.8
	20.00	3	2.5	2.5	2.5
	21.00	1	.8	.8	.8
	23.00	1	.8	.8	.8
	24.00	2	1.7	1.7	1.7
	25.00	6	5.0	5.0	5.0
	26.00	4	3.3	3.3	3.3
	27.00	8	6.7	6.7	6.7
	28.00	29	24.2	24.2	24.2
	29.00	26	21.7	21.7	21.7
	30.00	36	30.0	30.0	30.0
	31.00	2	1.7	1.7	1.7
	32.00	1	.8	.8	.8
	Total	120	100.0	100.0	100.0

HbA1c

➤ HbA1c

➤ 6.5 58

➤ 7.5 32

➤ 8.5 30

8.5 in 25 patients type 2 was present in 95 patients diabetic ketoacidosis in 16 patients diabetic foot in 70 diabetic retinopathy in 6 pulmonary TB 10 neuropathy 11 diabetic nephropathy 7.

Statistical analysis was done on SPSS 15 version.

Descriptive Statistics

	N	Min.	Max.	Mean	Std. Deviation
Age In Groups	120	15.00	60.00	42.9583	12.24703
Radium Blood Sugar evel	120	160.00	450.00	254.5833	86.09078
HbA1c Level	120	6.5	8.5	7.267	.8274
Becks Depression Scale status	120	19.00	32.00	28.1750	2.35026
Valid N (listwise)	120				

HbA1c Level

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	12.821	12	1.068	1.665	.085
Within Groups	68.646	107	.642		
Total	81.467	119			

ONEWAY

Becks Scale BY RBS

Becks Depression Scale status

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	247.972	37	6.702	1.343	.136
Within Groups	409.353	82	4.992		
Total	657.325	119			

ONEWAY

Becks Scale BY HbA1c

Becks Depression Scale status

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	10.495	2	5.247	.949	.390
Within Groups	646.830	117	5.528		
Total	657.325	119			

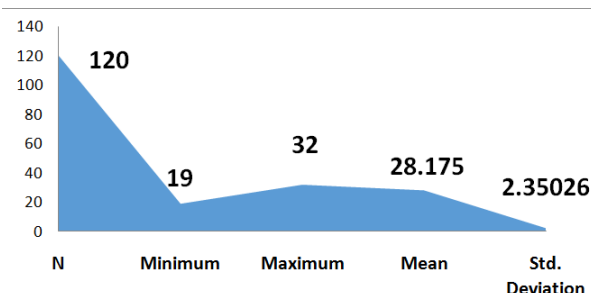
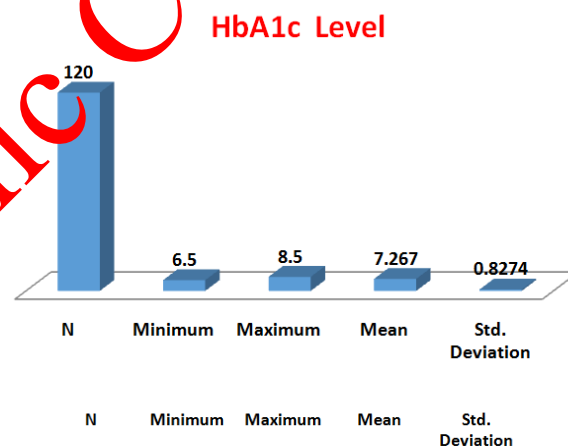
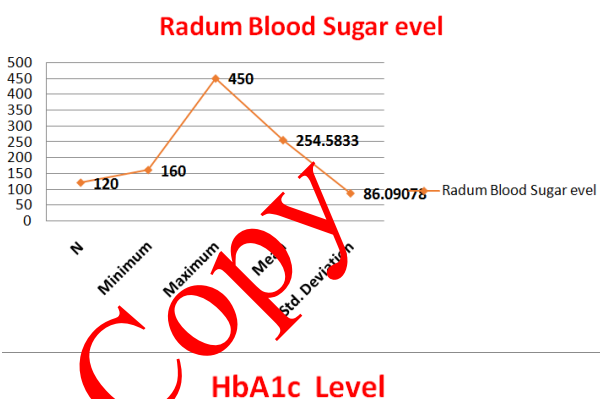
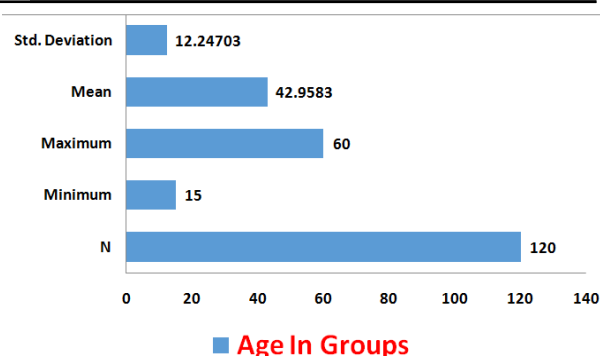
T-Test

PAIRS = HbA1c RBS WITH BecksScale BecksScale (Paired)

Criteria = CI(.95)

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	HbA1c Level & Becks Depression Scale status	120	-.035	.704
Pair 2	Radium Blood Sugar evel & Becks Depression Scale status	120	-.006	.949



DISCUSSION

Depression is common problem in diabetes prevalent and negative impact in clinical outcomes, quality of life, associated with increased mortality in DM.¹⁹

The factors could explain the occurrence of depression in diabetes. Dietary restrictions, financial problems, treatment demands and hospitalization contribute to depression. Severe Depressive symptoms associated with less adherence to dietary recommendations. Depression associated with high level of HbA1c level. Depression in Diabetes mellitus is higher in younger as compared with older age²⁰. It has been found that patients with Depression in diabetes mellitus are knowledgeable about Diabetes and more likely depressed. 10 to 15 percent patients with diabetes have major Depression.²¹ Depression associated with social withdrawal disengagement from social activities, patients with increased level of depression report more.²² Study has shown that in Diabetes Depression is associated with poor glucose control than HbA1c levels. Depression associated with poor physical health.²³ With poor glucose control there are changes in autonomic nervous system hypothalamic adrenal axis and neurotransmitter.²⁴ According to winokur et al Depression associated with insulin resistance compared with without depression²⁴. Depression is directly related to Diabetic complications, retinopathy and macrovascular complications.²⁵ Depression diabetes and cardiovascular disease are closely related, depression in diabetes increases risk of cardiovascular disease^{26,27}. Depression and diabetes associated with decrease in physical activity, smoking and diet.²⁸ Depression associated with activation of the hypothalamic pituitary adrenal axis and release of cytokines disturbance in sympathetic nervous system and increases the risk of mortality²⁹ It has been shown that antidepressants and cognitive behavioral therapy reduces HbA1c level.³⁰ In this study screening for depression in Diabetes mellitus is compulsory. Screening, identification and treatment of depression improve symptoms and functional outcome in primary care patients.³¹ keton et al report in a study 44 out of 85 patients incomplete rate of correct recognition depression over a year of study.³¹ American diabetic association recommends in DM with poor control should be screened for depression.³² We found weaker relationship between depression diet, and medication adherence, management of depression in Diabetes mellitus seems to be costeffective.³³ Missed appointments are associated with increased provider frustration and decreased empathy.³⁴ It has been found that there is no evidence to suggest that relationship between depression self-care varied as a function of type of diabetes and major depression it was found that severity of depression BMI total fat mass and HbA1C decreased during acute phase treatment and adherence to diet and exercise improved.³⁵ Randomized controlled trials suggesting treatment of depression in diabetes has positive effects on diabetes self-care has been lacking trial of antidepressants cognitive behavioral therapy³⁶. There are data to suggest

that Depression is associated with poor blood glucose control³⁶

CONCLUSION

Depression in diabetes is a chronic illness of unknown etiology several neuroendocrine and neurotransmitters abnormalities are same to diabetes and depression. Treatment of depression with antidepressant drugs improve mood and blood glucose level in diabetes mellitus. Glycemic control is improved by antidepressant drugs and anti diabetic drugs quality of life is improved.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Diabetes care and research in Europe: an action programme for the implementation of St. Vincent Declaration for the improvement of diabetes care, Copenhagen: WHO Regional office for Europe: 1991.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes; estimates for the year 2000 and projections for 2030, Diabetes care 2000;27:1047-53.
3. Wexler DJ, Grant RW, Wittenberg E, Bosch JL, Cagliero E, Delahanty L, et al. Correlates of health-related quality of life in type 2 diabetes. Diabetologia 2006;49:1489-1497.
4. Lin EH, Von Korff MV. Mental disorders among persons with diabetes- Results from the world Mental Health Surveys. J Psychosom Re 2008; 65:571-580
5. Fischer L, Skaff MM, Mullan JT, Areant P, Glasgow R, Masharani U. A longitudinal study of affective and anxiety disorders, depressive affect and diabetes distress in adults with type 2 diabetes. Diabet Med 2008;25:1096-1101.
6. Dimatteo RM, Lepper HS, Croghan TW: Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence Arch Int Med 2000;160:2101-2101.
7. Tell-Zenteno JF, Cardiel MH, Risk factors associated with depression in patients with type 2 diabetes mellitus. Arch Med Res 2002;33:53-60.
8. Mezuk B, Eaton W, Albrecht S, Golden SH. Depression and type 2 diabetes over life span, Diabetes Care 2008;31:2383-2390.
9. Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia 2010; 53:2480-2486.
10. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults; there is link? Diabetes Care 2000;23(10):1556-1562.

11. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus . A meta-analysis, *Diabetologia* 2006;49(5):837-845.
12. Musselman DL, Betan E, Larsen H, Philips LS. Relationship depression to diabetes types 1 and 2; epidemiology, biology and treatment, *Boil Psych* 2003;54(3):317-329.
13. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control; a meta-analytic review of literature, *Diabetes Care* 2000;7(9):934-942.
14. Wagner JA, Abbot GL, Heapy A, Yong L. Depressive symptoms and diabetes control in Africans Americans, *J. Immiger Minor Health* 2009;11(1):66-70.
15. Gonzalez S, Safren SA, Delahanty LM, Cagliero E, Waxler DJ, Meigs JB, et al., Symptoms of depression prospectively predict poorer self-care in patients with type 2 diabetes, *Diabetic. Med* 2008; 25 (9):1102-1107.
16. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a metaanalysis. *Diabetes Care* 2008;31(12):1102-1107.
17. Lin EH, Katon W, Von Korff M, Ruttler C, Simon GE, Oliver M, et al. Relationship of depression and diabetes self care, medication adherence, and preventive care. *Diabetes Care* 2004;27(9): 2154-2160.
18. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
19. Hamilton W, Round A, Sharp D: Patient, hospital, and general practitioner characteristics associated with non-attendance a cohort study. *Br J Gen Pract* 2003;52:317-319.
20. Robin L NedRegio DA and Psychiatric Disorders in America: The Epidemiological Catchment Area Study. New York, NY Free Press 1991;
21. Lustman PJ, Clouse RE, Freedland KE. Management of major depression in adults in adults with diabetes: implications of recent medical trials. *Semin Clin Neuropsychiatry* 1998;3:102-114.
22. Lustman PS, Clouse RE, Carney RM. Depression and the report in of diabetes symptoms. *Int J Psychiatry Med* 1988;18:295-303.
23. Katon W J The effect of major depression on medical chronic illness. *Semin Neuropsychiat* 1998;3:82-86.
24. Winouker A, Maislin G, Phillips JL, Amsterdam JD. Insulin resistance after oral glucose tolerance testing in patients with major depression. *Am J Psychiat* 1988;145:325-330.
25. Carney RM, Freedland KE, Lustman PJ, Griffith LS. Depression and coronary artery disease in diabetic patients: a 10-year follow up. *Psychosom Med* 1985; 47:372-38
26. Black SA, Markides KS, Ray LA. Depression predicts increased incidence of adverse health outcomes in older Mexicans Americans with type 2 Diabetes. *Diabetes Care* 2003;26:2822-2828.
27. Lin EH, Heckbert SR, Rutter CM, Caton WJ, Ciechanowski P, et al. Depression and increased mortality in diabetes: unexpected cause of death. *Annals Family Medicine* 2009;7: 414-421.
28. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, et al. Depression and diabetes treatment nonadherence: a meta analysis. *Diabetes Care* 2008;31: 2398-2403.
29. de jonge P, Rosmalen JG, Kema IP, Dooranpos B, van Melle JP, et al. Psychophysiological biomarker explaining the association between Depression and prognosis in coronary artery patients: a critical review of literature. *Neuroscience and behavioral Reviews* 2010;35: 84-90.
30. Lustman PJ, Griffith LS, Clouse RE. Effects of nortriptyline on depression and glycemic control in diabetes: results of double-blind, placebo-controlled trial. *Psychosom Med* 1997; 59:241-250.
31. Katon WJ, Von Korff M, Lin E, et al. Population-based care of depression: effective disease management strategies to decrease prevalence. *Gen Hosp Psychiat* 1997; 19:169-178.
32. Lustman PJ, Freedland KE, Griffith LS, Clouse RE: Fluoxetine for depression in diabetes. *Diabetes Care* 2000;23:618-623.
33. Lustman PJ, Griffith LS, Freedland KE, Clouse RE: Course of major depression in diabetes, *Gen Hosp Psychiat* 1997;19:138-143.
34. Lustman PJ, Griffith LS, Freedland KE, Kissel SS, Clouse RE. Cognitive behavior therapy for depression in type 2 diabetes mellitus *Ann intern Med* 1998;129:613-621.
35. Fris R, Nanjundappa G, Diabetes, depression and employment status, *Soc Sci Med* 1986;23:471-75.
36. Lustman PJ, Griffith LS, Clouse RE, Cryer PE. Psychiatric illness in diabetes, relationship to symptoms and glucose control. *J Nerv Ment Dis* 1986;174, 736-42.

Frequency of Perforated Appendicitis and its Causes in Patients Underwent Appendectomies at Tertiary Care Hospital

Agha Taj Mohammed, Rasool Bux Behan and Zameer Hussain Laghari

ABSTRACT

Objective: The objective of this study was to find out the frequency of perforated appendicitis and reasons of perforated appendicitis at tertiary care Hospital.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Department Surgery, LUMHS from February 2014 to January 2015

Materials and Methods: Total 107 patients were admitted in the surgery ward, out of those 75 were underwent appendectomy. All the patients who underwent appendectomy were included in the study after taking informed consent while other patients and patients having co morbidity were excluded from the study. All the information regarding their presenting symptoms, cause of appendectomy etc was recorded on self-designed proforma. Data was entered on SPSS version 16.

Results: Mean age of the patients was 35+- 2.09. 21(28%) patients belong to age group of <30 years, 33(44%) belonged to age group of 30-40 years and 15(20%) were from age group of 41-60 years. Majority of the patients i.e 56(74.66%) were males while 19(25.33%) were females. In this study, 15(20%) patients had perforated appendicitis, 48(64%) had inflamed appendicitis while 10(13.33%) had gangrenous appendix and 2(2.66%) had normal appendix. In our study, the most common cause of perforated appendix was misdiagnosed by doctors as seen in 6(40%) patients followed by delay in reaching hospital seen in 4(26.66%), while 3(20%) were reluctant for surgery. 45(60%) patients had presented with pain in right iliac fossa, 16(21.33%) had fever and 10(13.33%) had nausea.

Conclusion: We concluded that frequency of perforated appendicitis is 20% and its main associated factors are; misdiagnosis by general practitioners and delay in reaching the Hospitals where surgeons and surgical facilities are available.

Key Words: Appendectomy, perforated appendicitis, appendectomies

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INTRODUCTION

Appendicitis is characterized as the inward lining inflammation of the vermiform appendix which spreads to its different parts. Regardless of symptomatic and advancement in medication, an inflamed appendix remains a clinical crisis and is one of the more typical reasons for the acute pain of the abdomen. Acute appendicitis may because appendiceal lumen obstructions. Important reasons of the luminal obstructions including hyperplasia of the lymphoid and secondary to bowel inflammation disease or infection (mostly in young adults and children), focal stasis and the fecaliths (mostly in elderly cases) or more commonly neoplasm and the foreign bodies.

Approximately 7% peoples having history of appendicitis in their life¹ with peak prevalence around ages of 10 to 30 years.² Assessing an elderly cases who having pain of the abdomen is a difficult challenge and one that we would face extra often as mean age increases. Sympathetic why elderly cases having different presentation as compare to Youngers, counterparts can recover the outcomes through decreasing the diagnostic mistakes and big delays in the management. Acute appendicitis is the disease also occurring in the elderly, and is subject to both late presentation and the diagnosis. When compared to the younger generation, the elderly have high ratio of morbidity and mortality. Surgical treatment of the appendicitis is the standard treatment for over a century. Above than 300000 surgeries for appendicitis performed each year in United States.³ Appendicular mass, gangrene, perforation; abscess and generalized peritonitis are the complications which can occur if appendicitis is not treated in a timely manner. The life time risk for development of acute appendicitis in males and females is 8.6% and 6.7% respectively.⁴ Appendicitis is frequently misdiagnosed and is among the major reasons for malpractice by the emergency room physicians. Appendicular perforation is highly

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linked with high rate of morbidity and mortality comparing with non-perforated appendicitis. The purpose of this study was to find out the frequency of perforated appendicitis and reasons of perforation of appendix.

MATERIALS AND METHODS

This cross sectional study was conducted in the surgery department of LUMHS from February 2014 to January 2015. Patients with all age groups either gender were incorporated. Total 107 patients were admitted in the surgery ward, out of those 75 were underwent appendectomies. All the patients who underwent appendectomy were further studied. Informed consent was taken. Patients having other severe comorbidities co morbidity were excluded from the study. All the information regarding their presenting symptoms, cause of appendectomy etc was recorded on self-designed proforma. Data was entered and analyzed in SPSS 20.

RESULTS

Total 100 patients were admitted in the surgery ward, out of those 75 were underwent appendectomies. Mean age of the patients was 35+- 2.09. 21(28%) patients belong to age group of <30 years, 33(44%) belonged to age group of 30-40 years and 15(20%) were from age group of 41-50 years. Majority of the patients i.e 56(74.66%) were males while 19(25.33%) were females. Table 1

45(60%) patients had presented with pain in right iliac fossa, 16(21.33%) had fever and 10(13.33%) had nausea.

In this study, 15(20%) patients had perforated appendicitis, 48(64%) had inflamed appendicitis while 10(13.33%) had gangrenous appendix and 2(2.66%) had normal appendix. Table 2

In our study, the most common cause of perforated appendix was misdiagnosed by doctors as seen in 6(40%) patients followed by delay in reaching hospital seen in 4(26.66%), while 3(20%) were reluctant for surgery.

Table No.1:Patients distribution according to age and gender n=75

Age and gender	Frequency	%
AGE		
<30 years	21	28.0%
30-40 years	33	44.0%
41-50 years	15	20.0%
➤ 50 years	06	08.0%
GENDER		
Male	56	74.66%
Female	19	25.34%

DISCUSSION

This study was conducted to find out the frequency of appendectomy and causes of perforated appendicitis in

our setup. In this study, 15(20%) patients had perforated appendicitis, 48(64%) had inflamed appendicitis while 10(13.33%) had gangrenous appendix and 2(2.66%) had normal appendix. Main reason for perforation of appendix is obstruction in the lumen of appendix, and the important reason for luminal obstruction is fecolith, which accounts for 90 % of perforation in appendix. Major factors responsible for appendicular perforation are delay in reaching the hospital after the start of symptoms. As more time will pass, the risk of complications tends to be increases. Diagnostic findings of acute inflammation of appendix on ultrasound are presence of blurriness of fat around the appendix with small exudates in periappendiceal region. In various studies the percentage of these findings varies between 68-100%.⁵

Acute obstructive appendicitis occurs due to formation of closed enteric loop with inflammatory infiltration and mucosal edema, formation of pseudo membrane, hemorrhagic infarction, ulcerations, gangrene and finally perforation of the necrotic appendiceal wall. If gangrenous appendicitis perforation occurs, than risk of spillage of its contents in peritoneal cavity increases many fold which results in serious life threatening complications, leading to paralytic ileus, generalized peritonitis and even systemic sepsis.⁶ In our study, the most common cause of perforated appendix was misdiagnosed by doctors as seen in 6(40%) patients followed by delay in reaching hospital seen in 4(26.66%) , while 3(20%) were reluctant for surgery. In the study conducted by, AsadS et al⁷ in 30 (23.08%) of the patients diagnosis was missed initially by physicians and they were sent home as OPD case, while 40 (30.77%) were conservatively treated by non-doctors as such OPD case.

It is most important to diagnose this condition, because if it is missed than it may lead to life threatening complications. On the other hand, its misdiagnosis is one of the five most important medical malpractice categories for law suits against attending doctor. In Pakistan health care system, it is seen frequently that mostly patients are first checked by general practitioner's, quacks etc , and they mostly decide whether should be managed. Because of this delay in referral, the morbidity increases,^{8,9} which may result in increased risk of perforation.¹⁰

In our study, 45(60%) patients had presented with pain in right iliac fossa, 16(21.33%) had fever and 10(13.33%) had nausea. Results of the study conducted by Salahuddin O, also shows that all their patients had presented with pain in the right iliac fossa which was seen in in 24 (66%) patients, while pain in lower abdomen was seen in in 6 (17.5%), in right hemi abdomen in 2 (6%) patients, and diffused pain was found in 4 (10.5%) patients.¹¹ Similarly in study conducted by Rasool AG et al also found that non-medical practitioners, hakeems etc are responsible for

delay in the appendicitis diagnosis.¹² The main presenting cases complaints with acute appendicitis is pain in the abdomen. Categorization of colicky central pain of the abdomen followed by nausea, vomiting and pain radiating to right iliac fossa was 1st described through Murphy. This classical presentation of perforate appendicitis is seen in only 50% of patients. Pain is mostly 24 h of colicky peri-umbilical pain followed by migration to the right iliac fossa. However in study conducted by Hall and Wright¹³ also found right side abdominal pain was found in 83% patients which is main symptom in patients with appendicitis. This progression of pain is because in the start, pain is referred from the visceral innervation of the midgut followed by more localized pain when the parietal peritoneum is involved due to acute inflammatory process. Associated symptoms of appendicitis are nausea, vomiting, loss of appetite. There are many studies which suggest that delay in surgery for appendicitis leads to increase complications.¹⁴⁻¹⁶

CONCLUSION

We concluded that frequency of perforated appendicitis is 20% and its main associated factors are; misdiagnosis by general practitioners and delay in reaching the Hospitals where surgeons and surgical facilities are available. Early diagnosis of appendicitis may reduce the morbidity and mortality. General practitioners should be taken the surgical opinion in patients having pain at right iliac fossae or suspected appendicitis.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Addiss DG, Shaffer N, Fowler BS, Tarr PI. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990;132: 910-25.
2. Schwartz SI. Appendix. In: Schwartz SI, editor. *Principles of surgery*. 6th ed. New York: McGraw Hill; 1994.p.1307-18.
3. Livingston EH, Fomby TB, Woodward WA, Haley RW. Epidemiological similarities between appendicitis and diverticulitis suggesting a common underlying pathogenesis. *Archives Surg* 2011;146(3):308-14.
4. England RJ, Crabbe DC. Delayed diagnosis of appendicitis in children treated with antibiotics. *Pediatr Surg Int* 2006;22(6):541-5.
5. Keyzer C, Tack D, de Maertelaer V, Bohy P, Gavenois PA, Van Gansbeke D. Acute appendicitis: comparison of low-dose and standard-dose unenhanced multi-detector row CT. *Radiol* 2004;232:164-172.
6. Maingot S. *Abdominal Operations*, Eighth Edition, Acute appendicitis 2003;1258-1262.
7. Asad S, Ahmed A, Ahmad S, Ahmed S, Ghaffar S, Khattak IU. Causes of delayed presentation of acute appendicitis and its impact on morbidity and mortality. *J Ayub Medical College Abbottabad* 2015;27(3):620-3.
8. Khalil J, Muqim RU. Impact of delay in acute appendicitis. *Pak J Surg* 2010;26(1):31-5.
9. Jalil A, Shah SA, Saaq M, Zubair M, Riaz U, Habib Y. Alvarado scoring system in prediction of acute appendicitis. *J Coll Physicians Surg Pak* 2011;21(12):753-55.
10. St Peter SD, Aguayo R, Fraser JD, Keckler SJ, Sharp SW, Leys CM, et al. Initial laparoscopic appendectomy versus initial non-operative management and interval appendectomy for perforated appendicitis with abscess: a prospective, randomized trial. *J Pediatr Surg* 2010;45(1):236-40.
11. Salahuddin O, Malik MA, Sajid MA, Azhar M, Dilawar O, Salahuddin A. Acute appendicitis in the elderly; Pakistan Ordnance Factories Hospital, Wah Cantt experience. *Hypertension* 2012;16:64.
12. Basool AG, Obaid M, Akhter MA, Shehbaz L, Nasir S, Ali Z. To determine the factors that affect the delay in diagnosis of acute appendicitis, affecting the morbidity and mortality of patients, at a tertiary care center in Karachi, Pakistan. *Pak J Surg* 2016;32(4):213-7.
13. Elangovan S. Clinical and laboratory findings in acute appendicitis in the elderly. *J Am Board Family Practice* 1996;9(2):75-8.
14. Udgiri N, Curras E, Kella VK, Nagpal K. Cosgrove J: Appendicitis, is it an emergency? *Am Surg* 2011;77 (7): 898-901.
15. Ditillo MF, Dziura JD, Rabinovici R. Is it safe to delay appendectomy in adults with acute appendicitis?. *Ann Surg* 2006;244 (5):656-660.
16. Earley AS, Pryor JP, Kim PK, Hedrick JH, Kurichi JE, Minogue AC, et al. An acute care surgery model improves outcomes in patients with appendicitis. *Ann Surg* 2006;244(4):498-504.

Functional Outcome of Fasciocutaneous Flap Used for Soft Tissue Coverage For Open Tibia Fracture (Gustilo Type IIIB), Remote Area Hospital of Pakistan Experience

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ABSTRACT

Objective: To study the role fasciocutaneous flap as a method of soft-tissue reconstruction in Gustilo type IIIB open tibia fractures, LUMHS experience.

Study Design: Observational study.

Place and Duration of Study: This study was conducted at the Department of Orthopaedics, Liaquat Medical University Hospital, Hyderabad/Jamshoro from 18th Aug 2015 to 18th Jan 2016.

Materials and Methods: A total of 49 patients with open tibia fractures (type IIIB) were selected for this study. Patients were operated using a standard prescribed surgical technique. The quantitative variables were described by mean $\pm$ SD. The qualitative variables were presented by frequency and percentage. Effect modifiers were controlled by stratification. Chi-square test was applied post stratification and p-value ≤ 0.05 was considered as significant.

Results: Mostly young patients were involved in the tibia bone fracture with the mean age of the cases was 38.4 years. Major cause of injury was road traffic accidents 32(65.3%). Anatomically leg was divided in three parts, proximal open tibia fracture were found in 15(30.6%) cases, middle in 20(40.8%) cases and distal in 14(28.6%) cases. Rotational pattern of fasciocutaneous flap was applied in majority of the cases 31(63.3%), while Random pattern fasciocutaneous was used in 11(22.4%) cases and Cross-leg fasciocutaneous was used in 07(14.3%) cases. According to the complications superficial infection was found in 05(10.20%), followed by Tenderness, Pinctact infection, Deep infection, and Marginal Necrosis were found with percentage of 04(8.16%), 02(4.8%), 02(4.8%) and 01(2.4%). External fixation was applied in all the cases and union was found in 42(85.71%) of the cases, while malunion, nonunion, Muscle wasting, Knee stiffness and Ankle stiffness were found with percentage of 05(10.20%), 02(4.8%), 05(10.20%), 08(16.32%) and 06(12.24%).

Conclusion: Fasciocutaneous flap is best option to cover open tibia fracture specially gustilo type III B. It helps to achieve a safe and early durable coverage, avoid nosocomial infection and optimize the healing and facilitate the future reconstruction. The benefit of fasciocutaneous flap is that they have their own blood supply producing a good durable cover.

Key Words: Functional Outcome, Fasciocutaneous flap, Open tibia fracture, Gustilo type IIIB.

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INTRODUCTION

Open tibia fractures are serious wounds to a great extent influencing many peoples and take normally 43 weeks to unite¹. There is 13% non-union rate in well developed centres. There have been various developments in the different procedures to enhance rate of early union of open tibia fractures and early wound coverage for open wounds².

Multidisciplinary and coordinated orthopedic methodology, has additionally prompted critical upgrades in patient outcomes. Gustilo Anderson type IIIB wounds with open tibia fractures is a real challenge for today's clinicians, it needs early and prompt attention, sufficient observation and early flap cover for delicate tissue defect³.

The most widespread injury mechanism in these patients is road traffic accidents. Most of the traumatic injuries to the tibia are caused by motor cycle or automobile accidents. Motor cycle related tibia injuries have high incidence of skin and soft tissues loss. To decrease the morbidity, an activities spectrum is required, including injury prevention, injury surveillance and improvement in care of wound e.g. by use of fasciocutaneous flaps. Fasciocutaneous flaps have been utilized effectively as a part of huge clinical arrangement to early cover for open tibia fractures^{4,5}.

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The vascularity of a bone is more important than alignment and fixation, and in case of subcutaneous bone, the status of soft tissue envelope is the one and only significant factor influencing the outcome. The significant playing point of neighbourhood fasciocutaneous folds is their relative effortlessness of strategy. In open tibia fractures, timing for soft-tissue coverage is controversial. Some promote early flap coverage, while others promote late wound closure. A healthy soft tissue envelope and good vascularity are fundamental factors in the management⁶.

In open fractures delayed wound cover was established as standard of care prior to the advent of current antibiotics, modern debridement methods, and improved fracture stabilization procedures. Currently standard of treatment is early, and aggressive debridement of wounds, early stabilization of the fracture, and initiation of broad-spectrum antibiotics. wound dressings and debridements are done after every 48-72 h, with closure of the wound after final adequate debridement. It has been observed that delayed wound coverage are associated with high infection rate. That is why established open fracture management is based on initial wound debridement and lavage, stabilization of fracture, and early wound closure. Purpose of this study is to assess the efficacy of fasciocutaneous flaps, in covering soft tissue defects in open tibial fractures, Gustilo IIIB at Liaquat Medical university Hospital Hyderabad/Jamshoro (LUMHS).

MATERIALS AND METHODS

This study was conducted in Department of Orthopaedics at Liaquat Medical University Hospital Hyderabad/Jamshoro Pakistan. Duration of study was one year between 18th Aug 2015 to 18th Jan 2016. In this study total 49 cases of open tibia fracture (Gustilo type IIIB) were included. Initial resuscitation of all trauma patients was carried out following advanced trauma life support guidelines. Soft tissue reconstruction was carried out within 2-5 days of initial trauma. Before the procedure complete blood base line (Blood CP, RFT, LFT. Coagulation profile, Blood sugar, Hepatitis B and C profile) workup was done, for preanesthesia assessment. Xrays were taken in two planes. Patients were resuscitated in A/E department . Analgesia, antibiotics, Iv fluids, Blood, and tetanus prophylaxis were given. Wounds were washed thoroughly with copious amount of normal saline, betadine, and hydrogen peroxide. wounds were classified according to gustilo Anderson classification system and only patients with type IIIB were sorted out for this study. Limbs were splinted After preop anesthesia assessment patients were prepared for operation theatre where fractures were fixed with external fixator. Soft-tissue defect with bone exposed at the fracture site were covered by using the fasciocutaneous flap. Donor site from where the flap

was raised the secondary defect were covered with SSG harvested from thigh. All patients were kept on iv antibiotics for 7 days, changed to oral from 8th day for one wk . Analgesia was given and supportive treatment was given. Flap was monitored regularly for any hematoma or infection. Graft dressing was carried out on 7th post-operative day and flap sutures were removed on the 14th post-operative day. Patient was discharge with advised to follow up regularly in OPD. All patients were followed clinically and radiologically until bony union or for 1 year. Post-operatively, external fixation was removed once union was confirmed radiologically.

RESULTS

Generally young patients were involved in our study, the mean age was 38.4 years. Men were observed in the majority 41(83.67%), women 08(12.33%). Mean duration of the injury was found 8.2 ± 3.7 Months. Mostly patients were injured due to road traffic accident 32(65.3%), following by Fall from height, Slip, Gunshot with percentage of 06(12.2%), 08(16.3%) and 03(6.1%) respectively (Table No.1).

Table No.1: Demographic Variable

Variable	No. Patients	Percentage
Gender		
• Male	41	83.67%
• Female	08	12.33%
Mode of Injury		
• RTA	32	65.3%
• Fall from height	06	12.2%
• Slip	08	16.33%
• Gun shot	03	6.1%
Site Of Fracture		
• Proximal	15	30.6%
• Middle	20	40.8%
• Distal	14	28.6%
Types of fasciocutaneous flap		
• Cross-leg	07	14.3%
• Random pattern	11	22.4%
• Rotational	31	63.3%

According to site of fracture proximal fracture were found in 15(30.6%) cases, middle in 20(40.8%) cases and distal in 14(28.6%) cases. Rotational pattern fasciocutaneous flap was applied in majority of the cases 31(63.3%), while Random pattern fasciocutaneous was used in 11(22.4%) cases and Cross-leg fasciocutaneous was used in the 07(14.3%) of cases. According to the complications, superficial infection was found in 05(10.20%), following by Tenderness, Pinctact infection, Deep infection , and Marginal Necrosis were found with percentage of

04(8.16%), 02(4.8%), 02(4.8%) and 01(2.4%) (Chart No.1). External fixation was applied in all the cases and union was found in 42(85.71%) of the cases, while Male union, Non union, Muscle wasting, Knee stiffness and Ankle stiffness were found with percentage of 05(10.20%), 02(4.8%), 05(10.20%), 08(16.32%) and 06(12.24%) (Chart No.2).

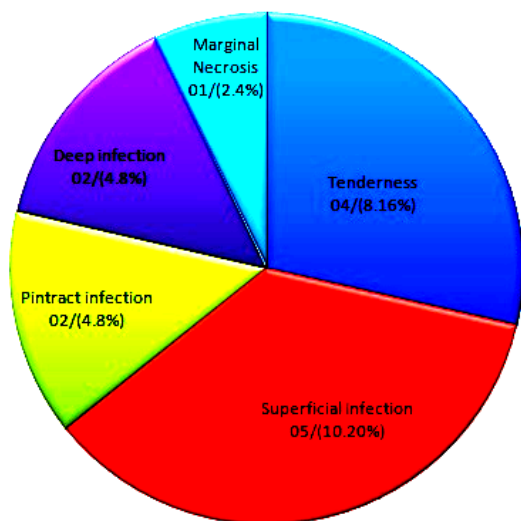


Chart No.1: Distribution of the Cases According To Complications N=49

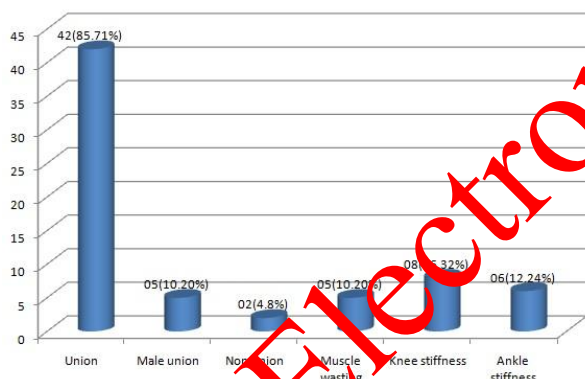


Chart No.2: Distribution of the Cases According To Final Assessment N=49

DISCUSSION

Tibia is the most usually fractured long bone because of its superficial position. Fracture of tibia is common in all ages and is a major reason for morbidity in cases with lower limit injuries. The mean age of 50 cases was (33.28 ± 13.83) years with the youngest patient being 17 years of age and oldest 60 years. Similarly in this series mostly young patients were involved in the tibia bone fracture with the mean age of the cases was $38. \pm 7.2$ years. In this study male were found in the majority 41(83.67%) as compare to female 08 (12.33%). 88% patients were male and 12% patients were female. This shows that in our society male are more exposed to

accidents. 56 cases of tibia fractures in India in which 52 were male and only 4 were female and road traffic accidents was cause in most of cases. Another study by Ali et al⁷ conducted in Karachi, Pakistan, also noted a demography of 88.39% male patients and 14.6% female patients with tibia fractures. In this study rotational pattern fasciocutaneous was applied in majority of the cases 31(63.3%), while Random pattern fasciocutaneous was used in 11(22.4%) cases and Cross-leg fasciocutaneous was used in the 07(14.3%) of the cases. There are several procedure that have been described for the coverage of defects in distal third Leg and foot starting from the simple split thickness skin graft^{10,11} to the different types of the flaps including muscle flap¹² septocutaneous flap, axial flaps and free flaps⁶. In this study external fixation was applied in all the cases and union was found in 42(85.71%) of the cases, while Male union, Non union, Muscle wasting, Knee stiffness and Ankle stiffness were found with percentage of 05(10.20%), 02(4.8%), 05(10.20%), 08(16.32%) and 06(12.24%). Irfanullah Khan et al⁷ reported that overall union rate was 92% and average time to union was comparable to previous studies. Drosos et al.¹³ fixed 157 fractures and shown overall union rate of 97.5% with average time to union 25.8 weeks. In another study by Nork et al.¹⁴ who operated 36 tibial fractures and had mean union time of 23.5 weeks. In another study, the overall union rate was 90.6% and average time to union was 24 weeks. Shah et al.¹⁵ fixed 36 tibial fractures and his overall union rate was 97.2% and mean time to union was 22 weeks.

In our study according to the complications superficial infection was found in 05(10.20%), followed by Tenderness, Pintact infection, Deep infection, and Marginal Necrosis were found with percentage of 04(8.16%), 02(4.8%), 02(4.8%) and 01(2.4%). Shah et al.¹⁵ reported 36 fractures achieved 86.1% union within 6 months, 11.1% delayed union and 2.77% non-union. Drosos et al.¹³ had 75.2% union in 6 months, 12.4% delayed union and 12.4% nonunion. The external fixation techniques enables early postoperative functioning and rehabilitation of limits which decrease the treatment period and offers good outcome. Shaw et al.¹⁶ achieved 100% union in a 44 closed group of tibial shaft fractures and open fractures Gustilo type I and Gustilo type II, treated with the external fixation technique. Keating et al¹⁷. achieved 95% union proportion after the external fixation of 100 fractures of tibial shaft (53 open and 47 closed) with Orthofix external fixator. The same authors had 6 per cent nonunion in the same series after the external fixation, 14 per cent malunion after the external fixation of closed tibial shaft fractures, and 32 per cent malunion after the external fixation of open fractures. Krettek et al¹⁸ obtained 10.9 per cent nonunion after the external fixation of 202 tibial shaft fractures (70 closed and 132 open).

CONCLUSION

The goals of soft-tissue coverage in open fractures are to achieve a safe and early durable coverage, avoid nosocomial infection and optimize the healing and facilitate the future reconstruction. Advantages of fasciocutaneous flap is that they have their own blood supply produce good durable cover and can be reopened for bony surgery. The timing of wound closure is debatable and that delayed primary closure at 5-7 days is probably optimal. This study provides better outcome with early local fasciocutaneous flap coverage with less hospital, early rehabilitation, help in early fracture union, and decreased infection.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. "Chan JK, Harry L, Williams G, Nanchahal J. Soft-tissue reconstruction of open fractures of the lower limb: muscle versus fasciocutaneous flaps. *Plast Reconstr Surg* 2012;130(2):284-295."
2. Lissenberg-Thunnissen SN. Use and efficacy of bone morphogenetic proteins in fracture healing. *Int Orthop* 2011;35(9):1271-1280.
3. Mackenzie EJ, et al. The impact of trauma-center care on functional outcomes following major lower-limb trauma. *J Bone Joint Surg Am.* 2008; 90(1):101-9.
4. Hussain SH, Khalid, Khan AS, Afsar SS. External fixator in the treatment of open Fractures of tibia. *JPMI* 2011;25;1:62- 67.
5. Iqbal MZ, Malik MR2, Azeem M, Mehbub U. Soft tissue defects in open tibial fractures and their management by fasciocutaneous flaps. *J SZMC* 2010;1(3):98-100.
6. Hong JP, et al. The use of an anterolateral thigh perforator flaps in chronic osteomyelitis of the lower extremity. *Plast Reconstr Surg* 2005; 115(1): 142-7.
7. Ali A, Anjum MP, Humail SM, Qureshi MA. Results of interlocking nails in tibialdiaphyseal fractures. *JPOA* 2009;21:36-44.
8. Hartrampf CR Jr, Schefflan M, Bostwick J. The flexor digitorum brevis muscle island flaps. A new dimension in heel reconstruction. *Plast Reconstr Surg* 1980; 66: 264-70.
9. Townsend PL. An inferiorly based soleus muscle flap. *Brit J Plast Surg* 1978; 31: 210-3.
10. Yoshimura M, Imura S, Shimamura K, Yamauchi S, Nomura S. Peroneal flap for reconstruction in the extremity: Preliminary report. *Plast Reconstr Surg* 1984;74: 402-9.
11. Chang SM, Zhang F, Yu GR, Hou CL, Gu YD. Modified distally based peroneal artery perforator flap for reconstruction of foot and ankle. *Micro Surg* 2000; 24: 430-6.
12. Lin SD, Chou CK, Lin TM, Wang HJ, Lai CS. The distally based lateral adipofacial flap. *Brit J Plast Surg* 1998;51: 96-102.
13. Drosos GI, Bishay M, Karnezis IA, Alegakis AK. Factors affecting fracture healing after Intramedullary nailing of the tibial diaphysis for closed and grade I open fractures. *J Bone Joint Surg* 2006; 88:227-31.
14. Nork SE, Schwartz AK, Agel J, Holt SK, Schrick JL, Winquist RA. Intramedullary nailing of distal metaphyseal tibial fractures. *J Bone Joint Surg* 2003; 87:1213-21.
15. Shah RK, Moehring HD, Singh RP, Dhakal A. Surgical Implant generation network (SIGN) Intramedullary nailing of open fractures of the tibia. *Int Orthop* 2004;28:163-66.
16. Shaw DL, Lawton JO. External fixation for tibial fractures: clinical results and cost effectiveness. *J R Coll Surg Edinb* 1995;40(5): 344-6.
17. Keating JF, Gardner E, Leach WJ, Macpherson S, Abrami G. Management of tibial fractures with the orthofix dynamic external fixator. *J R Coll Surg Edinb* 1991;36(4): 272-7.
18. Krettek C, Haas N, Tscherne H. Results of treatment of 202 fresh tibial shaft fractures, managed with unilateral external fixation (monofixateur). *Unfallchirurg* 1989; 92(9): 440-52.

Functional Outcome of Diaphyseal Tibial Fractures Treated by Intramedullary Interlocking Nail, LUMHS Experience

Diaphyseal Tibial Fractures Treated by Interlocking Nail

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ABSTRACT

Objective: To evaluate the functional outcome of Diaphyseal Tibial Fractures treated by Intramedullary interlocking nail by looking at the rate of infection, time of union and knee range of motions.

Study Design: Non randomized controlled trial.

Place and Duration of Study: This study was conducted at the Orthopedic Department of Liaquat University of Medical and health Science Jamshoro from January 2016 July 2016.

Materials and Methods: Forty patients with diaphyseal tibia fractures (the fractures 7cm below the articular surface of knee and 4 cm above the ankle joint) were included in this study. Diagnosis was made on clinical grounds & radiological examination. Closed intramedullary nail were performed in all skeletally mature (the patients whose epiphysis has been united) patients with diaphyseal tibial fracture. Intramedullary interlocking nail were performed in static method in all closed as well as open tibial fractures upto Gustillo Anderson type III-b. Skeletally immature patients, patients who showed signs and symptoms of infection at the site to be operated or elsewhere in the body, pathological fractures, having any medical illness which effect the bone healing, any previous knee or ankle disease and Gustilo Anderson open fractures with neuro-vascular injuries (Gustilo III-C) were excluded from the study.

Results: In our study there were 34 (85%) male, 6 (15%) female patients with mean age of 42 yrs. 27 (67.5%) patients presented with close fractures, while 13 (23.5%) patients had open fractures. 10 (25%) patients were operated within six hours and remaining 30 (75%) were operated within 24 hours. No patient had any infection either deep or superficial, at the end of our study. Wounds of all of the patients became clean at the end of 12th week. Full weight bearing was allowed to 39 (97.56%) patients at the end of 24th wks. At the end of our study most of our patient's 40 (100%) got knee range of motion from 0 to 135 degree. Fracture union was observed in 39 (97.5%) patients, while one (2.5%) patients did not show any sign of union at the end of study. The overall results were excellent in both close as well as open fractures.

Conclusion: Intramedullary interlocking nail is the treatment of choice in all diaphyseal tibial fractures. Both open and closed fractures can be managed effectively by this method of treatment. It provides early mobilization of the patient and decreases hospital stay. Early rehabilitation and early return to work makes it economical for the patients.

Key Words: Tibial Shaft Fractures, Intramedullary Interlocking Nail, Intramedullary Fixation, and Diaphyseal Tibia Fracture

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INTRODUCTION

Fractures of the tibia and the fibula are subject of ongoing controversy and discussion. Despite newer innovations in implants and external fixation devices, tibial fractures essentially remain unresolved; they are among the most challenging fractures to be treated by an orthopedic surgeon.

This problem is predominantly attributed to the high prevalence of concomitant closed and open soft-tissue injuries. Approximately, 90% of all open tibial fractures are located in the shaft.¹ The annual incidence has been estimated to be 5.6 per 100,000 persons a year.² Significant rates of infection, non or delayed union are reported complications of those injuries.^{2,3}

The ideal treatment for open fractures of the tibia is less clear. However, Intramedullary (IM) nailing has been the treatment of choice for closed diaphyseal tibial fracture as demonstrated by excellent results of multiple clinical studies.¹ Twenty years ago an open fracture was the classical indication for the treatment with an external fixator.⁴ Since the 1990s, a number of studies demonstrated favorable outcomes with intramedullary nailing, resulting in amendment of policy. Advances in

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the surgical technique, antibiotic therapy, and tissue coverage have occurred concurrently, enabling surgeons to reduce the rates of infection and improve overall clinical outcomes in open fractures. Delayed-union, non-union and knee range of motion remains a challenging complication not only in the treatment of open but also closed tibial shaft fractures.

Patients with open fractures are known to be at higher risk for superficial or deep wound infection, soft tissue infection or acute purulent infection of the medullary cavity.^{5,6} The literature shows deep wound infection rates in open tibial fractures treated by intramedullary nails, varying greatly from 2.5% to 33.3%.⁷⁻¹¹ In a current multicenter analysis of open tibial fractures treated with unreamed, small diameter tibial nails, Gaebler et al. published a rate of deep wound infections ranging from 2.5% to 5.4%.¹⁰

Delayed union of tibial fractures treated by intramedullary interlocking nails range for 0%–11% for closed and from 9% to 47% for open fractures. In published data, non-union occurs in 0% to 8% of the closed and 3% to 17% of the open cases.^{9,12-15} In Gustilo type I fractures, the average time to union was 19 weeks, whereas for Gustilo types II and III, it was 26 and 39 weeks, respectively.¹⁶

The objective of the study was to evaluate the functional outcome of diaphyseal tibia fracture treated by closed intramedullary interlocking nail by looking at the rate of infection, time of union and knee range of motions. This study was undertaken with the view to have a clear picture of the intramedullary interlocking nailing modality, so the same could be used in future in diaphyseal tibial fracture with confidence

MATERIALS AND METHODS

This was a non randomized controlled trial of patients with diaphyseal tibia fracture treated by intramedullary interlocking nail. Study was conducted at Orthopaedic department of our hospital. Duration of study was six months from November 2007 to December 2008.

Forty patients with diaphyseal tibia fractures (the fractures 7cm below the articular surface of knee and 4 cm above the ankle joint) were included in this study. Diagnosis was made on clinical grounds & radiological examination. Closed intramedullary nail were performed in all skeletally mature (the patients whose epiphysis has been united) patients with diaphyseal tibial fracture. Intramedullary interlocking nail were performed in static method in all closed as well as open tibial fractures upto Gustillo Anderson type III-b. Skeletally immature patients, patients who showed signs and symptoms of infection at the site to be operated or elsewhere in the body, pathological fractures, having any medical illness which effect the bone healing, any previous knee or ankle disease and Gustilo Anderson open fractures with neuro-vascular injuries (Gustilo III-C) were excluded from the study.

The functional outcome was measured in terms of the rate of infection. Union was assessed both clinically and radiologically. Clinical assessment was done for local tenderness; radiological assessment was done with presence of callus or loss of fracture line. Knee range of motions was measured with the help of Goniometer. Normal range of movements was taken from 0° to 135°.

RESULTS

A total of 40 patients with diaphyseal tibial fracture diagnosed on clinical and radiological examination by taking X-ray AP and lateral view. The average age of the patients was 42.57 ± 13.45 years. Out of 40 patients, 34 (85%) were males and 06 (15%) females with 5.7: 1 male to female ratio. Regarding type and sub type of fracture, linear type of fracture was observed in 20 (50%) patients in whom subtype linear fracture was transfer 14 (35%), oblique 4 (10%) and spiral 2 (5%). Comminuted type of fracture was observed in 16 (40%) patients and segmental type fracture was in 4 (10%) patients as shown table 1. According to the modified Gustilo- Anderson classification: Out of 13(32.5%) open fracture, type I was the most common that was found in 11 (84.6%) patients, 1 (7.7%) type II fracture, 1 (7.7%) type III-A.

Superficial infection was found in 4 (10%) patients at 2nd weeks follow-up but at 12 weeks infection was completely resolved ($p=0.012$) as shown in table 2. Partial weight bearing at 6th week and full weight bearing were allowed after clinical and radiological evidence of union. 34(85%) patients were allowed partial weight bearing in 6 week, while 4(15%) patients were not allowed weight bearing in 6th weeks (Table 3).

Table No.1: Type and Subtype of Fracture (n=40)

Type of Fracture	Number of patients	Percentage
Linear	20	50
Transfer	14	35
Oblique	4	10
Spiral	2	05
Comminuted	16	40
Comminuted < 50%	10	25
Comminuted > 50%	6	15
Segmental	4	10
Two level	4	10
Type of open fracture	13	32.5
Type I	11	27.5
Type II	1	2.5
Type III-A	1	2.5
TYPE III-B	0	0

36(90%) patients were allowed full weight bearing in 12th weeks while 4 (10%) patients were not allowed. 22(55%) patients were allowed full weight bearing in 18th weeks and 18 (45%) patients were allowed full weight bearing in 18th week. Finally at 24th week

39(97.5%) patients allowed full weight bearing while 1 (2.5%) patient was only allowed partial weight bearing ($p=0.0001$), as shown in table 3.

Radiological evidence of union according to follow-up visit of patients is presented in table 3. Union occurred in 39 (97.5%) cases in 24th weeks while one (2.5%) case had non-union at 24 weeks ($p=0.0005$), as shown in table 3. Range of motion according to follow-up is presented in table 3. Four patients 10% patients had range of motion was 0 to 125° and one patients (2.5%) had 0-90° range of motion but at 18th weeks all patients had improved their range of motion ($p=0.002$).

Table No.2: Postoperative complications:

Complications	Follow-Up Visit				
	2-Weeks	6-Weeks	12-Weeks	18-Weeks	24-weeks
Wound condition					P=0.0005
Clean	32 (80)	35 (87.5)	38 (95)	39 (97.5)	40(100)
Inflamed	08 (20)	05 (12.5)	02 (05)	01 (2.5)	0 (0)
Condition of infection					P=0.012
Non	36 (90)	38 (95)	40 (100)		
Superficial Infection	04 (10)	02 (05)	0 (0)		
Deep Infection	0 (0)	0 (0)	0 (0)		

Table No.3: Postoperative outcome

Outcome	Follow-Up Visit				
	2-Weeks	6-Weeks	12-Weeks	18-Weeks	24-weeks
Weight bearing					P-value 0.0001
Non	40 (100)	6 (15)	4 (10)	0 (0)	0 (0)
Partial	NA	34 (85)	36 (90)	22 (55)	1 (2.5)
Complete	NA	NA	0 (0)	18 (45)	39 (97.5)
Radiological union				P-value	0.0005
Non	40(100)	40(100)	1(2.5)	1(2.5)	1(2.5)
Progress in union	0(0)	0(0)	39(97.5)	29(72.5)	0(0)
Union	0(0)	0(0)	0(0)	10(25)	39 (97.5)
Range of motion					P=0.002
0-90°	1(2.5)	0(0)	0(0)	0(0)	--
0-125°	4(10)	4(10)	1(2.5)	39(97.5)	--
0-135°	35(87.5)	36(90)	0(0)	40(100)	--

DISCUSSION

Tibial shaft fractures are the most challenging fractures to fix for an Orthopedic Surgeon. Most of our

patients were young and very active. As most of the young patient's live active life, motorbike is their favorite vehicle to drive. That is the reason males are affected more common than females in our study. In our study 34 (85%) males are affected while remaining six (15%) were females. Study conducted in Toulouse by Bonneville P and friends in 2003 show involvement of 34 men (85%) and 15 women (15%).¹⁷ International studies show little difference as compared to our local studies because of cultural difference. Out of 13 open fractures, 11 were type I, one was type II and remaining one was type III A according Gustilo-Anderson classification¹⁸.

Only 10 (25%) patients received definitive treatment within 6 hours of injury. The remaining 30 (75%) of the patient's management was delayed. The causes of delay in definitive treatment were so many; out of them the most common was late presentation in our hospital. Out of 13 patients (32.5%) who presented with open fractures, 7 (17.5%) were operated within six hours in our hospital. All other patients were operated within 24 hours. In western world most of the tibia fractures were operated within 24 hours as proved by different studies.¹⁹ Our patients were also operated within 24 hours. All the open fractures were operated early, debrided and washed thoroughly and wounds were closed primarily. In the international literature immediate debridement, irrigation of the wound and its primary closure with stabilization of fractures is the routine.²⁰ Due to this protocol we obtain better results especially rate of infection as compared with other Asian studies.²¹ Time of union is as per other national and international studies.^{22,23} i.e: between 17 – 24 weeks. None of our patients were allowed full weight bearing in the first week of their operation. Partial weight bearing was allowed at 6th week and full weight bearing after clinical and radiological evidence of union. 36(90%) were allowed full weight bearing in 12th week while 4(10%) were not allowed. Finally at 24th week 39(97.5%) patients were allowed full weight bearing while only 1(2.5%) remained partial weight bearing at the end of our study because of associated ankle fracture on same side. Union was achieved in almost all patients, the radiological and as well as clinical union was achieved in our 39 (97.5%) patients. only one patient did not have radiological sign of union, although clinically he was pain free and was allowed full wt bearing at the end of this study. International studies also suggest excellent result in regard of union in diaphyseal fractures of tibia.²⁵ None of our patient got any wound infection either superficial or deep.

Knee range of motions remained remarkable at the end of our study. 35(87.5%) patients got almost full range of motions of knee at the end of 2 weeks, while 4(10%) patient's knee range of motions were restricted, they were able to move their knees from 0 to 125 degrees, while one (2.5%) had range of motion up to 90 degrees. This was because of lack of exercises and physiotherapy by these patients. At the end of our study all patients were able to move their knees with in full range of motion (0 to 135 degrees). As comparing with other national and international studies none of our patients had postoperative complications like infection, knee stiffness, and malunion, screw breakage, misplacement of screw.^{26,28}

Our study is comparable to other international studies. As compared to our national studies our study is so far superior to all other studies, due to better modern facilities with trained and experienced staff present in our hospital. Most of our patients were also educated and they were on regular follow-ups in our outpatient department throughout the study period.

CONCLUSION

Intramedullary interlocking nail is the treatment of choice in all diaphyseal tibia fractures. Both open and closed fractures can be managed effectively by this method of treatment. Intramedullary interlocking nail is now recommended worldwide. It provides early mobilization of the patient and decreases hospital stay, thus total cost of treatment is reduced. Early rehabilitation and early return to work make it more important and economical for the patients.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

- Schmidt AH, Finkemeier CG, Tornetta P. Treatment of closed tibial fractures. *Instr Course Lect* 2003;52:607–22.
- Court-Brown CM, Rimmer S, Prakash U, McQueen MM. The epidemiology of open long bone fractures. *Injury* 1998;29:529–34.
- Court-Brown CM, McBirnie J. The epidemiology of tibial fractures. *J Bone Joint Surg Br* 1995;77:417–21.
- Bach AW, Hansen ST Jr. Plates versus external fixation in severe open tibial shaft fractures. A randomized trial. *Clin Orthop Relat Res* 1989;241:89–94.
- Ostermann PA, Henry SL, Seligson D. Timing of wound closure in severe compound fractures. *Orthopedics* 1994;17:397–9.
- Seligson D, Klemm K. Adult posttraumatic osteomyelitis of the tibial diaphysis of the tibial shaft. *Clin Orthop Relat Res* 1999;360:30–6.
- Henley MB, Chapman JR, Agel J, Harvey EJ, Whorton AM, Swiontkowski MF. Treatment of type II, IIIA, and IIIB open fractures of the tibial shaft: a prospective comparison of unreamed interlocking intramedullary nails and halfpin external fixators. *J Orthop Trauma* 1998;12:1–7.
- Keating JF, O'Brien PJ, Blachut PA, Meek RN, Broekhuysen HM. Locking intramedullary nailing with and without reaming for open fractures of the tibial shaft. A prospective, randomized study. *J Bone Joint Surg Am* 1997;79:334–41.
- Bonatus T, Olson SA, Lee S, Chapman MW. Nonreamed locking intramedullary nailing for open fractures of the tibia. *Clin Orthop Relat Res* 1997;339:53–64.
- Gaebler C, Berger U, Schandelmaier P, et al. Rates and odds ratios for complications in closed and open tibial fractures treated with unreamed, small diameter tibial nails: a multicenter analysis of 467 cases. *J Orthop Trauma* 2001;15:415–23.
- Smith JE. Results of early and delayed internal fixation for tibial shaft fractures. A review of 470 fractures. *J Bone Joint Surg Br* 1974;56B:469–77.
- Puno RM, Vaughan JJ, Stetten ML, Johnson JR. Long-term effects of tibial angular malunion on the knee and ankle joints. *J Orthop Trauma* 1991; 5:247–54.
- Gaebler C, Stanzl-Tschegg S, Heinze G, Holper B, Milne T, Berger G, Vécsei V. Fatigue strength of locking screws and prototypes used in small-diameter tibial nails: a biomechanical study. *J Trauma* 1999;47:379–84.
- Singer RW, Kellam JF. Open tibial diaphyseal fractures. Results of unreamed locked intramedullary nailing. *Clin Orthop Relat Res* 1995;315:114–8.
- Wiss DA, Stetson WB. Unstable fractures of the tibia treated with a reamed intramedullary interlocking nail. *Clin Orthop Relat Res* 1995; 315:56–63.
- Kulshrestha V. Incidence of infection after early intramedullary nailing of open tibial shaft fractures stabilized with pinless external fixators. *Int J Orthopaedic* 2008; 42 (4):401–9.
- Fan CY, Chiang CC, Chuang TY, Chiu FY, Chen TH. Interlocking nails for displaced metaphyseal

- fractures of the distal tibia. *Injury* 2005;36(5): 669-74.
18. Gustilo RB, Anderson JT. Prevention of infection in the treatment of 1,025 open fractures of long bones. *J Bone Joint Surg* 1976; 58:453-8.
19. Gustilo RB. Management of open fractures and complications. *Instr Course Lect* 1982; 31:64-75.
20. Edwards CC, Simmons SC, Browner BD, Weigel MC. Severe open tibial fractures: results treating 202 injuries with external fixation. *Clin Orthop* 1988; 230:98-5.
21. *Rev Chir Orthop Reparatrice Appar Most* 2003; 89:423-32.
22. Blachut PA, O'Brien PJ, Meek RN, Broekhuysen HM. Interlocking intramedullary nailing with and without reaming for the treatment of closed fractures of the tibial shaft: a prospective, randomized study. *J Bone Joint Surg Am* 1997; 79:640-6.
23. Bone LB, Johnson KD. Treatment of tibial fractures by reaming and intramedullary nailing *J Bone Joint Surg* 1986; 68 :877-8.
24. Freedman EL, Johnson EE. Radiographic analysis of tibial fracture malalignment following intramedullary nailing. *Clin Orthop* 1995; 315: 25-33.
25. Reuss BL, Cole JD. Effect of delayed treatment on open tibial shaft fractures. *Am J Orthop* 2007;36: 215-20.
26. Court-Brown CM, Gustilo T, Shaw AD. Knee pain after intramedullary tibial nailing: its incidence, etiology, and outcome. *J Orthop Trauma* 1997; 11:103-5.
27. Orfaly R, Keating JF, O'Brien PJ. Knee pain after tibial nailing: does the entry point matter? *J Bone Joint Surg Br* 1995;77 :976-977.
28. Krettek C, Glüer S, Schandelmaier P, Tscherne H. Intramedullary nailing of open fractures. *Orthopade* 1996; 25: 223-33.

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Gynecological Encounters in Emergency Surgical Procedures

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ABSTRACT

Objective: To determine the incidence and management outcome in female patients who come to general surgeon with acute abdomen due to certain gynecological reason.

Study Design: Descriptive / randomized study

Place and Duration of Study: This study was conducted at the Emergency Department, K.M.C/Civil Hospital Khairpur (Mir's) from 1st August 2014 to 30 May 2016.

Materials and Methods: All those female cases were included in this study, who went through the process of exploratory laparotomy with accidental finding of underlying gynecological pathology. All described cases were documented in specific proforma, tabulated and statically classified and the final results were prepared.

Results: Over the period of two years, 314 female patients were received in A/E department of this hospital with acute abdomen and were managed. Among these 53 (17%) were those patients, where the cause of acute abdomen was certain gynecological pathology. The mean age was 37 years and most of them were married, 42 (79.24%) and multiparous, 35 (66%). Pain in Right lower quadrant was the commonest symptoms, pelvic inflammatory disease 13 (24.53%) was major cause, followed by ovarian torsion 10 (18.86%) and ruptured ovarian cyst 9 (17%). Clinical diagnosis and Ultrasonography were little helpful to reach at correct diagnosis in present series of cases. Here the reason of exploration was due to the clinical findings of appendicitis, its complications or peritonitis.

Conclusion: Acute abdomen in females, requires full clinical, laboratory and radiological evaluation. If such situation arises where gynecological pathology is encountered after exploration, then the gynecological help and advice should be taken before doing any procedure.

Key Words: Acute abdomen in female, exploratory laparotomy, gynecological encounter/

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INTRODUCTION

As a general surgeon we often asked to evaluate acute abdominal pain, when reported in outdoor as well as in emergency room. The differential diagnosis of abdominal pain is broad, and includes disorders of the gastrointestinal, urogenital, gynecologic, vascular, and pulmonary system. During our daily practice sometimes the situation arises, when surgeon is confronted with an unexpected gynecological disorders while doing the exploratory laparotomy. These diseases may or may not be related to pregnancy include torsion of normal ovary, ovarian cyst or mass, hemorrhage or rupture of an ovarian cyst, pyelonephritis pelvic inflammatory disease, acute salpingitis, tubo-ovarian abscess, ectopic pregnancy, pyosalpinx, torsion or degeneration of a uterine fibroid and endometriosis. In certain good hospitals where the departments are established, if such situation is faced then, help is sort out from concerned

gynecological colleague. However in certain circumstances it becomes necessary for the surgeon to take over the role of gynecologist, to perform that required surgical procedure independently with satisfactory results. Up to 13% women, who present to general surgeon having symptoms of acute abdomen, have gynecological problems¹. The commonest general surgical emergency dealt by surgeon all around the world is acute appendicitis², and is also the most common cause of non-gynecological pelvic pain³. Many gynecologic conditions can mimic acute appendicitis, making the diagnosis obscure and controversial between two working departments. Female pelvic pathology may also be confused with other intra-abdominal disease processes. In such situations, complete clinical and physical assessment should include abdomino-pelvic, rectal, vaginal and bimanual examination, in particular to careful inspection for vaginal discharge or bleeding. However, any disease process causing pelvic inflammation may result in cervical motion tenderness, but other diagnoses should not be excluded on the presence of this sign.⁴ For example, diverticulitis may be mimicked by an ovarian cyst or tubo-ovarian abscess on either sides of lower abdomen, pelvic inflammatory disease may be misdiagnosed as generalized peritonitis secondary to a perforated viscera, acute appendicitis and cholecystitis may be confused with ovarian, or uterine pathology in

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the right upper quadrant during pregnancy. In such situations clinical examination becomes more reliable than the scoring method and investigations in diagnosing appendicitis. However even then sometime there is overlapping between acute appendicitis and a right side tubo-ovarian pathologies. Ninety five percent of ectopic pregnancies occur in the uterine tube, usually in the ampullary portion. This an emergency which can mimic the clinical scenario of other acute surgical disorders, like peritonitis secondary to gut perforation. The clinical signs and symptoms of ectopic pregnancy can be variable, if the patient present with hemodynamic instability, urgent laparotomy with simultaneous resuscitation is mandatory.

The purpose of this study is to discuss common obstetrical and gynecological abnormalities, which the general surgeon may encounter, while dealing the female patient with acute abdominal pain. In particular those cases where the diagnosis was unclear before exploration, but recognized per-operatively, have been discussed with their clinical presentation, ultrasound findings and surgical management.

MATERIALS AND METHODS

This randomized prospective study was conducted in 80 bedded, two surgical units of Khairpur Medical College/ Civil Hospital Khairpur Mir's, over the time of 02 years, from 1st August 2014 to 30 May 2016. This is our public sector, newly established Medical College and hospital, which provides health facilities to all sick peoples, without any territorial difference. Those patients who seek medical advice due to any reason, as well as referred from different primary and secondary health care units, come here and get admission to this hospital. In our present study all those pregnant and non-pregnant females patients are included, who presented with severe abdominal pain, in emergency department of KMC/Civil hospital Khairpur. Over all we sort out 314 women over the period of two years, who were admitted in surgical wards for further workup, and full investigations. These reports include, basic blood tests, ultra sound of the abdomen and pelvis, x-rays of abdomen and chest in non-pregnant women, pregnancy test and human gonadotrophic hormone in urine, to rule out early pregnancy. All those haemodynamically unstable patients were resuscitated, prior to any surgical procedure. Among these 314 women, 53 were those, where the reason of abdominal pain was due to underlying gynecological pathology. These all cases were diagnosed per-operatively, earlier to that, diagnosis was not conclusive, even after all possible clinical and laboratory workup was fulfilled. The management of that group of cases, was not only exclusively handled, but also advice and help was seek from available senior gynecological colleague. Latter on those patients were excluded from this study, who were owned by gynecological department from

emergency or after investigations. The data of each case was entered in specifically designed proforma, then tabulated, analyzed and final results were prepared with the help of SPSS.

RESULTS

Out of a total 314 patients in this study, 53 patients (17%) were found to have some gynecological cause of acute abdomen. Age ranges from 15-65 years, and mean age was 37 years, most of the patients were in the childbearing age, 42 patients were married and 11 patients were unmarried. Majority of the patients, 35 (66%) were multipara, 12 (22.64%) were primipara and 06(11.32%) were those, who did not have any past history of pregnancy (Table 1). In this study we also sort out the different gynecological diseases, which we faced while performing the emergency laparotomy. Majority among them was the category of those patients who have pelvic inflammatory disease, 13 (24.53%), after this adnexal torsion (ovarian torsion) 10 (18.86%), and ruptured ovarian cyst, 7 (13.20%) was third frequent cause (Table 2). Clinical features of various gynecological pathologies were mimic by acute abdominal pain in it's different regions, very similar to other surgical causes. Pelvic inflammatory disease (P.I.D) presented with pain in right lower abdominal quadrants, and also associated with nausea, vomiting and fever. Torsion of ovarian cyst also presented with severe right and left lower quadrant pain, and most of them also had nausea and vomiting. In certain number of cases, where the acute abdomen turned out to be secondary to ruptured ovarian cyst, presented clinically with pain all over the abdomen but more marked in both lower quadrants. In 07 cases of uterine perforation and 06 cases of ectopic pregnancy, clinical features were similar to gut perforation, like generalized abdominal pain, guarding and rigidity, which was more marked in lower abdomen and associated with fever, vomiting, raised w.b.c count, with unstable vitals and the state of shock (Table 3).

Table No.1: Age, marital status, and parity. Status of the patients (n=53).314

Characteristics		Number (%)*
Age Category	15-24 years	13 (24.52%)
	25-34 years	15 (28.30%)
	35-44 years	9 (16.98%)
	> 45 years	16(30.19%)
Marital Status	Married	42(79.24%)
	Unmarried	11(20.75%)
Parity	Multipara	35(66%)
	Primipara	12 (22.64%)
	Nullipara	6 (11.32%)

In all the cases ultrasonographic study was also added & performed soon after admission in the emergency department by a trained radiologist. 13(24.53%) cases of P.I.D were misinterpreted clinically either with

appendicitis or perforated gut. That latter diagnosis was also supported by emergency ultrasound modality, except in 03 cases where it reported normal. In 10(18.86%) cases of adnexal torsion (ovarian torsion) findings of ultrasound, co-related with the clinical diagnosis of appendicitis, and in some cases described it's complications. In 09(17%) cases of ruptured ovarian cysts and 07(13.20%) cases of uterine perforations, ultrasound reported free fluid in peritoneal cavity, where clinical diagnosis of peritonitis due to gut perforation was boldly established, followed by exploratory laparotomy. Ruptured ectopic pregnancy was found in those 06 (11.32%) cases where the early ultrasound showed, moderate collection in peritoneal cavity and pelvis, describing these cases of gut perforation with peritonitis. 03 (5.66%) cases of

complicated fibroid and 02(3.77%) cases of endometriosis were also misdiagnosed clinically, and here similarly ultrasound could not recognize actual underlying pathology.(Table 4).

Table No.2: Gynecological acute abdomen causes.

Pathology	n= 53 (%)
Pelvic Inflammatory Disease	13 (24.53%)
Adnexal torsion	10 (18.86%)
Ruptured Ovarian cyst	9 (17%)
Uterine perforation	7 (13.20%)
Ectopic pregnancy	6 (11.32%)
Tubo-ovarian abscess	3 (5.66%)
Complicated fibroids	3 (5.66%)
Endometriosis	2 (3.77%)

Table No.3: Symptoms and Signs at the time of Examination.

	R.L.Q pain	L.L.Q pain	B.L.Q pain	H.G pain	Gen.Abd: pain	Fever	Nausea/vomiting
Pelvic Inflammatory Disease	+	+	+	+	+/-	+/-	+
Adnexal torsion (ovarian cyst)	+/-	+/-	-	-	-	-	+
Ruptured ovarian cyst	+	+	+	+	+/-	+/-	+
Uterine perforation	+	+	+	+	+/-	+	+
Ectopic pregnancy*	+/-	+/-	+/-	+	+	-	-
Tubo- ovarian abscess	+	-	-	+	-	+	+
Complicated fibroids	+/-	+/-	+	+	+	+/-	-
Endometriosis	+/-	+/-	+/-	+/-	+/-	-	-

Table No. 4: Ultra sound findings, clinical diagnosis, per operative diagnosis and procedure.

No. of Patient	Clinical Diagnosis	Ultrasound Findings	Per Operative Diagnosis	Operative Procedure
13(10) (3)	Appendicitis Peritonitis (perforated appendix, gut perforation)	Probe Tenderness +ve dilated loops with collection in R.L.Q & Pelvis Normal report	Pelvic Inflammatory Disease (PID)	Appendectomy Exploratory laparotomy Abdominal cavity toilet and placement of nelaton drain
10	Appendicitis / Appendicular abscess/ Mass	Appendicitis / Appendicular abscess/ Mass	Adnexal torsion	Ovariectomy / salpingoOvariectomy / salpingoophorectomy
9	Peritonitis (gut perforation)	Free fluid in peritoneal cavity/ pelvis	Ruptured Ovarian cyst	Partial Excision of cyst
7	Peritonitis (gut perforation)	Dilated loops of gut with pelvic collection	Uterine perforation	Repair of perforation/ hysterectomy
6	Peritonitis (gut perforation)	Moderate collection in peritoneal cavity/ pelvis	Ruptured Ectopic pregnancy	Salpingectomy salpingo / Oophorectomy
3	Appendicular/ pelvic abscess	Appendicular/ pelvic abscess/ psoas abscess	Tubo-ovarian abscess	Lower midline laparotomy Ovariectomy Salpingectomy peritoneal toilet Placement of nelaton drain
3	Peritonitis/ sub-acute intestinal obstruction	Degenerative changes in fibroid uterus/pelvic mass/collection	Complicated fibroids uterus	Myomectomy/ hysterectomy
2	S.A.I.O/ Mesenteric cyst	Dilated loops with Cystic lesion in bowel/ mesentery	Endometriotic cyst Endometriosis	Exploratory laparotomy Excision/ biopsy

DISCUSSION

Acute abdomen is broad term comprising group of surgical, medical and gynecological life threatening conditions, requiring immediate hospitalization with

close monitoring, and often need surgery. There is a long a list of possible causes of acute abdomen varying from vascular pathology to psychogenic pain, their clinical features are also variable from patient to patient, with identical or totally different disease

entities. It requires careful history taking, thorough clinical examination and appropriate use of laboratory and radiological investigations to reach at correct diagnosis. It is also fact that, sometimes it becomes difficult to diagnose the underline disease in significant number of patients despite all possible measure. The general surgeon continue to face the various gynecological encounters, presenting with acute abdomen⁵⁻⁶. Lower abdominal pain remains challenging and conflict zone between general surgeon and gynecologist. In that respect, there are certain serious conditions in women which must be evaluated and managed properly, when they present in emergency. The commonly faced acute gynecological conditions are pelvic inflammatory disease, ectopic pregnancy, ruptured or twisted ovarian cyst with or without peritonitis, benign and malignant ovarian tumors and endometriosis. These gynecological diseases come in the differential diagnosis of different acute surgical emergencies, like acute appendicitis, perforated appendix, peritonitis, acute intestinal obstruction and haemo-peritoneum etc.^{7,8,9} The correct management of these gynecological condition demands thorough knowledge of female pelvic anatomy and complete knowledge of disease process and their surgical treatment.^{10,11,12} In our present study, we found significant number of patients, which were accidentally encountered with gynecological pathologies while performing routine general surgical procedures. The incidence of these particular encounters remained 17% which compares almost equally with another study in Pakistan, where it is reported 17.59%.¹³ In another overseas center gynecological emergencies mistaken for other surgical emergencies were counted in 12% cases,¹⁴ this is not a significant difference with our rate of mistakes in diagnosis. Another interesting observation was found in this series, that emergency surgeon initially diagnosed gynecological cause only in, 07 patients (11.86%), out of 53 cases, in remaining cases diagnosis was made for rational general surgical conditions. Many of the signs and symptoms of acute appendicitis overlapped with those of the gynecologic disorders in this series of patients. In fact, acute appendicitis has been shown to occur simultaneously with a variety of gynecologic diseases, including endometriosis, ovarian cysts, uterine fibroids, and hydrosalpinx.¹⁵ On physical examination majority of patients have abdominal tenderness localized to the right lower quadrant in over 90% of cases, the others have signs of peritoneal irritation. These features were also described by other peoples working abroad at certain well reputed centers.¹⁶ P.I.D is found a common entity in our series which presented like appendicitis or peritonitis. Similarly pelvic inflammatory disease was the most common gynecological emergency in district hospital kasur, Pakistan.¹⁷ It is thought to be ascending infection from lower genital tract and is a common

complication sexual transmitted disease in women.¹⁸ this is followed by adnexal torsion and ruptured ovarian cyst, which is slightly un matching with the results of other local and foreign studies where ruptured ovarian cyst, supersedes P.I.D.¹³⁻¹⁴ Uterine perforation was present in 13% of our series, whereas septic abortion with uterine perforation accounted in 7% of the gynecological emergencies in a study in Nigeria.¹⁹ Ectopic pregnancy can present with abdominal pain and hemodynamic instability and may be encountered by the general surgeon, and is typically discovered between 06th to 10th weeks of gestation. Ectopic pregnancy is currently the leading cause of death during the first and second trimesters of pregnancy, accounting for 10-15% of all deaths during this time.²⁰ we found ruptured ectopic pregnancy in 06 cases which were all implanted in fallopian tube, and there was moderate collection of blood and clots in peritoneal cavity. Pelvic endometriosis has been reported in 5-15 of all pelvic operations.²¹ we also found 01 cases, where they were present in mesentery and on surface of small gut. We also faced some other rare pathologies which also were masked and misguided by both, clinical findings and ultrasound reports. Though these mentioned cases in this study are routinely dealt by gynecological team, but here they were handled and dealt by general surgeon, either because of unclear diagnosis or when the concerned department was reluctant to own these pathologies.

CONCLUSION

Whenever the acute abdominal emergency is faced in a female, then the underlying gynecological cause should always be kept in mind. Detail history, thorough clinical examination, utilization of possible diagnostic modalities and expert opinion from gynecological colleague, play important role to differentiate between gynecological and surgical causes of acute abdomen.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Brown SB, Eckersley IRT, Dudley HA. The gynecological profile of acute general surgery JR. Coll Surg 1988;33:13-15.
2. Karam AR, Birjawi GA, Sidani CA, et al. Alternative diagnoses of acute appendicitis on helical CT with intravenous and rectal contrast. Clin Imaging 2007;31(2):77-86.
3. Vandermeer FQ, Wong-You-Cheong JJ. Imaging of acute pelvic pain. Clin Obstet Gynecol 2009; 52(1):2-20.
4. Silen W. Cope's Early Diagnosis of the Acute Abdomen. 21st ed. Oxford University Press; Oxford: 2005.

5. Shahid G, Dar HM, Javaid H. A study of gynecological emergencies presenting as acute appendicitis. Proceeding Shaikh Zayed Postgrad Med Inst 2005;19(1):13-17.
6. Parsad H, Rodrigues G, Shenoy R, Role of Ultrasonography in non-traumatic acute abdomen. Int J Radiol 2007; 5:2.
7. livingstone JRB. Gynecological encounters in general surgery Farquar-son's textbook of operative surgery-8th Edition chapter 29.
8. Principles of gynecology – Sir Norman Jeffcott.
9. The Gynecological aspects of emergency surgery: the female Genital organs –J.D.O Loudon Hamilton Bailey- emergency surgery- 11th Edition.
10. FJ. Montz, Jonathan S.Berek: Gynecological pelvic procedures - Mainrgot's Abdominal opeations – Volume II, 10th Edition.
11. Cameron MD.1976 : Gynecological problems and the general.
12. Surgeon – in Hadfield J. Hobsley M, editor. Current surgical practice. 1st ed. Arnold: London; Chapter 15th.
13. Ateeq M. Gynecological Acute Abdomen. Journal of Rawalpindi Medical College (JRMC) 2012;16(1):48-50.
14. Madhuri K, Devi et al. The Study of Gynecological Emergencies in Surgery. JMSCR 2016;4(12): 14857.
15. Song JY, Yordan E, Rotman C. Incidental appendectomy during endoscopic surgery. JSLS 2009;13(3):376–383.
16. Lewis FR, Holcroft JW, Boey J, et al. Appendicitis. A critical review of diagnosis and treatment in 1,000 cases. Arch Surg 1975;110(5):677–684.
17. All S. Shah STA, Gynecological Emergencies, Professional Med J 2007;14(1):43-9.
18. Sweet RL. Treatment strategies for pelvic inflammatory disease. Expert Opin Pharmacother 2009;10(5):823–837.
19. Ibrahim NA, Oludara FO, surgical and Gynecological abdominal emergencies in adult, the Experience of Lagos State University Teaching Hospital, Ikeja, Lagos, State, Nigeria, Nigerian Hospital Practice 2010;5(3-4):31-5.
20. Murray H, Baakdah H, Bardell T, et al. Diagnosis and treatment of ectopic pregnancy. CMAJ 2005; 173(8):905–912.
21. Kisner RW: Gynecology. Principle and practice. Second edition Chicago, year book medical Publisher Inc; 1971.p.440–441.

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Hand Washing Compliance Among Surgeons and Physicians in Tertiary Care Hospital at Multan

Hand Washing
Among Surgeons
and Physicians

Allah Yar Malik¹, Asim Shafi² and Muhammad Siddique Qadri¹

ABSTRACT

Objective: To determine the Surgeons and Physicians compliance with the World Health Organization (WHO) prescribed five moments of hand hygiene.

Study Design: Descriptive / cross-sectional Study

Place and Duration of Study: This study was conducted at the Department of Community Medicine, NMC, Multan. from Dec.1, 2016 to Jan. 31, 2017.

Material and Methods: Non-probability convenient sampling was in this study. Hand washing compliance was compared among Surgeons and Physicians. A survey was performed in all surgical and medical units of teaching institution to observe the hand washing compliance randomly according to the WHO five moments of hand hygiene. Semi-structured proforma was used to collect the data secretly without the knowledge of the personnel who were being observed.

Results: The mean compliance among Surgeons and Physicians was very low, 1.33% and 6.11%, respectively. There was a strong association between surgeons and physicians regarding hand washing at 95% confidence level. ($P < 0.00$). Surgical wards sink to beds ratio was 1:24 and bar soap to beds ratio was 1:48. Medical wards sink to beds ratio was 1:33 and bar soap to beds ratio was 1:49. Alcohol-based hand gel or sanitizer was not available in both Surgical and Medical units during the study period.

Conclusion: Hand washing compliance was very low among surgeons and physicians. The reasons for poor adherence to hand hygiene was non-availability of good numbers of wash basins and bar soap. There is a necessity for regular education, re-education campaign and provision of amenities for hand hygiene.

Key Words: Compliance, hand washing, Surgeon, Physician

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INTRODUCTION

All patients in the hospital care are at risk of community-acquired and hospital-acquired infections. This is known fact since 150 years ago there is a strong association between hand contamination and infection. The hand washing is the main measure of prevention¹. The improvement in hand-washing practices by health care personnel is significantly associated with reduction in community-acquired infection rate.²

Unluckily, compliance with hand hygiene is still very poor at most institutions.^{3, 4} The phobia of hands allergy, distance from wash basins, and a dearth of time, are the main excuses mostly undertaken to explain poor adherence.^{5, 6} Overall hand washing compliance was under 50% in studies carried out in last 20 years^{7, 8}

Lately, the introduction of alcohol-based hand sanitising gel has been effective in snowballing the hand washing compliance, particularly in intensive care units^{9, 10}.

There have been few studies about hand washing; they found potential pathogens on the healthcare workers hands, such as *Staphylococcus aureus*, *E. coli*, *Enterococcus faecalis* and *Pseudomonas aeruginosa*.¹¹

MATERIALS AND METHODS

All four Surgical units and four Medical units were selected to collect data regarding handwashing compliance among Surgeons and Physicians of altogether 1800 bedded, Nishtar Hospital Multan. Teaching Hospital had an infection-control team. There was seven infection control personnel in the teaching hospital. No change was made in the team during the study.

The study was performed in 195 bedded surgical units, and 198 bedded Medical units. The study was carried out at the same time in surgical and medical units during a two-month period, from Dec.1, 2016 to Jan. 31, 2017. The students of fourth-year MBBS were

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divided into two groups to collect the data. One group observed hand washing opportunities for one hour daily during the daytime in surgical units and another group in Medical units under my supervision.

Each member of the study was directly observed. All the Surgeons and Physicians working in the Surgical and Medical units were not informed that the study was being carried out and feedback performance was not reported during the study period.

The following WHO desirable recommendations for hand washing were observed:

- Before and after direct examining the patients
- Before and after invasive procedures (including establishing intravenous line)
- After touching the patient surroundings. (Treatment chart, bed, etc.)

Handwashing Compliance was defined as hand washing with bar soap, Liquid Soap or washing hands with alcohol base hand sanitizer. The use of disposable gloves was also taken as compliance. Univariate analysis to examine the associations between Surgeons and physicians were compared by using Chi-square tests. The level of statistical significance was 0.05. SPSS statistical software 21 was used to analyse the data.

RESULTS

There were 314 opportunities for hand washing among the surgeons and 360 among the physicians

The mean compliance among surgeons and Physicians was 14.33% and 6.11%, respectively. Overall compliance for hand washing was poor however surgeon's compliance was better than physicians. There was a strong association between surgeons and physician regarding hand washing at 95% confidence level. ($P < 0.00$). (Table 1).

Table No.1: Hand washing opportunities compliance among Surgeons and Physicians (n = 674)

Type of Health – Care Worker	Hand washing Performed	Hand washing not performed	Row Total	P- Value
Surgeons	45/314 (14.33%)	269/314 (85.66%)	314	0.00
Physicians	22/360 (6.11%)	338/360 (93.88%)	360	
Column Total	67	607	674	

Surgical units sink to beds ratio was 1:24 and bar soap to beds was 1:48

Medical units sink to beds ratio was 1:33 and bar soap to beds was 1:49

Alcohol-based hand gel or sanitizer was not used in both surgical and Medical during the study time due to its non-availability. (Figure 1)

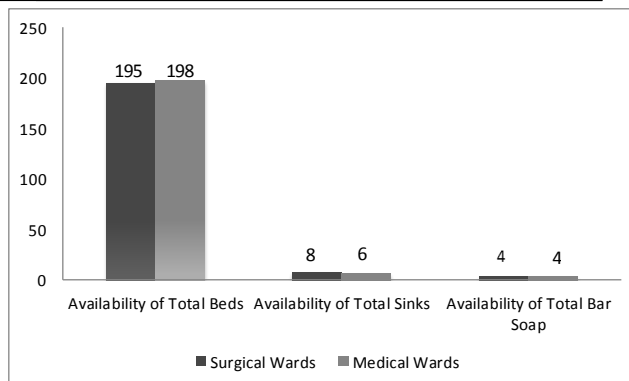


Figure No.1: During the study period, no epidemic outbreak was observed in both surgical and medical units.

DISCUSSION

Our study showed bothersome results: a very poor compliance with hand washing. The mean compliance among surgeons and physicians was 14.33% and 6.11%, respectively. There was a strong association between surgeons and physicians regarding hand washing at 95% confidence level ($P = 0.00$).

We also found an underlying relation between little numbers of wash basins and inadequate hand washing. The poor hand washing adherence was due to non-availability of hand sanitizers, washbasins facility nearby the patient's beds. Lack of education may be an essential factor,

A study was done by Gould D and found that a high demand for hand washing was associated with low compliance which was congruent with the present study¹²

A study was undertaken by Rotter ML. and Pittet D, Mourouga P, Perneger TV. In both studies, it was found that low hand hygiene compliance in tertiary care hospital in spite of infection control team of the hospital. There was the unavailability of hand sanitizer nearby patient's beds. This was consistent with our study^{13, 14}

A study performed in Argentina confirmed that hand washing practices and health-care worker (HCW) education considerably improved HCW adherence to hand hygiene; however, after routine feedback was assimilated, hand washing compliance improved to a far greater degree. Our study did not calculate steps to improve hand washing compliance since we only desired a baseline assessment of hand washing compliance in surgeons and physicians of tertiary care hospital.¹⁵ A study was undertaken by Pittet; it was observed a significant progress in hand hygiene compliance after an educational training program. There was also a reduction in nosocomial infection rates and MRSA communication.¹⁶

In another study, Harbarth also described a surge in hand hygiene obedience in a paediatric hospital, after the start of alcohol-based hand sanitizer and educational struggles.¹⁷ This did not inconsistent with our study, due financial constraints, lack of educational programs and scarcity of hand washing facilities, compliance was very low.

CONCLUSION

Hand washing compliance was very low among surgeons and physicians. The reason for poor adherence to hand hygiene was non-availability of good numbers of wash basins and bar soap. There was a necessity for regular education, re-education campaign and provision of amenities for hand hygiene.

A health education campaign should address properly in the health care workers to enhance their hand washing compliance. Further research studies should be carried out to emphasise issues of concern and achievable solutions of hand washing adherence in Surgeons and Physicians.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Larson EL, 1994 APIC Guidelines Committee. APIC guidelines for hand washing and hand antisepsis in health care settings. *Am J Infection Control* 1995;23(4):251-69.
2. Doebbeling BN, Stanley GL, Sheetz CT, Pfeiffer MA, Houston AK, Annis L, et al. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. *New Engl J Med* 1992;327(2):38-52.
3. Karabey S, Ay P, Derbentli S, Nakipoğlu Y, Esen F. Handwashing frequencies in an intensive care unit. *J Hospi Infec* 2002;50(1):96-101.
4. Roberts L, Bolton F, Asman S. Compliance of hand washing practices: theory versus practice. *Australian Health Review* 1998;21(4):238-44.
5. Voss A, Widmer AF. No Time for Handwashing!? Handwashing Versus Alcoholic Rub Can We Afford 100% Compliance?. *Infection Control & Hospital Epidemiol* 1997;18(03):205-8.
6. Kaplan LM, McGuckin M. Increasing handwashing compliance with more accessible sinks. *Infection Control* 1986;7(08):408-10.
7. McCormick RD, Buchman TL, Maki DG. Double-blind, randomised trial of scheduled use of a novel barrier cream and an oil-containing lotion for protecting the hands of health care workers. *Am J Infect Control* 2000;28(4):302-10.
8. Pittet D. Improving adherence to hand hygiene practice: a multidisciplinary approach. *Emerging infectious dis* 2001;7(2):234.
9. Bischoff WE, Reynolds TM, Sessler CN, Edmond MB, Wenzel RP. Handwashing compliance by health care workers: the impact of introducing an accessible, alcohol-based hand antiseptic. *Archives Internal Med* 2000;160(7):1017-21.
10. Maury E, Alzieu M, Baudel JL, Haram N, Barbut F, Guidet B, et al. Availability of an alcohol solution can improve hand disinfection compliance in an intensive care unit. *Am J Resp Criti Care Med* 2000;162(1):324-7.
11. Nogueras M, Marinsalta N, Roussel M, Notario R. Importance of hand gel contamination in health-care workers as possible carriers of nosocomial infections. *Revista do Instituto de Medicina Tropical de São Paulo* 2001;43(3):149-52.
12. Gould D. Nurses' hand decontamination practice: results of a local study. *J Hospital Infect* 1994; 28(1):15-30.
13. Rotter ML. Hand washing and hand disinfection. *Hospital epidemiology and infection control* 1999;2:1339-55.
14. Pittet D, Mourouga P, Perneger TV. Compliance with hand washing in a teaching hospital. *Ann Int Med* 1999;130(2):126-30.
15. Rosenthal VD, McCormick RD, Guzman S, Villamayor C, Orellano PW. Effect of education and performance feedback on hand washing: the benefit of administrative support in Argentinean hospitals. *Am J infect Control* 2003;31(2):85-92.
16. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *The Lancet* 2000;356(9238):1307-12.
17. Harbarth S, Pittet D, Grady L, Zawacki A, Potter-Bynoe G, Samore MH, et al. Interventional study to evaluate the impact of an alcohol-based hand gel in improving hand hygiene compliance. *The Paediatric Infect Dis J* 2002;21(6):489-95.

Maternal and Fetal Outcome in Placenta Praevia

Farah Naz Aziz¹ and Riaz Ahmad²

ABSTRACT

Objectives: To determine maternal outcome in terms of morbidity and mortality in cases of placenta praevia to determine the fetal outcome regarding morbidity and mortality in placenta praevia.

Study Design: Observational / descriptive study.

Place and Duration of Study: This study was conducted at the Aziz Bhatti Shaheed Hospital NSMC, University of Gujrat, for a period of one year 2015 and 2016.

Materials and Methods: Two types of patients were included in the study. The booked patients who were diagnosed by routine ultrasonography as cases of placenta praevia and the patients who presented with vaginal bleeding and were diagnosed by ultrasonography. The babies were followed up for seven days and maternal condition for six weeks after delivery.

Results: Total no of the patients included in this study was 104 and was done for a period of one year 2015-16 at Aziz Bhatti Hospital NSMC Gujrat. Majority of the patients who presented were multigravida and none of the primigravida had placenta praevia. Mean gestational age was 33.4 weeks, 1.92% of the cases had previous c-section. The patients who required admission for more than once were 19.23%, 46.15% of the patients had previous episode of bleeding. The patients who required blood transfusion were 65.3%. Eighty four percent patient had c section and the patient with PPH were 7.69%, 1.92% had cesarean hysterectomy and one patient died because of hemorrhage. The incidence of premature deliveries was 55.76%, and the percentage of the neonates who died because of this were 11.53%.

Conclusion: It is concluded, that in a country like ours, placenta praevia is still one of the important causes of fetal mortality and maternal morbidity. These cases should be screened and should be managed expectantly as suggested by Macafee. These cases should be managed in centres where facilities for advanced surgery, specialized anesthesia, ICU, blood transfusion and blood products and neonatal intensive care units are there and system should be backed by a proper referral facility.

Key Words: Placenta, Praevia, Maternal Mortality, Hemorrhage, Prematurity, Neonatal

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INTRODUCTION

The placenta which is implanted entirely or in part in the lower uterine segment is called placenta praevia. Minor degrees of placenta praevia include the lateral and marginal placenta praevia (type I and type II). Type I encroaches on the lower uterine segment and the marginal reaches the internal OS. The major degrees of placenta praevia are type III and type IV. Type-III partially covers part of the OS and complete type-IV covers whole of the OS. The incidence of placenta praevia is about 1 in 200, pregnancies as stated by Macafee in his work on placenta praevia. Croswell JA and associates¹ found that overall prevalence of placenta praevia was 52/1000 pregnancies.

Prevalence was highest among Asian (12.2/1000 95% CI 9.5-15.2) 3.6 / 1000 pregnancies in Europe, 2.9/1000 pregnancies in North America and Sub-Saharan Africa.

Ojha N in his study² found that placenta praevia contributed to .55% of the deliveries. The incidence of major placenta praevia was 21.4%, one patient required hysterectomy and ten patients required blood transfusions.

Low implantation was observed in 5-28% of pregnancies during the 2nd trimester on ultrasonography, but as the uterus grows the placental site appears to migrate upward and by term only 3% are previas.

Two percent of those with low lying placenta before 24 weeks, 5% of those at 24-29 weeks and 23% of those at > 30 weeks will still have a praevia at term. The exact cause is unknown, but the endometrial damage due to multiparity, increased age, previous C-Sections, gynecological operations e.g., ERCP, D&C, increased surface area of the placenta in pregnancies like twins and succenturiate lobe predispose to the occurrence of placenta praevia.

Anisodowleh Nankali and associates in their study found that patients with history of one previous

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c-section had mere chances of placenta previa and need for hysterectomy rather than more than one previous cesarean sections. The most common type of abnormal placentation was accrete, percreta and increta respectively.³

Smoking and cocaine use also predispose to the occurrence of placenta praevia. Cande V Ananth, and associates, found that there⁴ is a positive association between smoking and placental abruption but weak association with placenta previa and other uterine bleeding. The incidence is 0.2% in nulliparous, but it may be as high as 50% in the grand multipara. It occurs in 1% of the pregnancies after a single Cesarean section. The incidence after four to five C-section increases up to 10%, and forty fold increased risk compared with no C-sections. Placenta praevia doubles the risk of congenital anomalies.

The other risk factors for placenta previa are multifetal gestation, increased parity and maternal age.⁵

Placenta previa patients usually present with warning and severe painless hemorrhages and malpresentations late in pregnancy.

The management of patients of placenta praevia was expectant as revised by Macaffe. The aim was to attain the gestational age of 37 weeks with restricted physical mobility of the mother supported by multiple blood transfusions if required and liberal use of caesarean section for delivery of the patient.

Oppenheimer L⁶ stated that the important diagnostic tool is U.S.G. An overlap of more than 15mm (os and edge at 18 to 24 weeks) is associated with an increased likelihood of placenta praevia at term. The os placenta edge at 18-24 weeks is important for planning deliveries. When the placental edge lies > 20mm away from the internal cervical os, women can be offered a trial of labour with a high expectation of success.

The diagnosis was done by clinical presentation and was confirmed by ultrasonography. Placenta accreta may be predicted by a history of previous section, low lying placenta, I.V.F pregnancy, increased fetoproteins and estimation of the BHCG.⁷

When the bleeding is complicated by premature labour it would seem logical to inhibit uterine activity by means of tocolytic agents.

Vaginal delivery would be possible in women with minor degrees of placenta praevia, in whom the placenta is anterior and the head engaged. In such circumstances the bleeding usually controlled by amniotomy augmented by syntocinon infusion.

Amniotomy should only be carried out under anesthesia in an operation theatre with everything prepared for an immediate transfusion and C-section, if the examination provokes heavy bleeding, with the exception already mentioned, delivery by C-section is the method of choice for most women with any degree of placenta praevia

Pregnancy complicated by placenta previa is a high risk pregnancy, and it increases the morbidity and mortality of the mother because of the hemorrhages, these pregnancies are complicated by postpartum hemorrhages because of inadequate occlusion of the sinuses in the lower segment. There are more chances of surgical and anesthetic complications in major degrees of placenta previa. There are increased chances of air embolism. Postpartum sepsis is caused by ascending infection of the raw placental bed. There are 15% chances of placenta accreta in placenta previa and the risk of recurrence is 4% to 8% after one placenta previa. There are chances of DIC in major degrees of placenta previa because of repeated hemorrhages and multiple blood transfusions.

Fetal outcome is poor in cases of placenta previa because of preterm birth, the perinatal mortality increases with decreasing gestational age, the overall perinatal mortality ranges from 42 to 81 per 1000 but much higher in developing countries. Fetal growth restriction may occur in up to 16% of the cases. The incidence of serious malformation of the baby doubles in case of placenta previa. The other complications may be cord prolapse, cord compression, malpresentations, fetal anemia, unexpected intrauterine death because of rupture of vasa previa and severe feto maternal shock.

MATERIALS AND METHODS

The study was carried out for a period of one year in a prospective manner in Aziz Bhatti Shaheed Hospital, NSMC College, and UOG for a period of one year (2014-15) it was an observational descriptive study.

Two types of patients were included in the study, the booked patients who were diagnosed by routine ultrasonography as cases of placenta praevia and the patients who presented in emergency department with the complaint of vaginal bleeding in second or third trimester and were diagnosed as cases of placenta praevia.

The patients who presented with antepartum hemorrhage but were not diagnosed as cases of placenta previa were excluded from the study.

Maternal morbidity was assessed by the number of admissions and blood transfusions required during the pregnancy, the outcome was also measured by the mode of delivery, vaginal or operative, the number of retained placentas in vaginal deliveries.

Serious morbidity and mortality was measured in terms of cesarean hysterectomies.

Fetal outcome was assessed in terms of term and preterm deliveries, prematurity, NICU admissions and neonatal mortality.

The baby was followed up for seven days and maternal condition for six weeks after delivery.

Ultrasonography is of utmost importance in the diagnosis of placenta previa. Both abdominal and vaginal were used in the localization of the placenta.

Additional specific investigations were done according to the diagnostic requirement of the patient e.g. CT scan and MRI to confirm the findings. Statistical analysis was performed by using SPSS version 16.

RESULTS

The total no of the patients included in this study was 104. The number of un-booked patients was 86 as compared to the booked one which were 18%. The majority of the patients were in the age group 25-35 years.

None of the primigravida had placenta praevia and maximum number of the patients were gravida four and above.

Majority of the cases presented with painless vaginal bleeding which in most cases was of the severe variety which usually determines the mode of delivery and leads to perinatal mortality. None of the patients presented with reduced foetal movements, which reveals another factor that intrauterine death is very uncommon in cases of placenta previa, 42.3% of the patients presented with mal-presentation.

Mean gestational age at the time of presentation was 33.4 weeks, and about 59.6% patients presented with severe bleeding with clots.

The pain was only in 3.84% of the patients. However labour was associated in 26.92% of the patients.

E&C was the most common predisposing factor found in this study, 23.07% of patients were with previous history of this procedure.

History of previous C.Section was in 1.92% of the cases. 3.84% of the patients were smokers and the same was the history of previous placenta praevia.

Manual removal of placenta was in 1.92% of the cases and multiple gestations in 0.96%.

Table No.1: Maternal Morbidity in relation with placenta praevia

Morbidity (Foetus)	No. of Patients	Percentage
Patients required hospital admission more than once	20	19.23%
The patients who had previous episodes of bleeding	48	46.15%
No. of Patients who required blood transfusion	68	65.3%

As is obvious in the above table, the patients suffered a lot of morbidity due to placenta praevia because of multiple episodes of bleeding and transfusion as a mode of expectant management of placenta praevia.

About 19.23% required admission in a hospital before the final admission which shows the importance of this problem and why it needs more consideration. There are warning hemorrhages in placenta praevia, these

patients usually have an history of threatened abortions. The table shows that 46.15% of the patients had multiple episodes of bleeding and 65.3% of the patients required blood transfusions.

Table No.2: Maternal Outcome in cases of placenta praevia

Outcome	No. of Patients	Percentage
The patients who delivered vaginally	16	15.38%
The patients who had operative delivery by C-section	88	84.62%
P.P.H	8	7.69%
The patients who had retained placenta	2	1.92%
The Patients who had required caesarean hysterectomy	2	1.92%
The patients who had died due to placenta praevia	1	0.96

About 15.38% of the patients were grade I, out of these 25% had to be delivered vaginally, rest of all the patients were delivered by C-Section.

This shows the complete variety of the placenta praevia which is far greater compared to the minor variety, 7.69% had postpartum hemorrhage which is an important determinant of maternal mortality and morbidity.

There was only one patient with placenta accreta and another percreta for which caesarean hysterectomy had to be performed; however one patient died because of placenta praevia. About 8% of the patients had P.P.H which is an important determinant of the morbidity and mortality. Two patients presented with retained placenta and required cesarean hysterectomy and one patient died because of adherent placenta.

Table No.3: Foetal Outcome - Total no. of Cases =104. Mean gestational age 33.4 Weeks

Outcome	No. of Patients	Percentage
Full term alive delivery after 37 weeks of pregnancy	44	42.30%
Premature alive babies	58	55.76%
Required admission in Nursery	58	55.76%
Still births	2	1.92%
No. of neonates died in cases of placenta praevia	12	11.53%

Table 3 shows the fetal morbidity and perinatal mortality the mean gestational age was 33.4 weeks and about 55.76 of the babies were premature. Almost same percentage of the neonates required emergency

admission, which is in marked contrast to the normal deliveries.

There were only two still births (IUD's) and one was having placental abruption along with placenta praevia, other was with severe vaginal bleeding and could be a case of vasa praevia.

This was in marked contrast to the cases of placental abruption, in which most of the fetuses died in utero.

Out of the alive neonates, 11.53% of the babies died and majority within first week mostly due to the complications of prematurity, but the rate has reduced due to improved pediatric facilities.

DISCUSSION

Hemorrhage is the leading cause of maternal death worldwide and placenta praevia contributes to the hemorrhage as a leading entity, because of its nature and conditions associated with placenta praevia due to prior uterine trauma, previous C-Section, other uterine surgery and previous history of praevia⁸.

As is obvious in table 1, the patients required multiple times admission because of threatening hemorrhages and required multiple blood transfusions, and the morbidity is increased because of the transfusion, and the associated conditions e.g. P.P.H. In this study 65.3% of the patients required blood transfusion.

Multiple admissions or continuous hospitalization increases the cost and the psychological effects of separation on the families, Advantages include, easy resuscitation, prompt delivery and ensuring bed rest and limitation of activities.

Multiple blood transfusions increase the morbidity and sometimes sending with mortality of the mother. The complications could be acute e.g. acute hemolytic reactions leading to DIC, infective shock, transfusion related lung injury, fluid overload, non hemolytic reactions to transfusion of platelets and red cells, severe allergic reaction or anaphylaxis, graft versus host reaction presenting with pancytopenia, abnormal LFTs and deranged U&E and also transfusion related bacterial infections. Delayed complications of transfusion are delayed hemolysis of transfused red cells, development of antibodies to red cells in patients plasma, development of antibodies that react with antigens of white cells or platelets, post transfusion purpura, graft versus host disease, iron overload, infections and immune-modulations.

Regarding the maternal outcome majority (84.62%) required cesarean sections; operative delivery has more mortality because of the emergent nature of the situation, anesthesia related complications and increased incidence of hemorrhage in such cases, thus placenta praevia directly and indirectly leads to increased mortality and morbidity.

Retained placenta is one of the complications of placenta praevia especially if it is of accreta variety.

In a study by Olive E.C.⁹ and associates it was found, that 14% of the patients with placenta praevia suffered a major morbidity. The proportion of the morbidity that occurred among women delivered electively at term was 40% in hospitals with 24 hour blood banks and 55% in other hospitals ($P > 0.06$). In another study¹⁰ Gomal A Kassem and associates stated that incidence of placenta accrete was 25 out of 122 patient. The median intra-operative blood loss was 2,000 ml (mean 3,000 ml) with a loss of > 2000 ml occurring in 72% and > 5000 in 20%. The mean packed red blood cell transfusion requirement was 7.7 and 28% required > 10 units. In this study 1.92% of the patients required cesarean hysterectomy: Lovina S.M. Machado in his study¹¹ stated that the predominant indication for emergency peripartum hysterectomy was because of the placenta praevia accreta which was noted in 45 – 73.3%. The risk factors were previous C. Section, scarred uterus, age and multi parity.

The maternal morbidity ranged from 26.5 – 31.5 and mortality from 0-12.5%. Almost similar results¹² were found by A T Burou and C.F. Shehu in their study. The grand multiparas were more affected (50%) as compared to the multipara. The major types of the placenta (77.1%) were more prevalent than the minor variety (22.9%) most (83.3%) were delivered by C. Section. The maternal mortality was 1% and perinatal deaths (12.5%). Almost same pattern was found in this study. The patient with minor variety delivered vaginally were 15.38% and 84.62% required L.S.C.S.

Bamal A Kassem and Ali K Alzahravi in their study found that because of the increased risk of maternal morbidity placenta accreta should be excluded in all the cases of placenta praevia, especially in those who has uterine surgery, high parity and advanced maternal age. If available a second consultant should share in the surgery of placenta accrete. Elective delivery of patients with placenta accrete at 36 weeks should be considered unless there is maternal risk.¹³

Sheiner et al in this study stated that the pregnancies with placenta praevia had also much co morbidity in the form of higher rates of 2nd trimester bleeding, pathological presentations, abruptio placentae, congenital malformations, perinatal mortality, cesarean delivery, Apgar scores at 5 minutes lower than 7, placenta accreta, postpartum hemorrhage, postpartum anemia and delayed maternal and fetal discharge from the hospital. The maternal mortality from placenta praevia is a rare entity in developed countries now a days, but this is not the case in the developing countries. In this study 84% had caesarean delivery and 1.92% had caesarean hysterectomy, the patient developed disseminated intra vascular coagulation. The patient was with previous history of C. Section and was having placenta percreta.

In a similar study Afshan Ambreen and associates¹⁴ found that maternal mortality among such patients was 1.99% and this was due to P.P.H.

Shruthi Prasanth and associates in their study found that maternal mortality and morbidity is reduced because of placenta previa and it is mainly attributable to an increased use of blood transfusions, effective antibiotic therapy and better understanding of the shock and renal failure.¹⁵

Regarding the fetal outcome, it was found in this study that majority of the deliveries were preterm and mortality and morbidity was due to prematurity. Almost more than half > 55% required admission in the neonatal intensive care unit and the neonatal mortality was > 11%.

The results in this study are comparable with the national and international studies, the mean gestational age of the babies was 33.4 weeks, 58% were premature, 11.5% died and 55.7% required admission in nursery. In their study by Macafee et al,¹⁶ found similar results and suggested, that the expectant management was the answer to reduce their perinatal mortality and they found that fetal mortality reduced from 51% to 11.5%. Rabia Raheel and associates¹⁷ also found the similar findings, and suggested that due to high perinatal deaths associated with placenta praevia, such cases should be delivered in hospital with appropriate facilities.

CONCLUSION

It is concluded, that in a country like ours, placenta praevia is still one of the important causes of fetal mortality and maternal morbidity. These cases should be screened and should be managed expectantly as suggested by Macafee. These cases should be managed in centres where facilities for advanced surgery, specialized anesthesia, ICU, blood transfusion and blood products and neonatal intensive care units are there and system should be backed by a proper referral facility.

Conflict of Interest: This study has no conflict of interest to declare by any author.

REFERENCES

1. Cresswell JA, Ron's mans C, Calvert C. Filipe, Prevalence of placenta Praevia by world region; a systematic review and met analysis. *Trop Med Int Health* 2013; 18(6):712-24.
2. Ojha N. Obstetric factors and pregnancy outcome in placenta previa. *J Institute Med* 2012;34(2): 38-41.
3. Nankali A, Keshaverzi FN, Shajari A, Daaichin S. Frequency of placenta previa and maternal morbidity associated with previous cesarean section. *Open J Obstet Gynae* 2014;4:903-908.
4. Ananth CV, Savitz DA, Luthr ER. Maternal cigarette smoking as a risk factor for placental abruption and uterine bleeding in pregnancy *Am J Epidemiol* 1996; 144: 881-9.
5. Oyelese Yinka M.D; Smulian, John C. Placenta Praevia, placenta accreta and Vasa Praevia. *Obstet Gynecol* 2006;108(3):694.
6. Oppenheimer L, Diagnosis and management of Placenta Praevia. *J Obstet Gynaecol Can* 2007; 29(3) 261-73.
7. Balayle, Bondarentko HD, Placenta Accereta and risk of adverse maternal and neonatal outcome. *J Perinant Med* 2013;41(2):141-9.
8. M. Walfish, A Naucman and DD. Wlody. Maternal Haemorrhage. *Oxford Journals, Med Health > BJA* 103(suppl):i44 – i56.
9. Olive EC, Roberts CL, Algert CS, Morris JM. Placenta Praevia and Place of Birth. *Aust NZJ Obstet Gynaecol* 2005; 45(5) 499-504.
10. Gomal A Kassem, Ali K Alzahrani, Maternal and Neonatal Outcomes of Placenta Praevia and Placenta accreta. Three years of experience with a two – consultant approach. *Int J Women's Health* 2013;5:803-810.
11. Lovina S.M. Machado. Emergency peripartum hysterectomy. Incidence, Indications, risk factors and outcome. *N Am J Med Sci* 2011;3(8) 358-361.
12. Burodo, Ce Shehu., and Usmaun Danfodiyo University Teaching Hospital, Sokoto: A 5 year review 2013;16(2):56-59.
13. Gamal A Kassem, Ali K Alzahravi. Maternal and neonatal outcomes of placenta previa and placenta accrete: three years of experience with a two consultant approach. *Int J Womens Health* 2013;5: 803-810.
14. Ambreen A, Manzoor T, Intsar A, Khurshid S. One year review of maternal mortality and morbidity associated with placenta Praevia in a tertiary care hospital. *Annals KEMU* 2012;18(2).
15. Prasanth S, Metha P, Rajeshwari KS. Maternal and fetal outcome of placenta previa in a tertiary care institute; A prospective two year study. *Ind J Obstet Gynae Res* 2016;3(3) 274-278.
16. Macafee CHG, Miller WG, Harley G. Maternal and fetal mortality in placenta Praevia *BJG* 1962; 69(2):203-212.
17. Raheel R, et al. Fetal outcome in cases of placenta Praevia – A retrospective study *Medical channel* 2010;16(2): 256-59.

Hormonal Imbalance and Infertility Among Females

Riaz Ahmad¹ and Farah Naz Aziz²

Hormonal Imbalance
and Infertility
Among Females

ABSTRACT

Objective: Determine the association of hormonal imbalance and infertility and any other endocrine disorder in the causation of infertility among female patients.

Study Design: Observational / descriptive study.

Place and Duration of Study: This study was conducted at the Govt. Aziz Bhatti Hospital (NSMC) for one year 2014-2015.

Materials and Methods: Female patients who presented with primary and secondary infertility among patients who were married and in the reproductive age group (15-49). The hormone profile was advised on the day-2 of the menstrual cycle especially F.S.H, L.H and prolactin. The patients who presented with amenorrhea were given hormones for withdrawal bleeding and then profile done and at random in irregular bleeding. Thyroid hormones were advised depending upon the history and positive symptomatology. The study was not funded. The duration of infertility was not considered.

Results: Majority of the patients who presented with infertility were in the reproductive age group, 51.8% from 20 to 29 and 44.44% from 30 to 39. Majority of the patients had normal hormone profile (54.81%). About 11.11% presented with polycystic ovarian syndrome (P.C.O's), the same numbers with premature ovarian failure and about 7.4% with disturbed thyroid profile. Hyper-prolactinemia was not found as an important cause of infertility in this study.

Conclusion: Hormone profile is an important investigation in cases of infertility in addition to the history, examination and ultrasonography, especially in cases that are also having associated menstrual abnormalities. Polycystic ovarian syndrome and premature ovarian failure were important causes of infertility and to some extent disturbed thyroid functions among the study group.

Key Words: Infertility, P.C.O's, Premature Ovarian Failure, Hyperprolactinemia

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INTRODUCTION

If a couple is unable to conceive after one year of complete consummation of the marriage, should be labeled as infertile.

Both male and female factors are important in cases of infertility although this period may be reduced to 6 months in a woman of 35 and above because of less ovarian reserve.

In primary infertility, the couples have never been able to conceive while in secondary infertility there is a difficulty in conceiving having once conceived, conditionally that it was a confirmed pregnancy, whether it reached to the term or not. Secondary infertility is not present if there has been a change of the partner within one year period.

O.S. Philippov Et in their study found that infertility in Tamsk (Siberia) was 16.7%, the female reproductive cause was 52.7% and male reproductive disease in 6.4%. In 38.7% of couples, both spouses suffered from Infertility. In 2.2% of the cases the cause was not determined.¹

In another study² the incidence was 14.8% with a mean duration of 3.38 ± 1.65 years. Male factor was present in 26.8%, female factor in 51.8% and both male and female factor were contributing in 21.4% cases.

Majority of the infertile females are nulliparous (56.6%). About 73.3% of the patients were having secondary infertility. More than 70% were between 25-34 years of age and only a few (6%), were below the age of twenty five.²

Obesity is associated with hormonal derangements which may be responsible for infertility hence it should be primarily targeted in the management of the individuals before starting any therapy to correct their hormonal imbalance. The patients should be educated to adopt a healthy body weight by life style intervention before they undertake any medical or surgical management of infertility.¹⁹

The disturbances in thyroid gland functions, multicystic ovaries, and disturbances in prolactin secretion may affect the ovulation and thus causing subfertility.

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Out of 394 infertile women 23.9% were hypothyroid (T.S.H) > 4.2 Micro Liter U/ml. After treatment for hypothyroidism 76.6% of infertile women conceived within 6 weeks to one year.³

In infertile women the prevalence of autoimmune thyroid disease is significantly higher compared to parous age matched women. This is especially the case in women with endometriosis and polycystic ovarian syndrome. During the first trimester, however pregnant women with AITD carry a significantly increased risk of miscarriage compared to women without AITD.¹⁷

Hyperprolactinemia was found in 33.3%, irregular menstrual cycle 66%, amenorrhea 6.7% and oligomenorrhea 59.3%.⁴ Normal menstruation 33.3% and galactorrhea in 3.3% primary infertile women.

Ovarian factor contributes about 20% cases of infertility. It could be because of the congenital absence of the ovaries, or failure to ovulate.

Female infertility occurs in about 37% to 40% of all the cases. The infertile patients with ovulatory dysfunction usually present with primary infertility. They usually have higher than required BMI (>30) oligomenorrhea, amenorrhea, hirsutism and other associated hormonal abnormalities. However, the patients with normal or low BMI may present with anovulation.⁵

Pcos is not a single entity, rather a syndrome; there are two agreed definitions of P.C.O.S. In 1990 consensus workshop by NIH and NICHD suggested, that a person has PCOS if they have the following criterion.

i. Oligoovulation

ii. Signs of androgen excess. (Chemical or biochemical).

iii. Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism.

Another definition is that PCOS is present if any out 2 out of 3 criteria are met. In the absence of any other entities that might cause these findings oligoovulation and anovulation, excess androgen activity, polycystic ovaries by gynecological ultrasound.

Clinical hyperandrogenism is characterized by acne, male pattern of baldness and the elevated androgen levels. There are also minor criterion of PCOS e.g. insulin resistance and disturbed ratio of LH and F.S.H. >2.5 - 3. PCOS is present in 15-20% of cases of infertility and 95% cases must be further investigated to exclude other causes e.g. free insulin, DHEAS, morning 17 hydroxyprogesterone, 24 urine for cortisol. These patients should also be investigated for undiagnosed diabetes which is present in 10% of the cases and by GTT, which is disturbed in 35% of the cases. The long term consequences of PCOS are cardiovascular diseases and endometrial cancers, however it protects the patients from osteopenia and osteoporosis. The short term consequences are increased prevalence of diabetes, PIH and recurrent pregnancy losses.

There is no definite definition of PCOS however there are major criteria and minor ones. The major includes

menstrual irregularity due to oligo and anovulation. Clinically and biochemically these patients should be investigated for undiagnosed diabetes, in 10% of the cases and by GTT, which is disturbed in 35% of the cases.

An ovulatory infertility may be the result of ovarian failure, gonadotropin failure resulting from hyperprolactinemia, normoprolactinemia cases with tumors or low gonadotropin secretion, polycystic ovarian syndrome and thyroid disease.¹⁸

There is hyperandrogenism in PCOS a study on mice it was found that orally administered rhFSH restored estradiol level and reduce the percentage of cystic follicles. Further studies are needed although the present data supports the concept that orally administered FSH could attenuate some of the characteristics of the PCOS in the mouse model.

The causes of premature ovarian failure are chromosomal aberrations, e.g. 47xxy. There is a high risk of malignancy and they must be treated by gonadectomy. The other causes may be turner syndrome xx/xo mosaic pattern. It could be because of resistant ovarian syndrome. The premature menopause is less than 45 years of age. The incidence is 1:250 by the age of 35 and one in 100 by the age of 40. It usually presents with irregular periods and infertility and the symptoms are similar to menopause. There is high FSH, and LH 10-20% has a family history. It may be iatrogenic and treatment option is IVF with a donor egg.

Premature ovarian failure is another important cause of infertility especially in young women who presented with amenorrhea. Current evidence suggests that DHEA administration appears to objectively improve ovarian reserves.

Artificial reproductive techniques have given relief to such patients in the form of cryopreservation in females who are prone to have premature ovarian failure and who have to go under radiation therapy for certain malignant conditions.

However sometimes the only option for many such women is ova donation.⁶

Serum T3, T4 and TSH level were statistically highly significant among infertile woman. High incidence of hypothyroidism was found in infertile patients who presented with menstrual irregularities,⁷ the hyperthyroidism patients presented with amenorrhea or oligomenorrhea.

Thirty eight (38%) of the PCO's patients presented with infertility, primary or secondary and 85.3% presented with menstrual irregularities. Abnormal uterine bleeding was the most common presentation and 48.2% had weight disorders. Type II or gestational diabetes were diagnosed in 13.9%.⁸ Hyper prolactinemia is the presence of abnormally high prolactin levels in the blood, values lesser than 580 mille international unit/L were considered normal for woman, up to 2400, they

were because of micro adenomas and values greater than 4000 may be because of macro adenomas of the pituitary glands which may present with other physical symptoms also. The P.C.O's patients may present with amenorrhea (30-40%), oligomenorrhea, (75-90%) and an ovulatory infertility in about 70% of the patients. The BMI is usually more than normal in such patients; however 20-30% of the patients may be asymptomatic or have normal weight or even less than normal. Insulin resistance is the main pathology and it is inherited by an autosomal dominant mode. It also causes subfertility by causing early losses and recurrent miscarriages. Unexplained infertility is found in about 25 to 30 % of the cases. In a study it was found that data do not support the hypothesis that unexplained infertility is caused by an abnormality in pulsatile GnRH secretion or abnormal pituitary sensitivity to GnRH.²¹

MATERIALS AND METHODS

The observational descriptive study was done in Govt. Aziz Bhatti Hospital (NSMC) for one year 2014-2015. Infertile female patients who presented with primary and secondary infertility among patients who were married and in the reproductive age group (15-49). The hormone profile was advised on the day 2 of the menstrual cycle especially F.S.H., L.H and prolactin, the patients who presented with amenorrhea were given hormones for withdrawal bleeding and then profile done and at random in irregular bleeding. Thyroid hormones were advised depending upon the history and positive symptomatology. The study was not funded. The duration of the fertility was not considered. Data analysis was done on SPSS 16

RESULTS

About 108 patients were included in the study, majority of the patients were in the reproductive age group. Majority of the patients (51.8%) were in the 20-29 years age group. Forty four percent (44.44%) patients were in the 30 to 39 years age group. It is obvious in table one that there are only a few females in the 40 to 44 years age group and also 45 to 50 years, because either they have completed the family or they have accepted the eventuality. (Table I)

Table No.I: Age as a determinant of infertility (n=108)

Age in years	No. of patients	Percentage
< 20	0	0
20-29 years	56	51.8%
30-39 years	48	44.44%
40-44	Zero	Zero
43-50	04	3.7%

The various hormonal imbalances and their percentages are explained in the table 2.

As is obvious in table II, 64.81% of the patients were having normal hormonal profile; the reason is that either the couple is having psychological, male factor, other female factors, unexplained infertility and other reasons for secondary infertility.

Table No.2. Hormones Profile with infertility among the patients (n=108)

Category of the Patients	No of Patients	Percentage
Normal F.S.H & L.H	70	64.81
Patients of P.C.O's	12	11.11
Premature ovarian failure	12	11.11
Hypo gonadotrophic hypogonadism	02	1.85
Menopausal	04	3.7
With Thyroid disorders	08	
Hyperthyroidism	04	3.70
Hypothyroidism	04	3.70
Hyperprolactinemia		
< 400	08	7.4
> 400	00	

About 12(11%) of the patients presented with the hormone profile indicating PCO's with increased L.H and normal F.S.H.

It was strange to see that about the same number 11.11% patients presented with premature ovarian failure, they presented with primary and secondary infertility but majority were with secondary infertility. About 3.7% presented with a profile in the range of menopause and 3.7% each presented with hyper and hypothyroidism and 7.4% of the patients with hyper prolactinemia.

About 7.4% of the patients presented with hyper prolactinemia which was less than 4000 international units.

DISCUSSION

Age is an important determinant of the fertility, due to changing social scenario more women opting to have career present in the 3rd and fourth decade for infertility treatment. In a study by Korula George and Mohan S.Kamath.⁹ It was found that fertility and aging are closely linked and age of the female partner remaining the single most important factor in the treatment of infertility, although the tests for this are the poor predictors.

The same was evident in this study, that there was no patient < 20 years who presented with infertility. Majority of the patients were in the 3rd and fourth decade and a little number from 40 to 50 years.

It was found in this study that about 30% of the patients presented with hormonal imbalance. The various categories which were detected were patients with P.C.O's, premature ovarian failure, premenopausal and

a sizeable number with thyroid disorder. However none of the patients was found with significant hyperprolactinemia.

In a study by Kausta E and associates¹⁰ found that prevalence of P.C.O. was significantly higher in each of the infertility groups than in controls and a similar tendency was found among women with un-explained infertility. The similar trend was found in this study, the incidence of P.C.O's was 11%. However the patients with P.C.O's were the majority among the patients with hormonal imbalance, 12 out of 30.

The same number of patients was with premature ovarian failure which presented with primary, but majority were with secondary infertility, twelve patients out of thirty were with premature ovarian failure.

In his study by Paolo Beck – Pecoz and Luca Persani¹¹ it was found that this defect affects about 1% of the patients. It may present with primary or secondary amenorrhea. Beyond infertility, hormone defect may cause severe neurological, metabolic or cardio vascular consequences, and lead to early onset of osteoporosis.

About 7.4% patients presenting with infertility were having thyroid disorders equally as hyper and hypothyroidism.

However in their study by Priya DM, Akhtar N. and Ahmad J, it was found the incidence of hypothyroidism was 53.7% (TSH > 4.6 Micro Litter Units / ml). After treatment with thyroxin, 33.3% of the subclinical hypothyroid women conceived within six months to two years period and thus they concluded, that thyroid should be included in infertility profile work up.¹²

However no significant hyper prolectinaema was found in this study and only two patients of (1.85%) hypogonadotrophic, hypogonadism presented with infertility, and 3.7% of the patients were menopausal but still seeking for conception. Sharma N. & Associates concluded in their study that high incidence of hyperprolactinemia was found in fertile women and a positive correlation was found between hyperprolactinemia and hypothyroidism¹³.

Emokpae MA & Associates found in their study that 33.7% had hyperprolactinemia among infertility patients. Subclinical hypothyroidism was observed in 29.9% and 70.1 % in primary and secondary infertility respectively. Mean levels of thyroid stimulating hormones and prolactin were higher in secondary infertility than primary infertility. The ratio of proportions between hypothyroidism and hyperprolactinemia 1:7¹⁴

The hypo gonadotrophic hypogonadism patients are treated with exogenous hormones. They found that 12/14 women 80% achieved one or more live births after treatment¹⁵

CONCLUSION

In this study the patients who presented with infertility and associated hormonal imbalance, 64.8% of the

patients had normal hormone profile. The patients with PCO's and premature ovarian failure were among the patients with disturbed hormone profile presenting with infertility.

Unuane and associates (16) found in their study that female infertility occurs in 37% of all infertile couples and ovulatory disorders account for more than half of these.

The various endocrine disorders, found were, hypo gonadotrophic, hypogonadism, hyper prolactinemia, acromegaly and Cushing's disease, thyroid disorder and primary ovarian disorders such as, polycystic ovarian syndrome and primary ovarian infertility and they proposed an algorithm to investigate such patients.

Thyroid disorder was among the others whose patients presented with infertility. It is concluded that patients who presented with infertility and menstrual disturbances must be investigated regarding hormone profile. The normal hormone profile gives a psychological advantage and to search for other reasons of infertility. The cause of the hormonal imbalance were treatable, hormonal imbalance was one of the major reasons of amenorrhea and even if not treatable saves the patients from undue investigations, psychological trauma and looking for other causes. Hormonal imbalances presenting with menstrual irregularities is one of the reasons for ovulatory infertility also which if treated properly ends up in reassuring results.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Philippov OS, et al. Estimation of the prevalence and causes of Infertility in western Siberia. Bull world Health organ 1998;76(2):183-187.
2. Olatinji AO, Sule-Odu AO the pattern of infertility cases at a university hospital. West Afri J Med 2003;22(3):205-7.
3. Verma I, Sood R, Juneja S, Kaur S. Prevalence of hypothyroidism in infertile women and evaluation of response of treatment for hypothyroidism on infertility. Int J Appl Basic Med Res 2012;2(1): 17-19.
4. Salah Eldin A. Abdulghani, Abdul gadir A, Elmugadam, Mohammad Elsanousi M. Hyperprolactinemia as a cause of female primary infertility and its prevalence in Gezira State, Central Sudan. Egypt Acad J Biolog Sci 2013;5(1): 31-36.
5. Saadia SN, Waqar F, Akhtar T, Sultana S. Characteristics of infertile patients with ovulatory dysfunction and their relation to body mass index. J Ayub Med Loll Abbottabad 2009;21(3).
6. Kaya H, Sezik M, Ozkaya O. Evaluation of a new surgical approach for the treatment of clomiphene

- citrate-resistant infertility in polycystic ovary syndrome: laparoscopic ovarian multi-needle intervention. *Minim Invasive Gynecol* 2005; 12(4):355-8.
7. Sharma N, Singh SB. Prevalence of serum thyroid Hormones and menstrual irregularities with infertility in Utar Pardesh India. *1JPSR* (2012);(9): 3454-3457.
 8. Varghese U, Varughese S. Prevalence of polycystic ovarian syndrome in the Buraimi region of Oman. *Brunei Int Med J* 2012;8(5):248-252-.
 9. George K, Kamath MS. Fertility and age, *J Hum Reprod Sci* 2010;3(3):121-123.
 10. Kousta E, White DM, Cela E, Mccarthy M, Fromhs S. The prevalence of Polysystic Ovaries in women with infertility hum. *Reprod* 1999;(11): 2720-3.
 11. Paolo Beck – Pecoz and Luca Parsani. Premature ovarian failure. *Orphanet J Rare Dis* 2006;1(9). 10.1186/1750- 72-1-9.
 12. Priya DM, Akhter N, Ahmad J. Prevalence of hypothyroidism in infertile women and evaluation of response of treatment for hypothyroidism in infertility. *Ind J Endocrinol Metab* 2015;19(4): 504-6.
 13. Sharma N, Baliar Singh S. Kauskik GG. Biochemical association of hyperprolactinemia with hypothyroidism in infertile women. *Clin Lab* 2012;58 (7-8):805-10.
 14. Emokpae MA, Osadoler HB, Omole Ohnsi A. Subclinical hypothyroidism in infertile Nigerian women with hyperprolactinaemia *Niger J Physiol Sci* 2011;26 (1):35-8.
 15. Milson S, Daggan K, O'Scellivan S, Ogilvie M, Gunm AJ. Treatment of infertility with hypogonadism, hypogonadism; 10-year experience Auckland, Newzealand. *Aus NZ J. Obstet Gynacol* 2012;52 (3):293-8.
 16. Tournayeh US, Velkenier P, Poppe K. Endocrine disorders and female infertility. *Best Pract Clin Endocrinol Metab* 2011;25(6):861-73.
 17. Poppe K, Vekniers, Glinioer D. Thyroid disease and female reproduction. *Clin Endocrinol (oxf)* 2007; 66(3):309-21.
 18. Baired DT. Endocrinology of female infertility. *Br Med Bull* 1979;35(2):193 -8.
 19. Seth B, Arora S. Singh R. Association of obesity with hormonal imbalance in infertility. A cross sectional study in north india. *Ind J Clin Biochem* 2013;28(4):342-347.
 20. Tessaro I, et al. Effect of oral administration of low dose follicle stimulating hormone on hyperandrogenised mice as a model of polycystic ovarian syndrome. *J Ovarian Res* 2015; 8:64.
 21. Randolph JF et al. Elevated early follicular gonadotrophin levels in women with unexplained infertility do not provide evidence for disordered gonadotrophin releasing hormone secretion as assessed by luetinising hormone pulse characteristics. *Fertil Steril* 2003;80(2):302-7.

Atorvastatin, Rosuvastatin and Simvastatin

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ABSTRACT

Objective: To determine the myalgia association with atorvastatin, rosuvastatin and simvastatin

Study Design: Descriptive study

Place and Duration of Study: This study was conducted at the cardiac ward, civil hospital from March 2013 to August 2013

Materials and Methods: This study was done by taking the feedback of patients on a questionnaire set in conciliation of objectives. Data collection was done for six months. Myalgia was confirmed clinically via many questions asked directly to patients and its intensity through visual analog scale.

Results: Study involved 300 patients between age 25-70 years and mean age was 55.7yrs $\pm$ 7.575. Male patients were 218(72.67%) whereas females were 82(27.33%). Myalgia prevalence was categorized according to the type of statin as 10% in atorvastatin group, 11.34% in Rosuvastatin group and 16% was found in patients those were under treatment of simvastatin. In the atorvastatin group myalgia was found positively correlated with dose of atorvastatin as well as 5% cases were found with dose of 40mg. in the Rosuvastatin group majority of the cases 5.34% were found with 20mg, while in simvastatin group 8% cases were found with 10mg simvastatin. According to the VAS, 5% case was found with mild myalgia and 6.66% were noted with moderate myalgia while severe condition was not found in any case. 6% cases were found with moderate myalgia out of 133 cases in Rosuvastatin group, 8% cases were noted with moderate myalgia out of 50 cases in simvastatin group, while only 3% patients were found with moderate myalgia in atorvastatin group out of 100 cases.

Conclusion: Simvastatin is highly associated with myalgia as compare to others but not significant. Rosuvastatin, Atorvastatin and Simvastatin are positively associated with severity of myalgia after increases the dose.

Key Words: Rosuvastatin, Atorvastatin, Simvastatin, Myalgia

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INTRODUCTION

For the prevention CVD, developing part of inhibitors of 3-OH-3-methyl glutaryl coenzyme A reductase part of statins are horribly has been obvious in the clinical practice. As statins reduction LDL levels in cases with higher CVD chance, this molecule turned into the principal line operator for essential and auxiliary prophylaxis of MI and in addition in patients with adjusted and interrupted level of lipid.¹⁻³ For body cholesterol biosynthesis, there is the enzyme indicated as 3-OH-3-methyl glutaryl co-enzyme A reductase. Statins basically are firmly comparative with this enzyme consequently turning into its rival along these lines causes its modest hindrance. Statins is demonstrated with its wide therapeutics record with great safety for CVD prevention.⁴⁻¹⁰

In the first place statin was acquired from fungi (a form "Penicillium citrinum"). Right now statins are arranged in fundamentally in three generations, 1st generation incorporates Lovastatin, pravastatin and the fluvastatin and, 2nd generation incorporates simvastatin and the atorvastatin while 3rd generation has rosuvastatin.^{11,12} Myotoxicity because of Statin Cholesterol decrease in the myocyte membrane is because of unsettling influence of layers steadiness subsequent in disease of the muscles. A large number of the studies clarify that these kind of human skeletal muscles issues are because of diminishing of transitional pathways in the cholesterol biosynthesis. Farnesyl pyrophosphate is in center in the arrangement of ubiquinone recognized as co-enzyme Q10. Other new components clarify that this pathology of muscle is on the grounds that statins causes this cholesterol unsettling influence in isopentanylation of seleno cysteine-tRNA.¹³ Statins additionally indicate pleiotropic impacts including enhancement of expanded nitric oxide accessibility available for use, endothelial dysfunction antioxidant effects, anti-inflammatory, immune-altering property and atherosclerotic plaque strength. Inhibiting hypertrophy of the heart muscles is new area of interest among their pleiotropic effect.¹⁴ Purpose of our study

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was to determine the myalgia association with atorvastatin, rosuvastatin and simvastatin.

MATERIALS AND METHODS

Descriptive study was done at cardiac ward, civil hospital, Hyderabad by taking the feedback of patients on a questionnaire set in conciliation of objectives and myalgia severity was checked by visual analog scale. Data collection was done for six months from March 2013 to August 2013. Cases having myocardial infarction and on statin therapy for the secondary prevention had selected. Patient with presentation of any other illness which can cause the muscular pain was excluded. Informed consent had taken verbally from all cases those were agreeing to participate in the study. All the patients were categorized in three groups according to treatment as in group 1. Atorvastatin was advised to one hundred cases of MI, group 2 was contain 150 cases and advised rosuvastatin and Simvastatin was advised to fifty cases. Drugs were advised and doses were selected by senior consultant cardiologist according to the patient's condition. Patients were directed for not to alter their normal routine. All the data was recorded in the proforma. The data was analyzed in SPSS version 20.0.

RESULTS

Total 300 cases were selected in the study out of them 218 were male and 82 were female, myalgia was found in 35 cases out of 300. Mean age of the patients was $55.7 \text{ yrs} \pm 7.575$. Table:1

Myalgia prevalence was categorized according to the type of statin as 10% in atorvastatin group, 11.34% in Rosuvastatin group and 16% was found in patients those were under treatment of simvastatin. Figure 1. In the atorvastatin group myalgia was found positively correlated with dose of atorvastatin as well as 5% cases were found with dose of 40mg. In the Rosuvastatin group majority of the cases 5.34% were found with 20mg, while in simvastatin group 8% cases were found with 10mg simvastatin results showed in Table:2

Table No.1: Gender distribution according to Myalgia n=300

Gender	Myalgia		Total
	With Myalgia	Without Myalgia	
Male	28	190	218
Female	07	75	82
	35	265	300

Myalgia was categorized according to the VAS, 5% case was found with mild myalgia and 6.66% were noted with moderate myalgia while severe condition was not found in any case. Fig:2

6% cases were found with moderate myalgia out of 133 cases in Rosuvastatin group, 8% cases were noted with

moderate myalgia out of 50 cases in simvastatin group, while only 3% patients were found with moderate myalgia in atorvastatin group out of 100 cases. Table:2

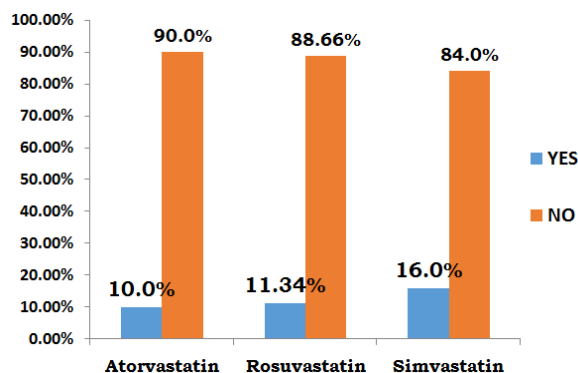


Figure No.1: Statin distribution according to occurrence of Myalgia n=300

Table No. 2: Myalgia according to statin dose n=35

Dose of statin	Myalgia	
	Frequency	Percentage
Atorvastatin n=100		
10mg	01	1.0%
20mg	04	4.0%
40mg	05	5.0%
Total	10	10.0%
Rosuvastatin n=150		
05mg	01	0.66%
10mg	06	4.0%
20mg	08	5.34%
40mg	02	1.34%
Total	17	11.34%
Simvastatin n=50		
05mg	01	02.0%
10mg	04	08.0%
20mg	03	06.0%
Total	08	16.0%

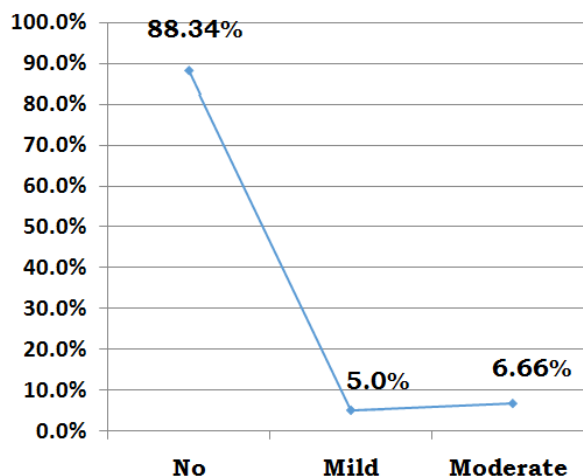


Figure No.2: Myalgia according to VAS n=300

Table No. 3: Severity of myalgia according to type of statin n=300

Dose of statin	Myalgia			Total
	No	Mild	Moderate	
Atorvastatin	90 (90%)	07 (7%)	03 (3%)	100 (100%)
Rosuvastatin	133 (88.66%)	08 (5.34%)	09 (6%)	150 (100%)
Simvastatin	42 (84%)	04 (8%)	04 (8%)	50 (100%)

DISCUSSION

Statins are the extremely influential and well established category of the drugs. Several clinical and experimental studies supported its uses for the wide range of indication and clinical conditions. Statin-linked to myopathy signify one of the commonest and frequent adverse effects of these medicines and also estimated that up to two 3rd of all statin-associated complications involve with the muscle tissue.¹⁴ It is characterized by the symmetrical involvement of large and proximal muscle groups, in particular the legs.¹³ Observational studies suggest that 10-15% of statin users develop some type of muscle problem.¹⁵ Similarly we found 11.33% myalgia in patients those were under treatment of statin. We had compared three statins to assess the myalgia as well as 100 patients were on Atorvastatin and out of them 10% patients were with complaint of Myalgia. Our findings are comparable with the some previous studies of Seip et al¹² and Colhoun et al¹³ reported that myalgia is the commonest occurring complication after Atorvastatin taken. In this series simvastatin and atorvastatin were without any serious complication of drug but showed significant incidence of the myalgia in the cases as 10% and 16% respectively. Similarly pedersen et al¹⁴ and Abourjaily et al,¹⁵ reported comparable results. In this study 150 cases were under treatment of rosuvastatin, out of them in 11.34% patients developed myalgia, in the contrast several studies of Mora et al,¹⁷ Hoek et al¹⁸ and Crouse et al¹⁶ demonstrated that rosuvastatin at various elevated doses showed positive association with severity of myalgia. As well as we found 8(14.54%) out of 55 patients showed complained of myalgia after taking Rosuvastatin 20mg complained. On other hand Mora et al¹⁷ also stated that myalgia is the commonest complication of drug reaction which may developed caused by discontinuation of treatment and further stated that 7.6% cases those were on crestor 20mg showed complain of myalgia as compare to 6.6% on the placebo.¹⁷ Total 50 cases were on simvastatin out of them 8(16%) patients showed complaint of the Myalgia was constant with several studies as well as Jones et al¹⁹, Larsen et al²⁰ and Bannwarth B et al;²¹ reported that the myalgia is the commonest complication of simvastatin. In our series cases those were advised statin, showed

soon myalgiasigns in response relationship those were giving clear symptoms of myopathy development in the long term, while no any case was noted with myositis or rhabdomyolysis, since newest cases had enrolled those were advised statin treatment at 1st time, therefore for the development of myopathy required prolonged duration, similarly in many other studies also reported similar findings. In this series showed that statins is positively related with effects of myalgia large quantity of the population taking it and showing big prevalent myalgia, which started even at the low doses and for short duration, while majority of the patients with high dose were seen.

CONCLUSION

Simvastatin is highly associated with myalgia as compare to others but not significant. Rosuvastatin, Atorvastatin and Simvastatin are positively associated with severity of myalgia after increases the dose. Myalgia proportion on three studied statins was different from global research studies which demands more extensive research needed particularly on the gene-myalgia association.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Vaughan CJ, Gotto AM. Update on statins: 2003. *Circulation* 2004;110(7):886-92.
2. Expert Panel on Detection E. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;285(19):2486-97
3. Armitage J. The safety of statins in clinical practice. *The Lancet* 2007;30;370(9601):1781-90.
4. Baigent C, Keech A, Kearney PM, Blackwell L. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *The Lancet* 2005; 366(9493):1267-78.
5. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *New England J Med* 2005;7;352(14): 1425-35.
6. Kapur NK, Musunuru K. Clinical efficacy and safety of statins in managing cardiovascular risk. *Vascular health and risk management* 2008; 4(2):341-353
7. Vaughan CJ, Gotto AM. Update on statins: 2003. *Circulation* 2004;110(7):886-92.
8. Jasińska M, Owczarek J, Orszulak-Michalak D. Statins: a new insight into their mechanisms of

- action and consequent pleiotropic effects. *Pharmacological Reports* 2007;1;59(5):483.
9. Raju SB, Varghese K, Madhu K. Management of statin intolerance. *Indian J Endocrinol Metab* 2013;17: 977-982
 10. Ahmad Z. Statin intolerance. *Am J Cardiol* 2014; 113:1765–71.
 11. Harris KP, Wheeler DC, Chong CC, Atorvastatin in CAPD Study Investigators. A placebo-controlled trial examining atorvastatin in dyslipidemic patients undergoing CAPD. *Kidney Int* 2002; 61(4):1469-74.
 12. Seip RL, Thompson P, Windemuth A, Kane JP, Pullinger CR, Wu A. CLN8: AN Atorvastatin-specific marker for common myalgia. *J Am Coll Cardiol* 2014;12(63):A1285.
 13. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis* 2009; 30;54(5):810-9.
 14. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005; 294(19):2437-45.
 15. Abourjaily HM, Alsheikh-Ali AA, Karas RH. Comparison of the frequency of adverse events in patients treated with atorvastatin or simvastatin. *AJC* 2003;15;91(8):999-1002.
 16. Crouse JR, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the Meteor Trial. *JAMA* 2007; 297(12):1344-53.
 17. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia. *Circulation* 2010; 9;121(9):1069-77.
 18. van den Hoek HL, Bos WJ, de Boer A, van de Garde EM. Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials. *BMJ* 2011;29;343:d7281.
 19. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller F et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (Stellar Trial). *Am J Cardiol* 2003;92(2): 152-60.
 20. Laanen S, Stride N, Hey-Mogensen M, Hansen CN, Bang LE, Bundgaard H. Simvastatin effects on skeletal muscle: relation to decreased mitochondrial function and glucose intolerance. *J Am Coll Cardiol* 2013;8;61(1):44-53.
 21. Bannwarth B. Drug-induced myopathies. *Expert Opinion on Drug Safety* 2002;1(1):65-70.

Not the Doctor's Order; Eunuchs Access to Health Care in Central Punjab

Tehseen Nuzhat¹ and Ali Zulqernain²

ABSTRACT

Objective: The study aims to identify the barriers in availing healthcare services by eunuchs. Explore the needs and concerns, and ascertain the attitude of General Practitioners towards eunuch in providing health care services.

Study Design: Descriptive / cross sectional study.

Place and Duration of Study: This study was conducted at the University of Health Sciences, Lahore from April 2010 to march 2011.

Materials and Methods: The total samples size was sixty. The group 1 included thirty eunuchs and group 2 included thirty General practitioners. A convenient non probability sample was identified from the target population. A questionnaire was used for the purpose of data collection.

Results: Poor access to the doctor and non-availability of medicines were the most difficult part of seeking and receiving medical care. Use of unethical practices, lack of confidentiality, admission into male ward and death of colleague due to negligence were the negative experiences they came across while seeking medical care. Responding practitioners seemed to be bit uncomfortable in providing consultation to eunuchs in their clinics. Majority of the practitioners remained neutral to the question about their attitude toward hijras and agreed that it is more challenging to conduct genitourinary examination and also discuss sexual behavior with them.

Conclusion: Hijras are neglected, discriminated against and not given the same rights as other Pakistanis, in matters of inheritance, employment, education and health care. This study reveals that marginalized population that have the health problems, both mental and physical and have the poor access to medical care. Similarly the health care providers are unable to provide appropriate care and devotion to these patients. There is a dire need to train health care providers to understand the psychosocial aspect of the Hijra culture and to deal with them without any prejudices. Health care policy makers must develop appropriate structures, policies and processes to enhance the social determinants of health so that equity in healthcare could be provided to all strata of the society.

Key Words: Health care, Hijra, Eunuchs, Central Punjab

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INTRODUCTION

Hijra is an umbrella term used for trans genders, eunuchs, transvestites, hermaphrodites or intersexe, bisexuals or homosexuals¹. South Asian hijras draw their cultural heritage from the 'Khwahsara' of Mughal era (1526-1858), who were employed by Mughal rulers, as care takers of their harems². Eunuch (Hijra) population size in Pakistan is estimated from 80,000³ to 300,000 (BBC News report, 2009) while a population of 5000 hijras is living in the district of Lahore⁴. Eunuchs usually live by performing at marriage or birth celebration, begging and prostitution⁵. National Study of Reproductive

Tract and Sexually Transmitted Infections of high risk populations in Lahore and Karachi during 2004 showed that 35.9 % in Lahore were suffering from Syphilis and 0.5% Hijras in Lahore were HIV positive⁶. Only few people consider them as a family person and friends but in majority of cases they are discriminated in all fields of life and even their access to openly avail the required health care needs is limited⁷. As Renate. (2003) described "The attitude of Pakistanis toward Hijras is contradictory: Some accept them, others hate them, many fear them, many are amazed by them, a few like them, many make fun of them, and no one invites them in. Eunuchs are ridiculed and treated poorly in health care settings by the health care providers⁸.

MATERIALS AND METHODS

This is descriptive cross sectional study carried out at University of Health sciences Lahore, while the data was collected from Lahore city. The duration of the study was 12 months periods started from April 2010 to march 2011

The total samples size was 60 selected samples were divided into two equal groups. The group 1 included thirty eunuchs and group 2 included thirty General

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practitioners with minimum of 5 years' experience of general practice. A convenient non probability sample was identified from the target population. The questionnaire was adopted from the work of Dutton L. 2008. Gynaecology "Care of the Female-to-Male Transgender Man". Formal permission from the original authors was sought out before using the tool in this study. The Urdu translation was done by back translation method.

RESULTS

Group I: Eunuchs

A= Demographic Information:

The age of participants ranged from 18-60 years with a mean of 31.57 ± 9.762 years.

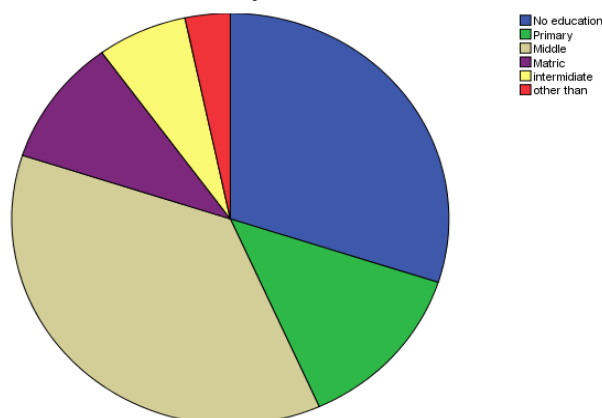


Figure No.1: Education of the participant.

The average monthly income was Rs.5000/- of 25(63%) participants, Rs.10,000/- of 4(13%) and only 0(3%) had monthly income more than 10,000 rupees.

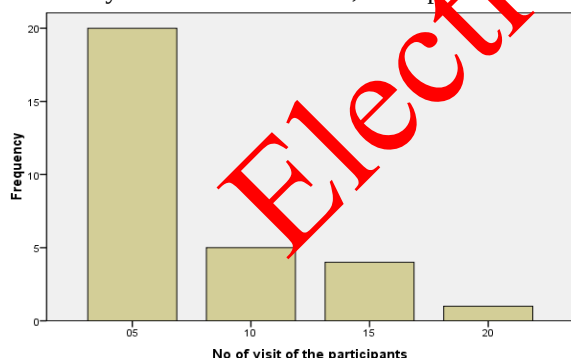


Figure No.2: Number of visits of the participants.

B. Healthcare Status: In this category 22 questions were asked from the participants to know about their health care status. To the question regarding "thoughts, feelings, and experiences with the health care system" the response showed that 9(30%) had positive feelings & experiences with the local healthcare system while 21 (70%) had negative feelings & experiences. The healthcare system was considered very bad and run by inefficient people by 14(47%) participants, while 07(23%) said that service providers are very cruel and

rude with them and only 9(30%) considered their attitude to be kind and friendly. Unnecessary questioning & irrelevant probing by the doctors was considered to be the barrier in availing healthcare facilities by 12 (40%) participants, while 11(37%) considered that doctors do not listen to them properly and have forgotten their ethics and duty, 4(13%) considered lack of respect and improper treatment as the barrier they experienced during receiving healthcare. To the question about the most difficult part of seeking and receiving medical care, poor access to the doctors was the response by 27 (90%) participants while 3 (10%) considered non-availability of medicine as the most difficult part. Use of unethical practices, abusive language and lack of confidentiality was considered to be the negative experiences that 14 (46%) participants experienced, 01 (3%) reported that admission into the male ward instead of female ward was her negative experience, 02 (7%) attributed the death of their colleagues due to negligence and non-availability of medical services at proper time while 13(43%) participants did not have any negative experience with health care providers

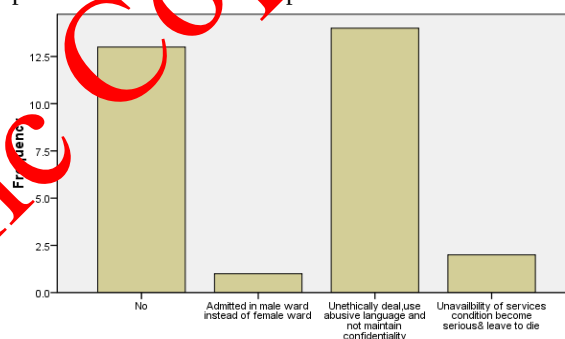


Figure No.3: What are the most negative experiences you have had with a health care provider, or his or her staff?

Majority 22(73%) of the participants responded that they did not have any positive experience when asked about the most positive experience they had with the health care providers while 08 (27%) did experience positive feelings. Among those responding that they had positive experience, 04(50%) informed that doctors checked them without charging any fee, 03(37%) said that they were given respect in spite of knowing them that they are eunuchs and 01(12%) said that a nurse looked after her very well and even paid money for her medicine,

To the question "What do you think would help to improve the healthcare system, clinics, or providers with respect to understanding healthcare of transgendered people?" 14(47%) responded that system can be improved by bringing the dealing of health care providers with them to be at par with normal patients 13(43%) think that provision of separate hospitals or ward for them would improve the system while 3(10%) thought that they should be treated as separate special

group. All the 30(100 %) participants reported that they have “major health concern” among whom 12(40 %) had hemorrhoids, 05 (17 %) had syphilis, 03(10 %) had hypertension, 03(10 %) had tuberculosis, 03(10 %) had depression and Hepatitis C and 02(10%) had skin infection as major health problems. At the time of sickness 22(73 %) participants prefer to visit doctors, 05(17 %) would visit hakeems, and 03(10 %) would visit others health care service providers. To the question whether they have an access to primary health care provider for advise and consultation, 21(70 %) participants responded in negative while 09(30 %) responded that they do have access to this facility. Government negligence was considered to be the reason for non-availability of the primary health care providers by 24(80 %) participants while 06 (20 %) thought it as a societal discrimination. Chronic medical condition was absent in 17 (57%) participants while 13(43%) were suffering from chronic conditions like Arthritis, Haemorrhoids, Tuberculosis, Hepatitis C & psychiatric disorders like depression.

Group II: General Practitioners: Questioner was filled by 30 General practitioners out of which 24(80%) were males, and 06 (20%) were female medical practitioners. All the 30(100 %) participants had experience of treating or provide consultation to the eunuchs. According to the study participants’ response to “attitudes towards transgender” showed that 02(6.7%) were very comfortable, 07 (23 %) were comfortable, 14 (47%) were neutral, 05(17%) were uncomfortable, and 01(3 %) was very uncomfortable. Whether it is more challenging to conduct physical examination of eunuch was responded as strongly agreed by 07(23%), agreed by 07(23%), neutral by 08(27%), disagreed by 07(23%) and strongly disagreed by 01(3%) participant. Similarly, 07(23 %) strongly agreed that “it is more challenging to conduct genito-urinary system examination”, 11 (37%) agreed, 11(37%) were neutral, and 1(3 %) disagreed. While, among total participants 08 (27%) strongly agreed that “it is more challenging to discuss sexual behavior with them”, 11(37%) agreed, 09(30 %) were neutral, 01(3 %) disagree, 01 (3 %) strongly disagreed. Among all the participants, 11 (37%) strongly agreed to the statement that “Transgender patient deserve the same level of quality care”, 13 (43 %) agreed, 01(3 %) was neutral, 02 (7%) disagreed, while, 03(10 %) strongly disagreed. Their facility provides an equal opportunity of healthcare to the eunuchs was claimed by 26 (87%) practitioners, while 04(13 %) thought that it is not same. When asked whether there is need for training to deal with the transgender patient, 25(83 %) participants agreed that training is required. No guidelines to deal with eunuch patients were followed by 28 (93 %) participating practitioners. Regarding separate health care services for transgender, 03(10 %) strongly agreed to this proposal, 03(10 %) agreed, 05(17 %) were

neutral, 14 (47%) disagreed, and 05(17 %) strongly disagreed to this suggestion

DISCUSSION

Eunuchs in our society are inadequately represented, discriminated against and marginalized. They are considered to be abnormal both physically and psychologically. They rarely access conventional health-care system due to distrust and fear of being rejected⁹. Although general perception in the society they gave that, they belong to a third gender which is neither male nor female. They claim to have men’s bodies and women’s souls¹⁰. As expected most of them were either illiterate or had primary level education. This is not surprising as harassment and jeering of the peers and school fellows prevents them from pursuing their education. Similarly most of the responder eunuchs belonged to low socio-economic class. Although some were doing jobs either part time/full time begging and prostitution was the main mode of earning. Poor access to the doctor and non-availability of medicines were the most difficult part of seeking and receiving medical care. Use of unethical practices, abusive language, lack of confidentiality, admission into male ward and death of colleague due to negligence were the negative experiences they came across. Medical checkup without charging fee, giving due respect and even giving money for medicine were some of the positive experiences they had. Their major health concerns were haemorrhoids, syphilis, hypertension, tuberculosis, depression, asthma, hepatitis C and skin infections. Qualified medical doctor was the choice of consultation by majority of the responders while hakims and quacks were the other choices. Government negligence and social discrimination was considered to be the reason for non-availability of the primary health care. The effectiveness and contributions of public health should be strengthened to reduce unfair differences in health among population groups, especially, the under privileged and marginalized groups¹¹.

Equal numbers of health care practitioners were questioned about their attitudes and experiences with transgender patient. Responding practitioners seemed to be bit uncomfortable in providing consultations to eunuchs in their clinics. This is perhaps due to the mocking and offensive behavior of eunuchs. It is possible that medical practitioners feel embarrassed to have such people in their clinic and fear that other patients would feel uncomfortable in their presence. There was a mixed response to the question whether it is more challenging to conduct physical examination, while majority agreed that it is more challenging to conduct genitourinary examination and also discuss sexual behavior with them. Physicians might have fear that by exposing genitals of their eunuch patients or asking about their sexual problems they might

themselves be blamed for sexual exploitation. Although there are no specific guidelines given by Pakistan medical and dental council or any other medical regulating body in Pakistan but most of the medical practitioners surveyed agreed that such patients deserve the same level of quality care as other patients, equal opportunity to receive health care should be given to them, and that there is a need for training and sensitizing health care professionals to deal with transgender patients. The idea of having separate health care facilities for such patients was not accepted by majority of the responders.

CONCLUSION

Hijras in conservative society like Pakistan live a life of fear and uncertainty. They are neglected, discriminated against and not given the same rights as others, in matters of inheritance, employment, education and health care. The social stigma attached to these patients, resulting in different barriers to access health care facilities. This study also reveals that marginalized population that have the greatest health problems, both mental and physical, have the least access to care. Similarly the health care providers are reluctant to provide appropriate care and devotion to these patients. There is a need to train health care providers to understand the psychosocial aspect of the Hijra culture and to deal with them without any prejudices. Health care policy makers must develop appropriate structures, policies and processes to enhance the social determinants of health so that equity in healthcare could be provided to all strata of the society. Future researches are needed to investigate this issue from multiple angles and provide strong evidence regarding experiences of eunuch to avail health care services and attitude of health care personnel towards this segment of society.

Conflict of Interest: The study has no conflict of interest to declare by any author.

1. Dutt N. 2008. Eunuchs -- India's Third Gender. (Online) (Cited 2008 Feb 2). Available from URL: (www.thingsasian.com/stories-photos/2022).
2. Gwinn, Peter & Goetz, 1990. p. 598; The Encyclopedia Americana, 2000, p. 661; Nanda, as cited in Brettle & Sargent, 1997; Sharma, 2000; Talwar, 1999.
3. Rehan N, Chaudhary I, Shah SK. Socio-sexual Behaviour of Hijras of Lahore. J Pak Med Assoc 2009;59:380-4.
4. Manzoor PDSM, Bajwa DMA, Anjum DA. Behavioral Study of eunuch population of Lahore regarding sexual practices and HIV. Abstract presented in 4th International AIDS society conference held 2007.
5. Coway L. 2002. How frequently does transsexualism occur? (Online) (Cited 2008 Feb2). Available from URL: www.lynnconway.com
6. Rehan N, Bokhari A, Nizamani NM, Jackson D, Naqvi HR, Qayyum M et al. National Study of Reproductive Tract and Sexually Transmitted Infections. National AIDS Control Programme 2005. URL: www.fhi.org/NR/rdonlyres/.../RTIStudyPakistan3.pdf
7. Curran B. Pakistan to recognise eunuchs. Pakistan. C.2009-[cited 2010 September 28].available from: <http://www.thenational.ae/article/20090701/FOREIGN/706309828/1103/ART>
8. Good N. Transgender People's Access to Sexual Health and Rights: A Study off Law and Policy in 12 Asian Countries. ARROW 2010;1-42.
9. Khaki MA et.al. 2009. constitution petition no. 43 of 2009. [Online], Available from: www.womenslinkworldwide.org/wlw/bajarDoc.php?tl=1&per=39
10. Syed R. Feminine Soul, Masculine Body. World Press Review 2003;50(1):1-7.
11. Pauly BB, MacDonald M, Hancock T, Martin W, Perkin K. Reducing health inequities: the contribution of core public health services in BC. BMC Public Health 2013;6(13):550.

Prevalence of Post-Traumatic Stress Disorder Among Internally Displaced and Undisplaced Children of Khyber Pakhtukhwa

Ruqaiya Gul and Erum Irshad

ABSTRACT

Objective: War against terror shattered all faculties of living in Khyber Pakhtukhwa. The present study was aimed to explore the prevalence of post-traumatic stress disorder (PTSD) among internally displaced and undisplaced children as these children are our true future and treatment or intervention facilities available for them.

Study Design: Observational / descriptive study.

Place and Duration of study: This study was conducted at the Department of Physiology, University of Peshawar in 2011.

Materials and Methods: IDP children were assessed at schools for internally displaced children at Jalozi Camp whereas undisplaced children were assessed at different schools in Peshawar. Independent sample t-test and chi square were used to assess the prevalence and intensity of PTSD among internally displaced and undisplaced children. Semi structured interview and Post Traumatic Stress Disorder, Child and Adolescent Questionnaire (PTSD CAQ) were used to assess the prevalence and intensity of PTSD.

Results: The results supported the hypothesis. It was found that traumatic experiences of war and displacement caused serious psychological problems in children. Internally displaced children reported high levels of PTSD than undisplaced children also internally displaced children scored high on all the three subscales of PTSD CAQ that shows the severity of their reaction to war trauma.

Conclusion: It was concluded that children who were exposed to the trauma of war and who faced the uncertain situation of displacement suffered more from PTSD than those who were not displaced from the secure environment of their homes. This study also found that there was no treatment or intervention plan for the psychological treatment of these children.

Key Words: War, Posttraumatic Stress Disorder, Children, Internally Displaced And Undisplaced

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INTRODUCTION

History records shows that there have been well over 100 conflicts in the past 50 years and until recent configuration almost all were in under developed countries, where 50% of the population used to be of children, and where the civilians are supposed to carry the burden of the violence of warfare. In most conflicts civilian's casualties have been around seventy five percent¹.

The most common psychological reactions to traumatic situations of war and conflict are depression and posttraumatic stress disorder² and relatively high prevalence of these disorders have been found among displaced children living in camps as opposed to the children living in urban or rural areas³.

In a study Pham⁴ assessed survival of 1994 genocide in Rwanda and found that among 2,091 participants 24.8% fulfilled the criteria for PTSD diagnosis.

In 1998-99 war in Kosovo directly affected large number of civilians. Respondents reported symptoms of PTSD and psychological illnesses were on increase with the increase in experiences of traumatic events. Psychiatric problems were expected to occur more in IDP's. These issues were considered important to return Kosovar Albanians to stable and productive environment⁵.

In a study⁶ studied 2,796 children age between nine to fourteen years from Bosnia-Herzegovina were assessed and high levels of post-traumatic symptoms and symptoms of grief were found among them.

Similarly in another study 27 young Cambodian children age between 8 to 12 years were assessed. Among them high occurrence of PTSD was found in 48% where as in 41% children depression was found.

In Iraqi Kurdistan at "Anfal" 5 years after the military operation forty five families were selected randomly from two camps that were arranged for displaced people. The posttraumatic stress symptoms were assessed among the caregivers and the oldest child in each family. 87% of the children and 60% of their caregivers reported PTSD⁸.

Laor et al.^{9,10} studied Israeli children and found that after Iraqi shelling Posttraumatic stress symptoms

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decreased in general population but the symptoms increased among displaced children.

Paardekooper, De Jong and Hermanns¹¹ assessed children and found that refugee children who experienced war related hassles also experienced more traumatic events and were using more coping modes. They also frequently reported PTSD-like complaints, behavioral problems, and depression symptoms.

Neuner et al.¹² studied Ugandans and Sudanese from west Nile Region. Randomly selected sample of 3,339 refugees and found that a DSM-IV criterion for PTSD was fulfilled by both male and female respondents (31.6% and 40.1% respectively). He also found that as the experiences of traumatic events increased the prevalence and occurrence of psychological strain also increases.

Hasanovic¹³ conducted a study and found that around half of the children from Bosnia reported clinically high levels of PTSD during the war in former Yugoslavia.

Kinzie, Sack, Angell, Clarke, & Ben¹⁴ assessed 27 young people age between 8 to 12 years from Cambodia for three years they experienced severe trauma. For assessment structured interview and self-rating scales were used. Among them high occurrence of PTSD was found in 48%. Depression was found in 41%. Ovuga, Oyok & Moro¹⁵ carried out a study on 58 girls and 44 boys in north Uganda 55.9% of the children had PTSD.

Pakistan started "War against Terror" after the incidence of 9/11. Evils of this war caused too much damage to the nation and huge cost was paid by the public especially people from the tribal areas Khyber Pakhtunkhwa (KP) faced lot of difficulties and pushed the people of Federally Administered Tribal Area (FATA) to migrate from their native homeland to a more secure place.¹⁶ Survey research found that IDP's faced endless problems in adjustment to resettled areas. A case study by Khalily¹⁷ reveals that war against terror increased the incidence of mental health problems in Swat Valley, but the health care system is not well developed to deal efficiently with these issues.

To assess the psychological and emotional reactions of Pakistani children towards "War against Terror" following study was designed. The main aim of the study was to assess the prevalence and intensity of PTSD among children who got internally displaced as compare to those who were not displaced and to assess the psychological treatment available for them.

Hypotheses

1. There will be high incidence of post traumatic stress disorder among internally displaced children as compare to undisplaced children.
2. Internally displaced children will score high on PTSD CAQ as compare to undisplaced children i.e. their intensity of PTSD symptoms will be high.

MATERIALS AND METHODS

Sample comprised of (N=282) subjects, including children from internally displaced camps (n=192) and undisplaced children (n=90). Children between ages 10 to 15 were included in the sample. Equal number girls and boys were included in the sample. Internally displaced children were randomly selected from schools of internally displaced people at Jalozi camp, KP. Whereas undisplaced children were randomly selected from schools located in different areas of Peshawar, KP.

Procedure: After taking formal permission from head of the schools and consent from parents semi structured interview was conducted with all the subjects to develop rapport and to collect information about history, intensity and duration of the problem, and the academic and behavioral problems of the children. Screening test i.e. Post-Traumatic Stress Disorder Children and Adolescents Questionnaire (PTSD CAQ) was administered on children at schools for internally displaced and undisplaced children to assess prevalence and intensity of PTSD among them. PTSD CAQ is a 35 items likert-type scale to assess the level of posttraumatic stress disorder in children. Reported reliability of PTSD CAQ is =.82. (steele & Raider, 2001).

It consists of three subscales

- i. Reexperiencing of traumatic events.
- ii. Avoidance of stimuli associated with traumatic event.
- iii. Symptoms of increased arousal due to traumatic event.

RESULTS

Table 1 shows that PTSD CAQ has three sub scales sub scale 1 assess reexperienceing of traumatic events. It has 12 items and cronbach's alpha reliability is .963 that indicates relatively high reliability. Sub scale II assesses symptoms of increased arousal. It has 13 items and cronbach's alpha reliability is .731 that also shows relatively high reliability. Sub scale III assesses symptoms of increased arousal due to traumatic events. It has 10 items and cronbach's alpha value is .93 that also indicates relatively high reliability. Skewness and kurtosis values of PTSD CAQ sub scales ranges between +1 to -1 that shows normal distribution of data. Table 2 shows that internally displaced children suffered significantly from PTSD as compare to undisplaced children. Internally displaced children showed symptoms of reexperiencing of traumatic events significantly more than undisplaced children (41.51 ± 7.66) with $t(280)=25.49$, $p=.000$. Internally displaced children also showed symptoms of avoidance of stimuli associated with traumatic events more than undisplaced children (22.76 ± 4.60) with $t(280)=10.31$,

$p = .000$. Table also shows that internally displaced children suffered more from symptoms of increased arousal due to traumatic events than undisplaced children (32.14 ± 5.73). with $t(280) = 31.33$, $p = .000$.

The mean values of sub scales I indicates moderate levels of symptoms of reexperiencing of traumatic events persist in general population of internally displaced children while mild symptoms are reported in undisplaced children. The mean of sub scale II indicates that mild levels of symptoms of avoidance of stimuli associated with traumatic events are reported in both the internally displaced and undisplaced children. Mean

scores of sub scale III that assess symptoms of increased arousal indicates that moderate levels of symptoms in internally displaced children while mild symptoms in undisplaced children are reported.

Standard deviation is high in internally displaced group than undisplaced group that indicates that more severe cases of PTSD were present in internally displaced group than undisplaced group.

Table 3 shows that the incidence of PTSD in internally displaced children is reported high than undisplaced children. There is significant difference between IDP and undisplaced children.

Table No.1: Psychometric properties of PTSD CAQ

Scales	No of items	α	$M(SD)$	Ranges		Skew	Kur
				Potential	Actual		
Reexperiencing	12	.96	36.15(11.90)	12-60	14-58	-.21	-.90
Avoidance of stimuli	13	.73	21.32(4.8)	13-65	13-54	1.95	9.65
Increased arousal	10	.93	26.97(10.1)	10-50	10-46	-.39	-1.04

Note. Sub scale I = reexperiencing of traumatic events, Sub scale II = avoidance of stimuli associated with traumatic events, Sub scale III = symptoms of increased arousal due to traumatic events. α = Cronbach's Alpha, M= mean, SD= standard deviation, Skew= skewness, Kur= Kurtosis.

Table No.2: Mean, Standard deviation, and t -values on the sub scales of PTSD CAQ between IDP's and Undisplaced children ($n=282$)

Sub scale	IDP's ($n=192$)		Undisplaced ($n=90$)		$t(280)$	p	95% CI		Cohen's d
	M	SD	M	SD			LL	UL	
Reexperiencing	41.51	7.66	19.79	3.7	25.49	.000	20.04	23.39	3.26
Avoidance of stimuli	22.76	4.60	17.38	2.6	10.31	.000	4.35	6.41	1.32
Increased arousal	32.14	5.73	12.46	2.3	31.33	.000	18.53	20.92	4.00

Table No.3: Cross tabulation of symptoms of reexperiencing of traumatic events, avoidance of stimuli associated with traumatic events and increased arousal due to traumatic events reported among internally displaced and undisplaced children.

	Internally displaced ($n=192$)	Undisplaced ($n=90$)	p
Re-experiencing			
Mild	8.9	98.9	.000
Moderate	45.6	1.1	
Severe	46.0	0.0	
Avoidance of stimuli			
Mild	13.1	70.0	.000
Moderate	52.4	30.0	
Severe	34.5	0.0	
Increased arousal			
Mild	10.7	100.0	.000
Moderate	45.2	0.0	
Severe	44.0	0.0	

DISCUSSION

In this study semi-structured interview and PTSD CAQ scales were used. PTSD CAQ has three sub scales sub scale 1 assess reexperienceing of traumatic events. It

has 12 items and cronbach's alpha reliability is .96 that indicates relatively high reliability. Sub scale II assesses symptoms of increased arousal. It has 13 items and cronbach's alpha reliability is .73 that also shows relatively high reliability. Sub scale III assesses symptoms of increased arousal due to traumatic events. It has 10 items and cronbach's alpha value is .93 that also indicates relatively high reliability. Skewness and kurtosis values of PTSD CAQ sub scales ranges between +1 to -1 that shows normal distribution of data (see table 1).

This study provided evidence that the incidence of PTSD is high among internally displaced children as compare to undisplaced children of KP (see table 2). Internally displaced children showed symptoms of reexperiencing of traumatic events significantly more than undisplaced children (41.51 ± 7.66) with $t(280) = 25.49$, $p = .000$. Internally displaced children also showed symptoms of avoidance of stimuli associated with traumatic events more than undisplaced children (22.76 ± 4.60) with $t(280) = 10.31$, $p = .000$. Internally displaced children suffered more from symptoms of increased arousal due to traumatic events than undisplaced children (32.14 ± 5.73). with $t(280) = 31.33$, $p = .000$.

The mean values of sub scales I indicates moderate levels of symptoms of reexperiencing of traumatic events persist in general population of internally displaced children while mild symptoms are reported in undisplaced children. The mean of sub scale II indicates that mild levels of symptoms of avoidance of stimuli associated with traumatic events are reported in both the internally displaced and undisplaced children. Mean scores of sub scale III that assess symptoms of increased arousal indicates that moderate levels of symptoms in internally displaced children while mild symptoms in undisplaced children are reported.

Standard deviation is high in internally displaced group than undisplaced group that indicates that more severe cases of PTSD were present in internally displaced group than undisplaced group.

PTSD is frequently caused by disasters but its intensity and frequency increases in internally displaced children mainly because they face the hazards of disaster as well as the trauma of displacement. Their whole living gets destroyed by displacement. This unexpected and severe threat to their existence cause severe PTSD. The present study also found high intensity of PTSD among internally displaced children as they scored high on all sub scales of PTSD CAQ as compared to undisplaced children (see table 3).

Through semi structured interview this study found a number of significant war associated factors that led to the development of PTSD e.g. all of the internally displaced children went through the experience of leaving their home in an emergency situation. Semi structured interview revealed that they lost their loved ones in this war situation, some witnessed the killing of their family members, received threats about kidnapping and killing, even some children were restricted in their madrassas (school) because of terrorist attacks, some children lost their families during displacement and later on met their families in internally displaced camps through the efforts of their family members and Government and Non-Government agencies. These war related risk factors shed significant effects on children.

School teachers in internally displaced camps reported that these children were fearful because of their traumatic experiences. Whenever they hear sound of a flying airplane they come out from their classrooms and pickup stones to hit the plane and to protect themselves. Findings of this study revealed that war and conflicts caused serious symptoms of PTSD among internally displaced children of KP. Children were feeling fearful because of threatening situation and guilty because of helplessness. They witnessed the unexpected terror at a very young age for which their capabilities were not well developed.

CONCLUSION

Children of Khyber Pakhtunkhwa faced unexpected terrors of war that caused serious physical, social as well as psychological problems to them. High prevalence of PTSD was found among internally displaced children than undisplaced children. They also scored high on all the sub-scales of PTSD CAQ that shows high intensity or severity of their psychological reaction to war and displacement. Moreover this study was conducted in Jalozi camp for IDPs and people there had no access to psychological interventions especially children who cannot express their feelings were at high risk.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Richman N. Annotation. Children in situations of Political Violence. *J Child Psychol Psychiat* 1993; 34(8):1286-302.
2. Hasanovic M. Psychological consequences of war-traumatized children and adolescents in Bosnia and Herzegovina. *Acta Medica Academica* 2011; 40(1):45-66.
3. Khamis V. Post-traumatic stress disorder among school age Palestinian children. *Child Abuse & Neglect* 2005;29(1):81-95.
4. Pham, Phuong N, Harvey M, Weinstein, Longman T. Trauma and PTSD symptoms in Rwanda. *JAMA* 2004;292(5):602.
5. Cardozo, Barbara L. Mental Health, Social Functioning, and Attitudes of Kosovar Albanians Following the War in Kosovo. *JAMA* 2000; 284(5):569.
6. Smith P, Perrin S, Yule W, Hacam B, Stuvland R. War exposure among children from Bosnia-Herzegovina: psychological adjustment in a community sample. *J Traumatic Stress* 2002; 15(2):147-56.
7. Kinzie JD, Sack W, Angell R, Clarke G, Ben R. A Three-Year Follow-up of Cambodian Young People Traumatized as Children. *J Am Acad Child Adolescent Psychiat* 1989;28(4):501-04.
8. Ahmad A, Sofia MA, Sundelin-Wahlsten V, Von Knorring A-LV. Posttraumatic stress disorder in children after the military operation "Anfal" in Iraqi Kurdistan. *Europ Child Adolescent Psychiat* 2000;9(4):235-43.
9. Laor N, Wolmer L, Mayes L C, Gershon A, Weizman R, Cohen DJ. Israeli preschools under

- Scuds: a 30 month follow-up. *J Am Acad Child and Adolescence Psychiat* 1997;36(3):349-356.
10. Laor N, Wolmer L, Cohen DJ. Mothers' Functioning and children's symptoms 5 Years after a SCUD Missile Attack. *Am J Psychiat* 2001; 158(7):1020-026.
 11. Paardekooper B, JTV M, De Jong, Hermanns JMA. The psychological impact of war and the refugee situation on South Sudanese children in refugee camps in Northern Uganda: an exploratory study. *J Child Psychol Psychiat* 1999; 40(4):529-36.
 12. Neuner F, Schauer M, Karunakara U, Klaschik C, Robert C, and Elbert T. Psychological trauma and evidence for enhanced vulnerability for posttraumatic stress disorder through previous trauma among West Nile refugees. *BMC Psychiat* 2004;4(1).
 13. Hasanovic M. Psychological consequences of war-traumatized children and adolescents in Bosnia and Herzegovina. *Acta Medica Acad* 2011; 40(1):45-66.
 14. Kinzie JD, Sack W, Angell R, Clarke G, Ben R. A three-year follow-up of Cambodian young people traumatized as children. *J Am Acad Child Adolescent Psychiat* 1989;28(4):501-04.
 15. Ovuga E, Oyok TO, Moro EB. Post traumatic stress disorder among former child soldiers attending a rehabilitative service and primary school education in Northern Uganda. *Afri Health Sci* 2008;8(3):136-41.
 16. Kazmi FS, Abbasi SB, Khan MA, Taj R. Stressful life events among internally displaced persons of KPK after military operations. *Ann Pak Inst Med. Sci* 2015;11(1):40-46
 17. Khalily MT. Mental health problems in Pakistani society as a consequence of violence and trauma: a case for better integration of care. *Int J Integrated Care* 2011;11(2).

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Radiotherapy Induced Adverse Effects in Cancer Patients at Cancer Hospital Jamshoro, Sindh

Tooba Khan¹, Arshad Lodhi², Muhammad Ali Ghoto¹, Abdullah Dayo¹, Fouzia Panhwar³,
Mudassar Iqbal Arain¹ and Ahsan Ali¹

ABSTRACT

Objective: The objectives of the study are to analyze adverse effects of radiotherapy on blood complete picture of patient after radiotherapy and to assess number of other potential adverse effects of radiotherapy on the basis of WHO guidelines.

Study Design: Observational study.

Materials and Methods: Data was collected from patients and diagnostic record files of the patients on a predesigned questionnaire over a period of six months in 2015. Total number of 120 patients was selected via random sampling from Cancer hospital Jamshoro. Data was evaluated and analyzed according to WHO guidelines.

Results: Out of 120 patients 72 were male and 48 were female. After receiving radiotherapy 30% of the patients were having anemia, 42.5% leucopenia, 37.5% lymphocytopenia, 55% thrombocytopenia, 20.8% neutropenia. Other adverse effects were with the frequency of 86.66% of the patients had insomnia, 20% nausea/ vomiting and 26% Acidity, 13.3% abdominal pain, 20% diarrhea, 80% oral mucositis, tachycardia 46.6%, bradycardia 6.66%, amnesia 13.33%, fatigue 93.33%, vision problems 33.33%, hearing problem 20%, tinnitus 26.66%, hair loss 46.66%, skin reaction 40%, 73.33% of the patients were feeling Numbness and 46.6% with loss of appetite.

Conclusion: Findings of the study concludes radiotherapy for cancer lead to various adverse Effects and these may prove fatal, if not treated early such as various effects including blood disorders which may weaken the patient's immunity

Key Words: Cancer, Radiotherapy, adverse effects

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INTRODUCTION

The highly potent and very fatal disease, Cancer, is caused by mainly the environmental. Factors that mutates gene codings of critical cells-regulatory proteins. As a result aberrant cell behavior leads to uncontrolled growth and spread of abnormal cells of the body¹. In all living organisms cell is the basic unit of life. Cell division occurs to form tissue increasing the body mass. When unwanted growth of cell occurs it forms increased abnormal mass of the tissue. This pathological disturbance of growth, characterized by excessive and unnecessary proliferation of cells is called Tumor. In all kinds of tissues, tumor can be formed.

There are only two kinds of tumor Benign and Malignant². Benign tumors mostly occur as non-cancerous. Usually, benign tumors are removable and they may grow back seldom. They are Non-invasive and remain localized. The growth rate of benign tumors is slow and might stop or regress. Benign tumors are not usually life threatening³. Malignant tumors are the cancerous cells. These cancers cells pervade and deteriorate the organs and tissues subsided by the tumor. They have an ability to escape from the malignant tumor and may either enter the lymphatic system or into the bloodstream. Rapid and uncontrollable growth are the characteristic features of malignant tumor cells. When there is spread of such cancer cells within the body to the other organs through the lymphatic system or the blood stream is known as Metastasis³. World Health Organization describes Cancer as a leading cause of death, accounted as 7.4 million deaths worldwide. The treatment for cancer depends upon its type, location and state of advancement⁴. There are three accepted conventional and standard cancer treatments: Surgery, Chemotherapy and Radiation therapy. The first treatment to remove solid tumors is Surgery, often required for early stage cancers and benign tumors in which abnormal growth

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of cells or mass is removed by incision of localized tumors⁵. The treatment which involves the use of drugs and medicines to kill cancer cells is called Chemotherapy. It is often given individually, when it is given along with other therapies such as surgery and radiotherapy, it is known as neo adjuvant chemotherapy⁴. In radiation therapy, radiations kill the cancer cells by directly targeting the tumor with high-energy rays. These radiations damage Deoxyribonucleic Acid and prevents the replication of the cells. Hence it preferably kills the cancerous cells that also may kills normal cells, especially those cells that are dividing. Surgery can often be used together with radiation therapy^{1,5}. Pharmaceuticals drugs. That contain radioactive materials called Radioisotopes or Radiopharmaceuticals that are taken either from mouth or they are placed inside body cavity to treat cancer. Radiations are defined as the energy emitted from one place to another. These energies can either be in the form of particles called Photons or in the form of waves like X-rays or visible light. Radiations are classified according to the extent of energy emitted to break the chemical bond and knock electrons out of the atom⁶. Evidence based estimations for cancer treatment indicates 52.7% to 60% of cancer patients receive radiotherapy⁷. Radiations that are used for cancer treatment are known as Ionizing Radiation as they form Ions. These ions are electrically charged particles which passes through tissues into the cells. They either kill the cancer cells or stop their growth by changing their genes. Ionizing radiation are of two kinds, Particle radiation and Photon radiation. Particle radiation includes beta particles, carbon ions, protons, electrons, neutrons and alpha particles whereas Photon radiation are x-rays and gamma rays. Ionizing energy of one type may possess more energy than the other one. Greater the intensity of the energy, more deep penetration of the radiations occur into the tissues^{8,9}. Radiotherapy can either be External Beam Radiotherapy or Internal beams Radiotherapy. In External Beam radiation therapy the cancer cells are aimed by a machine outside the body. In Internals beam radiation therapy the cancer cells are treated by the radiations that are either kept inside the body or near to that cancerous cell. Internal Radiotherapy is also named as Brachytherapy¹⁰. External Radiotherapy, according to its function, is further divided into three types: Intensity modulated radiotherapy (IMRT), No-exit Dose Proton Beam Therapy and Stereotactic Radio surgery (SRS)⁸. Adverse effects of radiotherapy is difficult to predict exactly, it simply depends upon the treatment type and the body area under treatment⁹. The stated adverse effects usually observed are skin reactions, Hair loss, Changes in the blood, Tiredness, eating and drinking problems, sickness and Dermatitis. Depending upon the size, dose and depth of penetration of emitted energy, radiation therapy often causes dermatitis. Radiotherapy

also alleviate Hemoptysis in 60 to 70% of cancer patients⁷. Radiotherapy also damages the cells that are normal and healthy like those in the salivary glands, moist and soft mouth linings, that may result in xerostomia and tooth decay^{10,11}. Anemia, lymphedema, infertility are also the side effects of radiation therapy. Almost 87% of the cancer patients that are under Radiotherapy and also receiving chemotherapy developed ADRs¹².

MATERIALS AND METHODS

A prospective observational study was conducted by collecting patient's data and diagnostic record file on a predesigned questionnaire of over a period of six months. Initially, a total number of 120 patients were enrolled via purposive sampling from Cancer hospital Jamshoro. Numbers of adverse effects reported by diagnostic lab reports were assessed and data will be compared against WHO Guidelines, Cancer Treatment Centers of America and Radiotherapy Risk Profile Technical Manual.

Inclusion Criteria: All patients receiving Radiotherapy and patients on chemotherapy along with Radiotherapy were included regardless of gender.

Exclusion Criteria: Patients with HIV, Hepatitis and Tuberculosis and pregnant ladies were excluded from the study.

RESULTS

Demographics Analysis: Among 120 patients, the majority of patients were female that is 68 (56.66%) and 52 (43.44%) male as mentioned in table 1, had suffered from adverse effects after receiving the cancer radiotherapy. Further classification based on the age revealed that maximum number of affected patients were belonging to the age group of 41-50 years as shown in table no: 2.

Table No. 1: Number of patients

Gender	Number of Patients	Percentage %
Male	52	43.33 %
Female	68	56.66 %
Total	120	100 %

Table No. 2: Age groups

Age	Frequency	Percentage %
18-30 years	11	9.1%
31-40 years	22	18.33%
41-50 years	44	36.66%
51-60 years	25	20.83%
61-70 years	18	15.08%
TOTAL	120	100 %

Adverse Effects Analysis: The study sample comprised of 120 patients, in which 36 patients making 30% of the total, after receiving radiotherapy suffered

from Anemia, 20.8% of the patients had Neutropenia, 42.5% Leukopenia and 55% were having Thrombocytopenia as shown in Table: 3.

Table No.3: Effects on blood reports after radiotherapy

Adverse Effects	Frequency	Percentage%
Anemia	36	30%
Thrombocytopenia	66	55%
Leukopenia	51	42.5%
Neutropenia	25	20.8%
Lymphocytopenia	45	37.5%

Table No.4: Other Adverse Effects

S.No	Adverse Effects	Percentage
1.	Vomiting	20%
2.	Acidity	26%
3.	Loss of Appetite	46.60%
4.	Abdominal pain	13.30%
5.	Diarrhea	20%
6.	Oral mucositis	80%
7.	Tachycardia	46.60%
8.	Bradycardia	6.66%
9.	Amnesia	13.33%
10.	Fatigue	93.30%
11.	Insomnia	86.66%
12.	Vision Problem	33.33%
13.	Hearing problem	20%
14.	Tinnitus	26.66%
15.	Numbness	73.30%
16.	Hair loss	46.66%
17.	Skin reactions	40%

In other adverse effects 80% of patients were suffering from oral mucositis. 86.66% of the patients were facing insomnia after having radiotherapy. 73.33% of the patients were feeling Numbness after having radiotherapy.

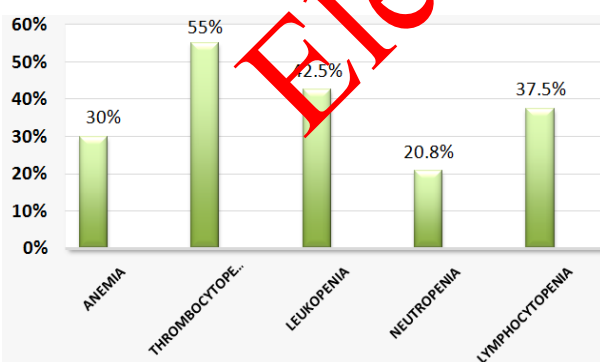
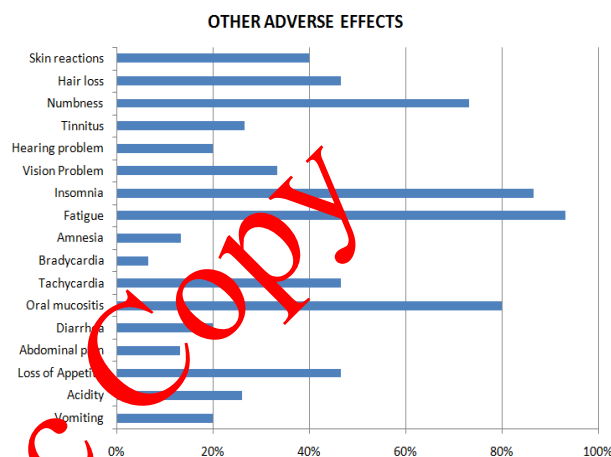


Figure No.1: Effects found on blood reports after radiotherapy

During treatment of different types of cancer with radiotherapy, the other potential adverse effects observed were concluding that 20% of the patients experienced vomiting, 26% of the patients had acidity, 46.60% of the patients were feeling loss of appetite,

13.30% of patients declared to have abdominal pain, 20% of the patients had Diarrhea. 80% of the patients had oral mucositis, 46.60% of the patients had Tachycardia, 6.66% of the patients had bradycardia, 13.33% of the patients had Amnesia, 93.30% of the patients were experiencing fatigue, 86.66% insomnia, 33.33% vision problem, 20% of the patients had Hearing problem, 26.66% of the patients had Tinnitus, 46.66% of the patients had Hair loss, 40% of the patients had skin reactions, 73.30% of the patients were feeling Numbness after receiving the required dose of their radiotherapy as given in table 4.



Graph No.1: Graphical Representation of Other Adverse Effects

DISCUSSION

In our study females were accounted to more than half of the cases. During the study, it was observed that the populations in the age group 41-50 years were more prone to the development of adverse effects after receiving radiotherapy. Numbers of adverse effects were found in blood reports of the patients. Commonly the patients were experiencing thrombocytopenia. After receiving radiotherapy 30% of Patients suffered from Anemia, 20.8% Neutropenia, 42.5% Leukopenia and 55% were having Thrombocytopenia. In other adverse effects 80% of patients were suffering from oral mucositis. 86.66% of the patients were facing insomnia after having radiotherapy. 73.33% of the patients were feeling Numbness after having radiotherapy.

CONCLUSION

Findings of study shows that Radiotherapy for cancer lead to various Adverse Effects and those proved to be fatal when not treated early such as various effects including blood disorders which weaken the patient's immunity. In noticeable number of patients different therapies were provided to prevent those adverse effects and to cure patient's health and quality of their life.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Alison MR. Cancer. Encyclopedia of Life Sciences. Nature Publishing Group 2001;1-8.
2. Agency for Toxic Substances and Diseases Registry (ATSDR), 2002, "What is Cancer", website:<http://www.atsdr.cdc.gov/COM/cancer.pdf>
3. World Health Organization 2009. Cancers the Problem. J Northwestern Memorial Hospital (NMH) Fact Sheet, http://www.who.int/nmh/publications/fact_sheet_cancers_en.pdf
4. American Cancer Society. Understanding Radiation Therapy: A Guide for Patients and Families. (2014) pg. 1-22, <http://www.cancer.org/acs/groups/cid/documents/webcontent/003028-pdf.pdf>
5. Leland Hartwell. Cell Biology and Cancer. Rediscovering Biology Molecular to Global Prospective, website:http://www.learner.org/courses/biology/support/8_cancer.pdf
6. American Society of Clinical Oncology. Radiation Therapy. Conquer Cancer Foundation of the American Society of Clinical Oncology (2014), website:http://www.cancer.net/sites/cancer.net/files/asco_answers_radiation_therapy.pdf
7. Sydney and central coast Radiation Oncology Centers. Common Side effects of Radiation Therapy. QF022 Rev 1.
8. Jay S. Loeffler, MD and Teresa M. McCue 'August Morning. What is Radiation Therapy. Radiation Oncology. Massachusetts General Hospital 1-12.
9. Macmillan 2013. Side effects of Radiotherapy", Macmillan Fact sheet ask Questions about Cancer, website:<http://www.nhs.uk/ipgmedia/National/Macmillan%20Cancer%20Support/assets/Sideeffectsofradiotherapy.pdf>
10. National Cancer Institute, "Radiation Therapy and You. Support for people with Cancer, U.S. Department Of Health And Human Services National Institutes of Health, NIH Publication 2007;12-7157, website: <http://www.cancer.gov/publications/patient-education/radiationtherapy.pdf>
11. Cassell GH. Infectious Causes of Chronic Inflammatory Diseases and Cancer. Lilly Research Laboratories 1998;4:3.
12. Prasad A, et al. Pattern of Adverse Drug Reactions Due to Cancer Chemotherapy in a Tertiary Care Teaching Hospital in Eastern India. J Pharmacovigilance 2013;1(2)-1-4.

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Role of Neck Dissection in N0 Neck for Cheek Cancer

Neck Dissection
in N0 Neck for
Cheek Cancer

Mushtaque Ali Memon¹ Danish Raheem¹ and Qambar Ali laghari²

ABSTRACT

Objective: To see the frequency of cervical nodal metastasis and involvement of different levels in Ca: cheek

Study Design: Descriptive study.

Place and Duration of Study: This study was conducted at the Department of ENT of DUHS Civil Hospital Karachi from January 2007 to October 2008.

Materials and Methods: Data recorded on prescribed proforma from all histopathologically proven cases of SCC of cheek with or without palpable node of neck node. All admitted through the Out Patient Department in ENT ward and confirmed after neck dissection for positive nodes at different level(s).

Results: Cervical metastasis found in the 33.33% of the patients. Level I in 99.98% cases and the level II in the 83.33% cases were usually involved neck levels with Cheek's carcinoma.

Conclusion: Study concluded that the elective neck dissection may be carried out as the routine case in the carcinoma of the cheek.

Key Words: Ca: Cheek, Neck dissection, Lymph node metastasis

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INTRODUCTION

Cancer is a universal problem. Since many years, the physicians are struggling for diagnosing and managing these cases. Oral carcinoma is second commonest cancer in Pakistan after lung carcinoma in males and breast carcinoma in females¹. A great several factors are associated with the Ca: Cheek and oral malignancies having strong association with chewing habits of tobacco, Naswar and BQ with tobacco or without tobacco²⁻⁴. In our region cheek is commonest site of SCC because of the chewing different types of tobaccos, which include naswar and betel quid with or without tobacco⁵ and it has comparatively low rate of metastasis⁴. Nodal metastasis is a very common poor prognostic factor in SCC of cheek, even there are controversies regarding their management. Increases nodal metastasis in turn to increase T stage⁶ once the neck nodes are involved the survival rate drops up to half⁷. Clinical examination is a frequent tool for assessment of regional cervical lymph nodes, but their reliability is doubtful, false positive or negative results are seen in about 20-30 percent cases. CT scan may detect malignant cervical lymph nodes in a better way. It is well known that the node which large from 1cm in the size on CT scan may have malignant disease, but those at lower level when present 1.5 cm size is considered to be malignant.⁸

In the N0 neck, it is considered that neck dissections has a therapeutic role and thus contribute in rising five-year survival rate for oral cancers since last five years.^{9, 10}

Many authors have query for comprehensive neck dissections roll in treatment of limited positive cervical nodal disease.^{11, 12} In another study demonstrated that when cervical node metastasis probability is occur greater than 20%, the neck may treated electively.⁴ This may include all stage III and most T2 cheek carcinomas.¹³

MATERIALS AND METHODS

This descriptive study was conducted at the Department of ENT of DUHS Civil Hospital Karachi from January 2007 to October 2008.

Inclusion Criteria: 30 patients, all the cases with all age groups either gender presented to ENT OPD or ENT ward of Civil Hospital Karachi with biopsy proven carcinoma of cheek with or without palpable neck nodes were included in this study.

Exclusion Criteria: Cases treated elsewhere or without documentary evidence, residual or recurrent diseases or exposed to chemotherapy or radiotherapy were excluded from this study.

Data Collection Procedure: This was descriptive case series study. All the patients irrespective to the age and sex with biopsy proven carcinoma of cheek and neck nodes proven clinically or radiologically presenting to ENT Department were incorporated. The demographic data like name, age, sex, contact no: of patient and address, clinical findings of cheek lesion whether ulcerative or exophytic, with site, size and clinical

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findings of neck nodes like palpable or not, level involvement with number of lymph nodes & size of largest one, CT scan findings (from base of skull to the root of neck), in clinically suspected cases of distant metastasis either present or absent on the basis of radiology like chest X-ray and abdominal ultrasound or C.T Scan of the chest and the abdomen in required cases. All data was entered in a prescribed proforma. Mostly Punch or Wedge Biopsies were taken and histopathological findings and stage of the disease were also noted. Primary lesion resections were done along with the dissection of the neck. Extent of the neck dissection contains on the presenting neck status. Cases having palpable neck nodes underwent a modified radical or radical neck dissection while clinically impalpable or occasionally limited N1 illness usually had selective for dissection of the neck. Specimens divided into anatomical levels in the operation theater and then sent for histopathology. All the results were entered in a prescribed proforma. Data was entered and analyzed by using SPSS version 16.

RESULTS

Total 30 cases were studied, out of them 18 (60%) were male and 12 (40%) were females with ratio of 1.5: 1 (Figure 1).

Mean age of the study cases was found 44.93 ± 12.15 years. Minimum age was 18-years and maximum was 68 years. (Figure 2).

The characteristic of primary lesion was exophytic in 20(66.6%) patients while 10(33.3%) patients were presented with ulcerative type of lesion.

In this study total 11 (36.66%) cases were found with presentations of positive neck nodes (cN+) while 19 (63.33%) were presented with clinically impalpable neck nodes. CT positive neck was found in all 30(100%) patients, while no distant metastasis had found in any patient. In this series 23 (76.66%) cases were with stage IV of the disease and 7 (23.33%) cases were with stage III of the disease (Table 1).

Neck dissection was done in all 30 cases according to clinical presentation, which was revealed that 20 (66.66%) patients were undergone in selective neck dissection, 8 (26.66%) cases underwent modified radical dissection of the neck and 2 (6.66%) cases underwent radical dissection of the neck.

Out of 30 cases 11 (36.66%) were shown histopathologically positive neck nodes while remaining 19 (63.33%) were histopathologically negative neck nodes. Histopathological differentiation found in this case series were 22 (73.33%) patients showed moderately differentiated SCC, 7 (23.33%) patients with well-differentiated SCC and 1 (3.33%) with poorly differentiated SCC. It was also revealed that out of 11 positive neck nodes 7 (63.63%) patients of moderately differentiated SCC, 1(9.09%) of poorly differentiated SCC and 3 (27.27%) of well-

differentiated SCC showed cervical metastasis.

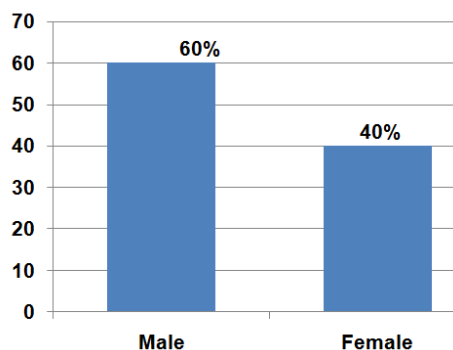


Figure No.1: Gender Distribution n=30

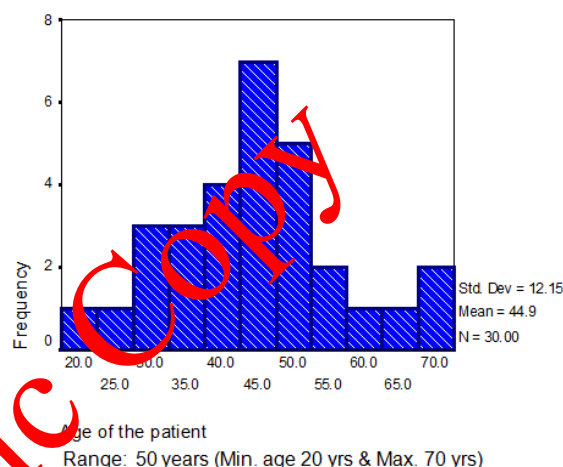


Figure No. 2: Presentation of Ca Cheek in different age group n=30

Table No.1: TNM Classification(staging with positive CT Scan) (n = 30)

Stage	No. of patients	Tumor size	Neck nodes	Metastasis	%
I	0	T1	N0	M0	0.00
II	0	T2	N0	M0	0.00
III	0	T3	N0	M0	0.00
	01	T1	N1	M0	3.33
	06	T2	N1	M0	20.00
IVA	03	T3	N1	M0	10.00
	0	T4a	N0,N1	M0	0.00
	01	T1	N2	M0	3.33
	10	T2	N2	M0	33.33
IVB	08	T3	N2	M0	26.66
	01	T4a	N2	M0	3.33
	0	Any T	N3	M0	0.00
IVC	0	Tb	Any N	M0	0.00
	0	Any T	Any N	M1	0.00

In these 11 cases of histopathologically positive neck nodes of Ca: Cheek, 10 (90.90%) patients were shown involvement at level I & II, 4 (36.36%) at level I, II & III, 1 (9.09 %) at level I and 1 (9.09%) at level I, II, III & IV (Table 2) while individual involvement of neck levels in Ca: Cheek were level I in 11 (99.98 %) patients, level II in 10 (83.33%) patients, level III in

6(54.54 %) patients, level IV in 2 (18.18 %) patients.

Table No.2: Histopathological proven neck levels involved in Ca: Cheek (n = 11)

Level (s)	No	%
I & II	10	90.90
I, II, III	4	36.36
I	1	09.09
I, II, III, IV	1	09.09

DISCUSSION

Head and neck cancers constitute about 5% of overall malignancies in the world, and incidence of head and neck tumors is rising. Mostly tumors are SCC, which shares about 95% in head and neck.¹⁴

The lymph node involvement is usually considered as most significant prognostic factor of the SCC of cheek and in fact the positive neck nodes decrease survival rate up to 50%.^{15,16} After all, cervical metastases at initial evaluation are present in nearly 30% of patients. When we consider in all T stages, the frequency of occult metastases varies in between 19% to 40%.¹⁷ There is strong relationship between patient's survival rate and +ve metastatic neck nodes at initial presentations. Mathew- Iypeetal (India) has mentioned statistically proven changes in illness of free survival having N0- N1 as compared to those having N2- N3.¹⁸ Ca cheek is common in our country⁴⁵ and it is almost a disease of elder people, because of their exposure to risk factors. Our study shows 53.33% persons are belonged to 50- 60 years of age which is comparable to study of Ali et al in which there is 54.55% of the same age group,¹⁹ while in contrast Jamal et al have seen majority of patients in between 60 and 70 years of age and Khan et al observed majority in 7th decade.²⁰ Comparatively mean age of our case series is 44.93 years which is resembling with Eftim et al 45.3 yrs²¹ and Kayembe et al 48.39 yrs²² this contradict to Andisheh-Tadbir et al shows 55.9 years.²³ Our study shows male preponderance 63.33% this is possibly because of chewing tobacco, eating gutka and using naswar is comparable with Wahid et al, 60% males while in contradict Anwer et al found 51% females²⁴ (SCC of the oral cavity is generally said to be exophytic, ulcerative or infiltrative on gross pathological appearance. In our study most of the lesion were exophytic (66.6%) followed by exophytic (33.3%).

In this case series moderately differentiated SCC was seen in 73.33% followed by well-differentiated SCC 23.33% and poorly differentiated carcinoma 3.33% which was in contrast to Chidzonga study in which there was 64.8% well differentiated SCC, 24.8% moderately differentiated SCC and 10.4% poorly differentiated SCC.²⁵ Lymphatic spread of SCC also depends upon the degree of differentiation and it was concluded from various studies that poorer the tumor

differentiation more are its chances of metastasis.^{26, 27,28,}

In our study cervical metastasis was high in moderately differentiated SCC as compared to poorly differentiated SCC and well-differentiated SCC. The difference in result may because small number of patients of poorly and well-differentiated SCC in our study. So it is advisable that if poorer the tumor differentiation, the neck may be treated more aggressively.

In our series 36.6% cases were with palpable neck nodes clinically. similarly G.I Smith et al²⁹ reported that clinically palpable nodes of the neck were in 21 cases out of 171 cases with the oral SCC.²⁹ At present, dissection of the neck with the histologic examination is the best staging procedure which keeps very important information regarding prognosis. In our series dissection of the neck was carried out in all cases whether neck node(s) were palpable clinically or not. Mostly in the cases (66.66%) elective neck dissection had carried out in clinically N0 disease and also in the several patients limited clinically N1 illness. In the some clinical N1 disease the neck remained addressed selectively from the level 1 to 4. As well as modified radical dissection of the neck had done in (26.66%) and only radical dissection of the neck in (6.66%) cases had done with presentation of palpable neck nodes. Umeda et al reported that CT scan very important diagnostic tool for early diagnosis of neck metastasis.³⁰ It is also suggested by us the CT scan prior to the treatment of the neck should be done in all cases. In the light of this study, it is suggested that elective dissection of the neck should be carried out on the routine base in the oral SCC.

CONCLUSION

It was concluded that oral cavity is favorable site for the cervical metastasis. Level I and level II are the most frequently elaborated neck levels than the other buccal SCC levels. The analysis of the study revealed that due to big prevalence of cervical metastasis in SCC of the cheek, neck dissection may be performed on near routine basis but whether to do selective or comprehensive neck dissection for clinically impalpable or palpable neck nodes, a properly designed study with sufficient number of cases is required.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Bhurgri Y, Rahim A, Bhutto K, Bhurgri A, Pinjani P, Usman A, et al. Incidence of carcinoma of the oral cavity in Karachi district south. J Pak Med Assoc 1998;48:321- 5.
2. Walsh PM, Epstein JB. The oral effects of smokeless tobacco. J Can Dent Assoc 2000;66: 22- 5.
3. Veness MJ, Morgan GJ, Sathiyaseelan Y, Gebiski V. Anterior tongue cancer and the incidence of

- cervical lymph node metastasis with increasing tumour thickness: should elective treatment to the neck be standard practice in all patients? *ANZ J Surg* 2005;75:101-5.
4. Webster K. Oral cavity tumors including the lip. In: Scott Brown's Otorhinolaryngology, Head and Neck Surgery 7th ed. Great Britain: Edward Arnold;2008.p.2543-76.
 5. Wahid A, Ahmad S, Sajjad M. Patterns of oral carcinoma of oral cavity reporting at dental department of Ayub medical college. *J Ayub Med Coll* 2005;17:65-6.
 6. Najeeb T. Clinic opathological presentation of tongue cancers and early cancer treatment. *J Coll Physician Surg Pak* 2006;16:179-82.
 7. Shaha AR. Neck dissection: an operation in evolution. *World J Surgical Oncol* 2005;3:1-3.
 8. Watkinson JC. Metastatic neck disease. In: Scott Brown's Otorhinolaryngology, Head and Neck Surgery. 7th ed. Great Britain: Edward Arnold; 2008.p.2711- 52.
 9. Haddadin KJ, Soutar DS, Webster MH, Oliver RJ, MacDonald DG, Robertson AG. Improved survival for patients with clinically T1/ T2, N0 tongue tumors undergoing a prophylactic neck dissection. *Head Neck* 1999; 21: 517- 25.
 10. Keski-Santti H, Atula T, Tornwall J, Koivunen P, Makitie A. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. *Oral Oncol* 2006; 42: 96-101.
 11. Ambrosch P, Kron M, Pradier O, Steiner W. Efficacy of selective neck dissection: A review of 503 cases of elective and therapeutic treatment of the neck in squamous cell carcinoma of the upper aerodigestive tract. *Otolaryngol Head Neck Surg* 2001;124:180-7.
 12. Kolli VR, Datta RV, Orner JB, Hicks WL, Loree TR. The role of supraomohyoid neck dissection in patients with positive nodes. *Arch Otolaryngol Head Neck Surg* 2000;126:113-8.
 13. Yuen APW, Lam JY, Wei W, Ho CM, Chow TL et al. A comparison of prognostic significance of tumor diameter, length, width, thickness area, volume, and clinicopathological features of oral tongue carcinoma. *Am J Surg* 2000;180:139- 43.
 14. Ng SH, Yen TC, Liao CT, Chang JT, Chan SC, Ko SF, et al. 18F-FDG PET and CT/MRI in oral cavity squamous cell carcinoma: A prospective study of 124 patients with histologic correlation. *J Nucl Med* 2005;46:1136- 43.
 15. Kowalski LP, Bagetto R, Lara JRL, Santos RL, Tagawa EK, Santos IRB. Factors influencing contralateral lymph node metastasis from oral carcinoma. *Head Neck* 1999;21:104- 110.
 16. Puri SK, Fan CY, Hanna. Significance of extra capsular lymph node metastasis in patients with head and neck squamous cell carcinoma. *Curr Opin Otolaryngol Head Neck Surg* 2003;11:119-23.
 17. Kaya S, Yilmaz T, Gursel B, SaracSennaroglu L. The value of elective neck dissection in treatment of cancer of the tongue. *Am J Otolaryngol* 2001; 22:59- 64.
 18. Mathew-Iype E, Pandey M, Mathew A, Thomas G, Sebastian P, Krishan Niar M. Squamous cell carcinoma of the tongue among young Indian adults. *Neoplasia* 2001;3:273- 7.
 19. Ali M, Bhati AH, Tariq M, Khan SA, Sarwar G, Waheed K, et al. An Epidemiological Study Of 202 Cases of Oral Cavity Cancer (OCC) in Pakistani Subjects. *Biomedica* 1998;14: 27-31.
 20. Khan M, Salam A, Qiamud Dins. Niswar as a risk factor in the aetiology of oral cancer. *J Pak Dent Assoc* 2007;16:77- 81.
 21. Effiom OA, Adeyemo WL, Omitola OG, Ajayi OF, Emmanuel MM, Gbotolorun OM. Oral squamous cell carcinoma: a clinicopathologic review of 233 cases in Lagos, Nigeria. *J Oral Maxillofac Surg* 2008;66:1595- 9.
 22. Kayembe MK, Kalenga MM. Histological and epidemiological profile of oral cancer in Congo (Zaire). *Odontostomatol Trop* 1999; 22: 29-32.
 23. Andisheh-Tadbir A, Mehrabani D, Heydari ST. Epidemiology of squamous cell carcinoma of the oral cavity in Iran. *J Craniofac Surg* 2008;19: 169- 702.
 24. Anwer M, Shiekh S, Naqvi QS, Mehmood K. Frequency of malignant tumors in clinically suspected lesions of oral cavity. *J Surg Pak* 2003;8: 18- 9.
 25. Chidzonga MM, Mahomva L. Squamous cell carcinoma of the oral cavity, maxillary antrum and lip in a Zimbabwean population: a descriptive epidemiological study. *Oral Oncol* 2006;42:184-9.
 26. Chen YW, Yu EH, Wu TH, Lo WL, Li WY, Kao SY. Histopathological factors affecting nodal metastasis in tongue cancer: analysis of 94 patients in Taiwan. *Int J Oral Maxillofac Surg* 2008;37: 912-6.
 27. Kurokawa H, Yamashita Y, Takeda S, Zhang M, Fukuyama H, Takahashi T. Risk factors for late cervical lymph node metastases in patients with stage I or II carcinoma of the tongue. *Head Neck* 2002; 24: 731- 6.
 28. Ahmed U, Khawar A, Ahmed J, Ajmal M, Bangash WK, Akhter MR. Occult metastasis in carcinoma of oral cavity. *J Coll Physicians Surg Pak Jun* 2007;17:313-5.
 29. Smith GI, O'Brien CJ, Clark J, Shannon KF, Clifford AR, McNeil EB, Goa K. Management of the neck in patients with T1 and T2 cancer in the Mouth. *Br J Maxillofac Surg* 2004;42:494-500.
 30. Umeda M, Nishimatsu N, Teranobu O, Shimada K: Criteria for diagnosing lymph node metastasis from squamous cell carcinoma of the oral cavity: A study of the relationship between computed tomographic and histologic findings and outcome. *J Oral Maxillofac Surg* 1998;56:585- 93.

Serum Zinc Levels in Patients Suffering From Various Clinical Types of Psoriasis in Pakistan

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ABSTRACT

Objective: The compelling evidence shows that proper Zinc (Zn) nutrition is important for human health. Hence an attempt was made to evaluate the serum Zn levels in different clinical types of psoriatic patients.

Study Design: Case-control study.

Place and duration of Study: This study was conducted at Bannu University of science and technology with the collaboration of Govt. Sifat Ghayur Shaheed Memorial Children Hospital Peshawar and National Physical Standard Laboratory PCSIR Islamabad from April 2013 to April 2015.

Materials and Methods: 500 psoriatics and 100 normal controls of both genders with an age range 18-60 years were selected for this study. Serum zinc levels were measured with atomic absorption spectrophotometer (AAS).

Results: The serum zinc concentration was found to be low in 80% patients. Mean $\pm$ SD of serum zinc were $585.50 \pm 1.70 \mu\text{g/L}$ in psoriatic patients and $770.15 \pm 3.32 \mu\text{g/L}$ in controls respectively. In psoriatic patients serum zinc concentration was significantly lower than that of healthy controls ($P < 0.001$).

Conclusion: We may conclude that Zinc deficiency may play a role in the pathogenesis of psoriasis since most patients have low serum Zn level

Key Words: Zinc, types of psoriasis, AAS, Pakistan

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INTRODUCTION

Among skin diseases, psoriasis is one of the most common. It is a chronic, inflammatory and autoimmune disease characterized by hyperproliferative disorders of the skin with unknown etiology and by production of reactive oxygen species due to activation of tumor necrosis factor alpha (TNF - α), which is considered to be an important factor in the induction and maintenance of psoriatic lesions^{1,2}. Between 2 and 4.8% of the world population have psoriasis³. This pathology occurs in all age groups, and it appears in both men and women⁴. More than 50% of patients report that the onset of psoriasis occurs before the age of 40⁵. Factors that may have modulatory effects on inflammatory diseases such as psoriasis are little known. In addition, psoriasis is characterized by a defect of keratinization⁶. It has been shown that the unique process of keratinization is a dependent enzyme

that cannot be influenced by deficiencies or excess trace elements⁷. Thus, it has been established that zinc plays an important role in the process of normal keratinization of the skin of animals⁸. Indeed, zinc is an essential trace element for the skin and has healing properties. Zinc is a cofactor of various functions including growth, immunity and skin repair and protects against free radicals^{9,10,11}. Therefore, the presence of zinc is essential for the proper functioning of the skin cells¹². Decreases in zinc levels have been observed for many skin disorders such as psoriasis¹³. In Pakistan psoriasis is a common dermatological disorder but still there is lack of data on the epidemiology and prevalence of psoriasis in Pakistan. There have been very few studies so far on the comorbidities and risk factors of psoriasis. Most of these are observational descriptive studies. And, little work has been done on the analysis of zinc in the serum of different clinical types of psoriasis in Pakistan.

MATERIALS AND METHODS

Selection of psoriatic patients: In this study 500 samples of psoriasis patients, including males and females with the age range of 18-60 years were selected from different hospitals and clinical Labs of Pakistan. All the patients were examined by the dermatologist and their complete medical history were documented.

Selection of control group: A total number of 100 male and female healthy individuals aged between 18-60 years were selected with the conditions of, no

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smoking habits, no history of viral hepatitis, no alcoholic and absence of any severe or chronic pathology.

Inclusion criteria: The following individuals were included, who were; Suffered with visible psoriasis and those looking apparently healthy.

Exclusion Criteria: The following patients were excluded, who were; On minerals, hormones and vitamin therapy. Non-co-operative patients (who refused or did not have an interest to participate in the study). Suffering with acute or chronic diarrhea. Pregnant and having cutaneous diseases other than psoriasis.

Chemicals and Reagents: All reagents used were of analytical grade. All standard solutions were prepared in a 0.01 M HNO₃.

Collection and preparation of samples: 5 ml blood was taken from the antecubital vein of healthy subjects and patients. The samples were transferred to vacutainers and left undisturbed for 1 hour to clot and then centrifuged at 5000 rpm for 15 min. The sera were stored in Eppendorff vials at -20°C until further analysis. 1 ml of serum was added to a Teflon beaker and digested in mineral acids under optimum heating. The temperature of the hot plate was increased steadily in a range 175 °C to 250 °C until fumes of HClO₄ appeared.

Analysis of serum samples: For the execution of this work, an AAS (Contra 700, Analytic Jena) was used and the digested serum samples were analyzed in triplicate. The standards used in the preparation of the working curve for Zinc were prepared daily by direct dilution of the concentrated solutions of the analyte in 0.01 M HNO₃ for a concentration range of 2, 4, 10, 20, 40, 80 µg/L of standard solutions.

Validation of the analytical methods: Inter lab comparison (ILC) for quality control of serum samples was used for validation purpose. In this regard a composite sample was prepared from 100 serum samples. The composite sample was properly centrifuged. The same composite sample was also analyzed by AAS. Both results were compared and a close relationship was observed.

Statistical Analysis: Statistical analyses in connection of data's significance were carried out using the student's T-test. P values <0.001 were considered significant.

RESULTS

The study included 500 psoriasis patients (M = 250, F = 250) and 100 age and sex matched healthy controls. The overall mean of serum Zn level in control group and patients with age range 18-60 years was 770±3.77µg/L and 585.50±4.30µg/L respectively (Table 2). A statistically significant difference (p<0.001) was found among patients and control group.

Table No.1: Inter-Lab comparison of the composite samples for Se

Laboratories	Sample Type	Zn (µg/L)
Chemical Metrology Division, NPSL (Contra 700, Analytic Jena)	Diseased	689±1.55
	Healthy	720±0.79
PCSIR Labs Complex, Karachi, (Hitachi 8000 with Zeeman background correction, Japan)	Diseased	677±1.90
	Healthy	705±0.75
Abdul Wali Khan University, KPK (AA Analyst 100, Perkin Elmer, with Zeeman Background Correction)	Diseased	680±1.95
	Healthy	710±0.55

Values are the mean of three replicates ± SD

Table No.2: Serum Zinc levels in control and patient groups

Samples	Age (Years)	No. of Individuals		Conc. (µg/L)
		Male	Female	
Control	18-60	50	50	770.15±1.3
Psoriasis patients	18-60	250	250	585.50 ±2.8

P<0.001 (highly significant)

Figure 1. Shows zinc concentration among control and different clinical types of psoriasis. A significant difference p<0.005 was found between control group and psoriatic groups and within psoriatic groups a statistically significant difference p<0.005 between the mean serum Zn levels of patients with plaque psoriasis (724.11±1.89µg/l) versus guttate psoriasis (699.23±1.50µg/l), scalp psoriasis (670.13±1.90µg/l), Erythrodermic psoriasis (630±1.22µg/l), and pustular psoriasis (620±1.77µg/l).

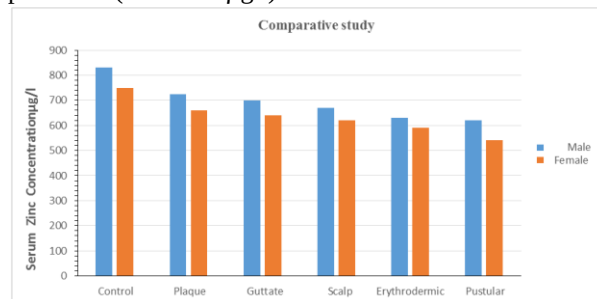


Figure No.1: Serum zinc concentration regarding to types of psoriasis.

Psoriasis is usually classified as mild, when it affects less than 3% of the body, moderate, when it affects 3 to 10% of the body, or severe > 10%. PASI is used for graduating the severity of psoriasis.

Figure 2 (a):- showed serum Zn Conc. in male and female groups whose affected body surface area is greater than 10 % of the total body surface area.

Figure 2 (b):- showed serum Zn Conc. in male and female groups whose affected body surface area is less than 10 % of the total body surface area. Thus, the deficiency sequence of serum Zn in relation to percentage of body involvement in different types of

Psoriasis is as pustular > erythrodermic > scalp > guttate > plaque.

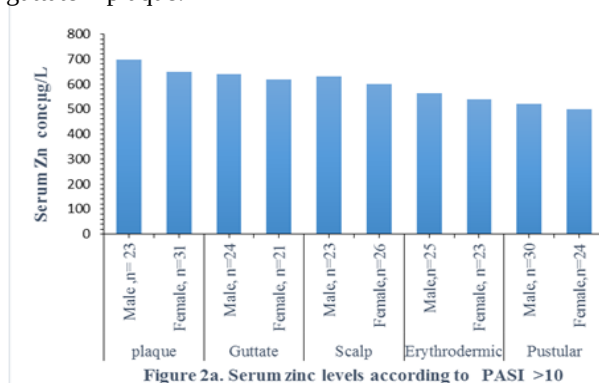


Figure No.2a: Serum zinc levels according to PASI > 10

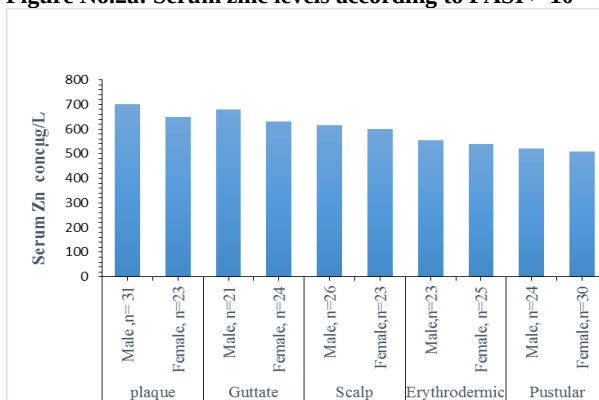


Figure No.2b: Serum zinc levels according to PASI < 10.

DISCUSSION

It is noted in our study that the mean serum zinc levels of the patients is significantly lower than that of the controls. It has been reported in the literature that normal skin and psoriatic skin do not show no significant differences for zinc¹⁴. Furthermore, no significant changes in serum zinc levels were observed in psoriasis on the basis of age, sex, duration of disease and involvement of joints and nails⁶. Many researchers have observed a significantly low level of serum zinc in psoriatic patients^{15,16} while others found normal levels¹⁷. Thus, the measurement of the plasma zinc level in psoriatics resulted in contradictory data, reduced¹⁸ high¹⁹ and normal zinc levels²⁰ were found. It has been suggested that the possible reason for the contradictory results of zinc levels in serum in psoriasis may be due to the lack of consideration of the degree of skin affected by psoriasis. As a result, the relationship between the skin surface affected by psoriasis and zinc levels in serum has been reported¹⁵. But Hinks et al have not demonstrated such a relationship in psoriasis¹⁹. Then, Sung YL. et al. reported that serum concentrations of zinc are influenced by several factors, including infections and trauma¹¹. In our study, a significant variation in zinc content in serum was observed in the general population of psoriatic patients compared to controls. This is in agreement with the findings of some studies^{21,22}. Bertazzo et al. reported

that sex had no influence on zinc content²³. While in our study, a significant decrease in zinc level was found in the Serum of psoriatic females as well as psoriatic males. Studies have shown that psoriasis is not primarily a skin disease but an immunological disturbance under the skin. Skin manifestations are the result of excessive stimulation of the superficial cells of the skin (Langerhans cells). Thus, psoriasis is considered as disorders, mainly epidermal keratinocytes, but now it is recognized as one of the most common autoimmune disorders²⁴. A first study in 1971 concerning the correlation between age and plasma zinc in 204 male subjects aged 20 to 84 and 54 female subjects aged from 20 to 58 years gave a significant linear decrease in plasma zinc with age in both groups²⁵. Also, a significant zinc reduction in serum was also found for the 'oldest age group' (≥ 90 years) in a comparative study between healthy elderly people aged 65-89 and elderly adults 20-64 years (26). Psoriasis is an inflammatory disease of chronic and recurrent skin. The forms of psoriasis are mild, moderate or severe according to the PASI (Psoriasis Area Severity Index) score. Patients with a body surface area of more than 20% psoriasis had significantly lower serum zinc levels than others (6). McMillin observed that the concentration of zinc in the serum of psoriatic patients with more than 10% of the area of the affected body was significantly lower than for those with less than 10% surface area¹⁵ which is in agreement with our study. A reduction in the concentration of zinc in the blood with the increase in psoriatic surface area may be due to the depletion of the secondary zinc by the loss of zinc by exfoliation. Another possibility is that the perturbation of the zinc state in the serum could actually be translated by a greater involvement of the psoriatic surface²⁷. The results obtained by Basavaraja K.H. et al²⁸ indicate that zinc concentrations in mild and severe psoriasis groups show a downward trend that is consistent with other studies²³. On the other hand, Bhatnagar M. et al. in their study of active and remission phases of psoriasis reported an increase in serum zinc²⁹. In their study, Nigam et al. reported no significant change in serum zinc levels in psoriasis on the basis of disease duration⁶. Factors which may have modulatory effects on inflammatory diseases such as psoriasis are not well known. It has been proposed that trace elements such as zinc may play an active role in psoriasis³⁰.

CONCLUSION

The comparison of the concentrations of trace elements in the serum of psoriatic patients must be done between subjects matched by age and sex. Finally, the data obtained in this study can guide physicians and other health professionals in the identification of essential trace element (Zn) deficiencies in biological samples the patients suffering from psoriasis.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Pujari VM, Suryakar AN, Ireddy S. Oxidants and antioxidant status in psoriasis patients. *Biomedical Res* 2010;21(2): 221-223.
2. Naziroğlu, Yıldız MK, Tamtürk B, Erturan I, Flores-Arce M. Selenium and Psoriasis. *Biological Trace Element Res* 2012;150 (1-3): 3-9.
3. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. 2005b. Prevalence and treatment of psoriasis in the United Kingdom: A population-based study. *Arch. Dermatol* 2005b; 141 (12):1537-1541.
4. Raychaudhuri SP, Farber EM. The prevalence of psoriasis in the world. *J Eur Acad Dermatol Venereol* 2001;15(1):16-1.
5. Naldi L, Gambini D. The clinical spectrum of psoriasis. *Clin Dermatol* 2007;25:510-518.
6. Nigam PK. Serum zinc and copper levels and Cu: Zn ratio in psoriasis. *Indian J Dermatol Venereol Leprol* 2005;71(3):205-206.
7. Afridi HI, Kazi TG, Jamali MK, Kazi GH, Shar GQ. The status of trace and toxic elements in biological samples (scalp hair) of skin disease patients and normal human subjects. *Turk J Med Sci* 2006;36(4):223-230.
8. Day C, McCollum EV, 1940. Effect of acute dietary zinc deficiency in rat. *Exp Biol Med* 1940; 45(1):282-284.
9. Halsted JA, Smith JC. Irwin MI. Conspectus of research on zinc requirements of man. *J Nutr* 1974; 104:345.
10. Bannister JV, Bannister,WH, Rotilio G, Aspects of the structure, function, and applications of superoxide dismutase. *CRC Crit Rev Biochem* 1987;22(2):111-180.
11. Sung YL, Hong KL, Jung YL, Jong SK. Analyses of serum zinc and copper levels in psoriasis. *Korean J Invest Dermatol* 1996;26(1): 27-38.
12. Pories WJ, Mansour G, et al. Prasad AS, Oberleas D, editors. *Trace Elements in Human Health and Diseases*. Acad Press New York 1976.p.115-142.
13. Prasad AS. Clinical, endocrinological and biochemical effects of zinc deficiency. *Clin Endocrinol Metab* 1985;14 (3):567-589.
14. Molokhia MM, Portnoy B. Neutron activation analysis of trace elements in skin. Copper in normal skin. *Br J Dermatol* 1969;81:110-4.
15. McMillan EM, Rowe D. Plasma zinc in psoriasis: Relation to surface area involvement. *Br J Dermatol* 1983;108(3):301-305.
16. Saxena N, Sharma RP, Singh VS. A study of serum zinc and copper levels in psoriasis. *Indian J Dermatol Venereol Leprol* 1990;56:216-218.
17. Portnoy B, Molokhia M. Zinc and copper in psoriasis. *Br J Dermatol* 1972;86(2):205
18. Greaves M, Boyde TRC. Plasma-concentrations in patients with psoriasis, other dermatoses and venous leg ulcerations. *Lancet* 1967;2:1019-1020.
19. Voorhees JJ, Chakrabarti SG, Botero F, Miedler L, Harrel ER. Zinc therapy and distribution in psoriasis. *Arch Derm* 1969;100:669-673.
20. Withers AFD, Baker H, Musa M, Dormandy TL. Plasma-zinc in psoriasis. *Lancet* 1968;(7562): 278-282.
21. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. The inflammatory response in mild and in severe psoriasis. *Br J Dermatol* 2004;150:917-28.
22. Kumar P, Lal NR, Mondal AK, Mondal A, Gharami RC, Maiti A. Zinc and skin: a brief summary. *Dermatol Online J* 2012;18:1.
23. Bertazzo A, Costa C, Biasiolo M, Allegri G, Cirrincione G, Presti G. Determination of copper and zinc levels in human hair: Influence of sex, age and hair Pigmentation. *Biol Trace Elem Res* 1996;52 (1): 37-53
24. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007;370:263-71.
25. Lindeman RD, Clark ML, Colmore JP. Influence of age and sex on plasma and red-cell zinc concentrations. *J Gerontol* 1971;26:358-363.
26. Ravaglia G, Forti P, Maioli, Nesi, Pratelli L, Savarino L, et al. Blood micronutrient and thyroid hormone concentrations in the oldest-old. *J Clin Endocrinol Metab* 2000;85:2260-2265.
27. Afridi HI, Kazi TG, Kazi N, Kandhro GA, Baig JA, Shah AQ, et al. Evaluation of Cadmium, Chromium, Nickel, and Zinc in Biological Samples of Psoriasis Patients Living in Pakistani Cement Factory Area. *Biol Trace Elem Res* 2010;142 (3): 284-301.
28. Basavaraj KH, Darshan MS, Shanmugavelu P, Rashmi R, Yuti Mhatre A, Dhanabal SP, et al. Study on the levels of trace elements in mild and severe psoriasis. *Clinica Chimica Acta* 2009;405 (1-2): 66-70.
29. Bhatnagar M, Bapna A, Khare AK. Serum proteins, trace metals and phosphatases in psoriasis. *IJDVL* 1994;60:18-21.
30. Donadini A, Fiora C, Regazzini R, Perini D, Minoia C. Selenium plasma levels in psoriasis. *Clin Exper Dermatol* 1992;17 (3): 214-216.

The Apolipoprotein-B/ Apolipoprotein-A1 Ratio in Normal Individuals Verses Patients with Metabolic Syndrome in Tertiary Care Units of District Peshawar, KPK

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ABSTRACT

Objective: The main objective of the study was to determine the ratio of Apo-B/Apo-A1 in normal individuals and patients with metabolic syndrome.

Study Design: Comparative / case control study.

Place and Duration of Study: This study was conducted at the Department of Pharmacology, KGMC, Peshawar from June 2015 to December 2015.

Materials and Methods: Total of 200-cases, including 150-Met-S and 50-controls were enrolled in different tertiary care hospitals of Peshawar. After formal consent, detail history and clinical examination, data was collected about height, weight, socioeconomic condition, blood pressure and waist circumference and diagnosis of Met-S was made accordingly. Blood glucose levels, Apo-B and Apo-A1 and lipid profile was done in all patients and normal individual.

Results: Among 200-study population, 150 were cases having Met-S, while 50 were normal control. The mean age was 47.75 ± 4.79 years in patients, while it was 45.16 ± 3.84 years in control group. In both cases and control groups, male-female ratio was 61/89 and 32/18 respectively. The ratio of Apo-B/Apo-A1 was calculated to measure the relative risk for coronary heart disease. The study showed $\frac{1}{2}$ average risks in subjects with Met-S, was 4.9% in males and 1.1% in females. In control, it was 3.1% in males and 5.5% in females. In my study majority of the cases in both Met-S (68.8% male, 70.7% female) and controls (96.8% male & 88.8% female) fall in twice-average risk category group. There was threefold risk in Met-S patients was 26.2% in male and 28% in female. No such association was found in the controls.

Conclusion. It is concluded from the study that ratio of Apo-B/Apo-A1 can be used as one of the best variable to quantitate the risk of coronary heart disease in normal individuals and patients with metabolic syndrome.

Key Words: Metabolic Syndrome (Met-S), Apolipoprotein, And Coronary Heart Disease.

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INTRODUCTION

Metabolic syndrome (Met-S) is a cluster of different components characterized by increased body fat around the waist, increased blood pressure, a high blood glucose level, raised triglycerides in the blood and reduced high density cholesterol that occur together^{1,2}. These factors increase the chance of having coronary heart disease, T2DM and stroke³.

The prevalence of Met-S is increasing worldwide and approximately affects 20 to 25% people. There is three-fold increase in stroke and coronary heart disease and

two fold increased incidence of mortality rate in such patients, compared to people without this syndrome. They also have fivefold risk of having Type 2 diabetes mellitus⁴. The contributing factors being age, race, obesity, gestational diabetes, family history of diabetes, non alcoholic fatty liver disease and polycystic ovarian syndrome^{5,6}.

Although LDL-Cholesterol, and more recently non HDL-Cholesterol are used for cardiovascular risk evaluation and for those patients who are using lipid lowering drugs, but newer studies have shown that in contrast to single lipid fractions, lipid ratios are stronger cardiovascular risk markers⁷. Nowadays, Apo-B/Apo-A1 ratio is one of the best variables to quantitate the risk of coronary heart disease^{8,9}. Research reveals that there would be great advantage of integrating Apolipoprotein into clinical practice¹⁰. According to a recent study done in Chinese population, Apo-B/Apo-A1 ratio of 0.80 & 0.85 in women & men respectively, proved to be a highly significant biomarker of Met-S¹¹. Studies carried out by Makaridze, Giorgadze, and

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Asatiani at Tbilisi state university Georgia revealed strong association of Apo B/ApoA1 ratio with Met-S as well as its components¹². Prospective risk studies such as, EPIC Norfolk¹³ AMORIS¹⁴ MONICA / KORA¹⁵ and ULSAM¹⁶ show that Apo-B/Apo-A1 is an effective marker of fatal and non-fatal myocardial infarction (MI).

Apo-B and Apo-A1 are responsible for the transport of lipids and if deranged, have the potential to cause atherosclerosis and its related complications¹⁷. Apo-B is a 550 KD protein, synthesized in liver and is considered atherogenic and abnormal values are seen in familial combined hyperlipidemia, acquired hyperlipidemia, acute angina & Myocardial Infarction (MI). The reference range is 40-125 mg/dl. Apo-A1 comprises 75% in HDL and is considered anti-atherogenic. Apo-A1 levels are inversely proportional to the risk of CAD. The reference range of Apo-A1 varies with sex i.e greater than 120 mg/dl in males & greater than 140 mg/dl in females. The ratio of Apo-B/Apo-A1 is a balance of atherogenic & antiathrogenic particles and high values indicate high cardiovascular risk. It is a much more precise and adequate index of statin therapy as compared to LDL^{18, 19}. In clinical practice, accurate detection of glucose intolerance and dyslipidemia is very important so as to find out patients at high risk for cardiovascular disorders²⁰. Various studies consider Apo-B/Apo-A1 ratio as an additional independent variable for the evaluation of this risk, especially in individuals with normal lipid profile^{21, 22}.

Therefore, this present study was carried out in our population to assess its significance in normal individuals and patients with Met-S in tertiary care units of district Peshawar, KPK. This study can be helpful in assessing individuals at high risk of cardiovascular complications, future treatment and follow up.

MATERIALS AND METHODS

This study, conducted from June 2015 to December 2015, enrolling total of 200-subjects, including 150-Met-S and 50-controls. After formal consent, data was collected about height, weight, and socioeconomic condition, blood pressure and waist circumference. The diagnosis of Met-S was made accordingly. Blood glucose levels, Apo-B and Apo-A1 and lipid profile was done in all patients and normal individual. All male and female with age 40 and above with metabolic syndrome were included. Non co-operative patients, patients who do not meet the criteria's mentioned in the definition of Met-S, smoker, pregnant women, patients using oral contraceptives and statins and patients with Nephrotic syndrome and hypothyroidism were excluded. In control all male and female with age group 40 and above and those who do not meet the criteria's mentioned in the definition of Met-S were included, while control with diagnosed Met-S, non co-operative

individuals, smokers, pregnant ladies, diabetics and central obesity ($WC \geq 90\text{cm}$ for male) and ($WC \geq 80\text{cm}$ for female) were excluded.

Data Collection: Data was collected from total 150-cases and 50-controls visiting outdoor clinics and fulfilling the inclusion and exclusion criteria. They were enrolled in a consecutive manner. After ethical committee approval and informed consent, the demographic information of the subjects such as names, age and gender were recorded. Blood glucose, TG, LDL, HDL, Cholesterol and Apo-B and Apo-A1 were done using, AKENZA MAX biochemistry analyzer and ARCHITECT analyzer ci8200. All collected information was recorded on pre-designed Performa.

Data Analysis: Analysis of the data was done by SPSS version 17. Results were expressed in the form of mean and standard deviation. Apo-B and Apo-A1 were determined and ratio was calculated. Comparison between Apo-B/Apo-A1 ratio with WC and comparison of WC among gender was done. Statistical significance was weighed when $P \leq 0.05$.

RESULTS

In studied 200 cases, 150 individuals fulfill the criteria and considered as cases, while 50 adults are taken as control. Age of all the participants both patient and controls ranges between 40 -55.

Age, gender, waist circumference, blood pressure and biochemical characteristics among all the subjects, due to the absence or presence of the Met-S are shown in Table-1.

Table No.1: Demographic characteristic of Met-S patients and Controls

	Met S (150)	Control (50)	P-value
Age (mean $\pm$ SD)	47.75 $\pm$ 4.79	45.16 $\pm$ 3.84	NS
Sex (male/female)	61/89	32/18	NS
ApoA-I (mg/dl)	121.73 $\pm$ 32.30	131.66 $\pm$ 18.65	.041
ApoB (mg/dl)	114.01 $\pm$ 94.82	84.40 $\pm$ 18.11	.030
ApoB/ApoA-I ratio	1.02 $\pm$ 1.08	0.61 $\pm$ 0.10	.007
SBP (mmHg)	140.99 $\pm$ 24.08	132.0 $\pm$ 20.07	.018
DBP (mmHg)	90.90 $\pm$ 10.57	86.90 $\pm$ 9.19	.018
WC (cm)	105.78 $\pm$ 11.31	84.80 $\pm$ 5.11	.001
TC(mg/dl)	222.04 $\pm$ 52.18	184.02 $\pm$ 43.47	.001
HDL-C (mg/dl)	38.47 $\pm$ 22.33	42.06 $\pm$ 6.91	.085
LDL(mg/dl)	143.33 $\pm$ 49.45	115.78 $\pm$ 43.60	.001
TG (mg/dl)	221.79 $\pm$ 91.49	124.66 $\pm$ 31.90	.001
FBS (mg/dl)	131.41 $\pm$ 59.37	86.78 $\pm$ 12.24	.001

Mean & standard deviations of WC, age, sex, systolic, diastolic blood pressure, TG, TC, LDL, and blood glucose were highly significant ($p < 0.001$) & HDL-C levels were reduced in Met-S group as compared to

control group. A value of Apo-B/Apo-A1 ratio in patients with Met-S was highly significant with $p \leq 0.007$ while Apo-B and Apo-A1 separately were also significant with $p \leq 0.03$ and $p \leq 0.04$ respectively in both the groups. This study included 53.5% female and 46.5% male subjects.

The comparison of waist circumference has been shown between male and female subjects. It was divided into three groups i.e. group-1, WC >90, group-2, WC ranges from 91-100 while group-3, WC >100. In this data it was shown that, WC of females is more than males. The mean and standard deviation in female is 104.69 ± 14.53 while in male is 95.75 ± 10.68 . WC is highly significant. P value is < 0.001 .

Table No.2: Descriptive characteristics between genders

	Female (n=107; 53.5%)	Male (n = 93; 46.5%)	P value
Age	47.36 ± 4.70	46.76 ± 4.64	0.366
ApoB/ApoA1 ratio	0.96 ± 1.03	0.87 ± 0.85	0.505
ApoA1 (mg/dl)	125.89 ± 32.62	122.28 ± 26.12	0.394
ApoB (mg/dl)	115.84 ± 110.15	95.98 ± 30.03	0.094
SBP (mmHg)	140.83 ± 20.40	136.34 ± 26.39	0.177
DBP (mmHg)	92.94 ± 9.29	86.40 ± 10.49	0.001
WC (cm)	104.69 ± 14.53	95.75 ± 10.68	0.001
TC(mg/dl)	222.55 ± 54.33	201.01 ± 42.52	0.004
HDL-C (mg/dl)	38.08 ± 9.77	40.85 ± 26.94	0.323
TG (mg/dl)	209.48 ± 95.84	183.28 ± 77.96	0.039
FBS (mg/dl)	129.76 ± 63.41	109.31 ± 41	.009

Anthropometric and biochemical characteristics were presented on gender basis and no difference was found in both the groups as shown in Table 2. The value of Apo-B/Apo-A1 ratio and Apo-B and Apo-A1 separately in patients with Met-S as well as in control group was not significant with p value of $p \leq 0.5$, $p \leq 0.09$ and $p \leq 0.3$ respectively.

Cardiovascular risk assessment in patients with Met-S and controls by Apo-B/Apo-A1 ratio is presented in Table 3. The ratio of Apo-B/Apo-A1 provides us the relative risk levels for future coronary heart disease. The study showed 1/2 average risks in subjects with Met-S in males 4.9% and in females it is 1.1%. In control males it is 3.1% and control females it is 5.5%. In my study, majority of cases in both Met-S (68.8% male,

70.7% female) and controls (96.8% male & 88.8% female) fall in twice-average risk category group. There was threefold risk in male Met-S patients i.e. 26.2% and in females it was 28%. No such association was found in the controls.

Table No.3: Cardiovascular risk assessments, among Met-S adults and control, by Apo-B/Apo-A1 ratios.

	Met-S(150)		Control(50)	
	Male (61)	Female (89)	Male (32)	Female (18)
1/2 Average Risk. (Male=0.4, Female=0.3)	3 (4.9%)	1 (1.1%)	1 (3.1%)	1 (5.5%)
Twice Average Risk (Male=0.5-1.0, Female=0.4-0.9)	42 (68.8%)	63 (70.7%)	31 (96.8%)	16 (88.8%)
Three Times Average Risk (Male ≥ 1.1 , Female ≥ 1.0)	16 (26.2%)	25 (28.0%)	0%	0%

DISCUSSION

Metabolic syndrome is a worldwide health problem. Met-S is the fastest growing chronic disease worldwide including Pakistan²³. For the diagnosis of Met-S and risk evaluation of cardiovascular disease, diabetes mellitus, hypertension and familial hyperdyslipidemia, there are certain biomarkers including lipid profile, including total cholesterol, TG, HDL-C, LDL, IDL and VLDL Apo-A1, Apo-B and their ratios^{9 10 11}. The researchers thought about a new approach to find out more convenient biomarkers for the diagnosis of Met-S patients as well as for those who are on lipid lowering treatment and for those who have a family history.

The two major apolipoproteins are Apo-B and Apo-A1, which are considered the new determinants of Met-S, before and after the development of the disease & all its components. The major protein in very low-density lipoproteins (VLDL) is Apo-B, as well as in the intermediate-density lipoproteins (IDL), and low-density lipoproteins (LDL), one protein per particle. The major protein in high-density lipoprotein (HDL) particles is Apo-A1⁶. Apo-B/Apo-A1 ratio being a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy has been reevaluated several times in healthy subjects and in patients with different clinical manifestations of atherosclerosis²⁴.

Laboratory services in the pathology department of university of Iowa United State gives the values of Apo-B/ApoA-1 ratio as relative risk factors in 2015, to find out the cardiovascular risk. These are

Apolipoprotein B/A	Male	Female
1/2 Average Risk	0.4	0.3
Twice Average Risk	1.0	0.9
Three Times Average Risk	1.6	1.5

In the present study it was found out that those individuals who are included in control group having WC 80-90cm in men and 70-80cm in female was at future CV risk. 1/2 average risk was 3.1% in male while 5.5% in female while twice-average risk in male was

96.8% and 88.8% in female. In our study patient with Met-S showed $\frac{1}{2}$ average CV risk 4.9% in male, 1.1% in female, twice average risk 68.8% in men, 70.7% in female, three times risk 26.2% in male and 28% in female.

Many authors have studied the importance of Apo-B, Apo-A1, and Apo-B/Apo-A1 ratios as significant markers of CV risk. Prospective risk studies, such as AMORIS¹⁴ INTERHEART²⁵, EPIC-Norfolk study¹³ and ULSAM¹⁶ indicated that Apo-B/ApoA-1 ratio is a valuable marker of risk of myocardial infarction. Interheart, a case-control study done in 52 countries, investigated that Apo-B/Apo-A1 ratio was the strongest factor in explaining risk of acute MI with Odd ratio of 3.25(2.81-3.76) with 95% confidence interval. It was also the most prevalent risk factor of all the nine conventional risk factors irrespective of sex, race, age and other lipids or lipid ratios²⁵.

Similar finding to our study were present in study done by Min Lu⁹ in china in 2011, showed that in Met-S group blood pressure, blood sugar, TC, TG, LDL Apo-B and Apo-B/Apo-A1 ratio were high while Apo-A1 and HDL were low.

Hanan Belfki and Samer Bin Ali have studied in a Tunisian population (330 adults aged 35–74) including Met-S subjects & a control group, showed that Apo-B/Apo-A1 ratio was very strongly associated with Met-S ($p < 0.001$). This study also showed that Apo-B (0.97 ± 0.23) and Apo-A1 (1.49 ± 0.28) were highly significant in Met-S group versus controls with $p < 0.001$ ²⁶. In our study Apo-B/Apo-A1 ratio showed strong correlation with Met-S versus controls (1.02 ± 1.08) with $p < 0.007$, however Apo-B ($p < 0.03$), Apo-A1 ($p < 0.04$) independently were also significant.

The present study showed that WC of females was more than males. The mean and standard deviation in female is 104.69 ± 14.53 while in male is 95.7 ± 10.68 . WC is highly significant p value is < 0.001 . Similar findings were observed in study of Tunisian population conducted in 2011 whose findings for WC were 100.1 ± 13.0 for female and 99.4 ± 11.1 for male¹². It is also found out in our study that mean and standard deviation in Met-S group is 105.78 ± 11.31 verses 84.80 ± 5.11 in control group with p value of .001, the results of our study are in concordance with the above mentioned Tunisian study showing $104.7 \pm 10.9/95.5 \pm 12.4$ in Met-S/controls¹². IDF recommended that the primary target of intervention in Met-S and without Met-S should be obesity¹.

Central obesity, which is the basic component of Met-S, is more important than body mass index (BMI). In Epic Norfolk study and Arsenault, S Rana studied in Norfolk UK population that physical inactivity and central obesity are the main killers of our population. Men and women both shows great variations in lipid profile analysis and Apo-B/Apo-A1 ratio even in those whose waist circumference is borderline i.e 80-90cm for men and 70-80cm for women²⁷. Anastasiya M. Kaneva studied 157-normolipidemic men aged 20-59. The median of Apo-B/Apo-A1 ratio was 0.52. Apo-B/Apo-A1 ratio > 0.9 was 19.1%.

Zaza Makaridze found in Georgian population in 2014 that previously in lipid profile, LDL-C was thought to be an independent risk factor for CV diseases and was recommended as first line diagnostic tool by different clinical guidelines but now the Apo-B/Apo-A1 ratio is more important predictor of CV risk. They found positive correlation of Apo-B/Apo-A1 with, blood glucose and TG (all $p < 0.001$) and negative correlation with HDL in both sexes¹².

G Leroux, I Lemieux and B Lamarche showed in their study that the levels of triglycerides in blood have a positive effect on the levels of Apo-B/Apo-A1 ratios there is a strong correlation between TG and Apo-B/Apo-A1 ratio ($p < 0.001$)¹⁷. Our study also demonstrated a strong correlation between TG and Apo-B/Apo-A1 ratio, that higher the TG level, higher will be Apo-B/Apo-A1 ratios.

On the Basis of the new studies, now it is the time to include Apo-B, Apo-A1 and the Apo-B/Apo-A1 ratio into new guidelines in our country as leading risk variables of parallel or higher importance than LDL, TC, TG and HDL C. The Apo-B/Apo-A1 ratio is a simple and precise test, can be done on non-fasted subjects. Also LDL-C, HDL-C, TG and lipid ratios are explained in many cumbersome numbers while Apo-B/Apo-A1 ratio can be expressed as only one number⁵. There are some limitations like small sample size and the positive relation between the Apo-B/Apo-A1 ratio and Met-S cannot be established fully because this was a cross-sectional study. Multiple risk factors, including dyslipidemia, diabetes mellitus & hypertension and other metabolic abnormalities were also affecting the finding.

CONCLUSION

It can be concluded from the present study that Apo-B, Apo-A1 and Apo-B/Apo-A1 ratio are newer and valuable markers for prediction of cardiovascular disease risk in Met-S patients & in normal population. It can be used as a follow up test to evaluate the response of lipid lowering drugs. Further studies addressing the all-possible confounders with huge sample size is recommended for further validation.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Alberti KG and Zimmet P. Metabolic syndrome a new worldwide definition. A consensus statement from the International Diabetes Federation, Diabetic Medicine 2006; 23(5): 469–480.
2. Eckel RH, Alberti K, Grundy SM, and Zimmet PZ. The metabolic syndrome, The Lancet 2010; 375(9710):181–183.
3. Ford ES. Risks for all-cause mortality, cardiovascular disease and diabetes associated with the metabolic syndrome a summary of the evidence. Diabetes Care 2005;28(7):1769–1778.
4. Apurva S, Ranjit M, Swarup S, et al. Prevalence of Metabolic Syndrome in Urban India. Cholesterol 2011; (7).

5. Taslim S and Tai E S. The relevance of the metabolic syndrome. *Ann Acad Med Singapore* 2009; 38(1):29-5.
6. Walldius G. The apoB/apo A-1 ratio is a strong predictor of cardiovascular risk, Frank Sand Kostner G. Lipoproteins-Role in health and diseases. *J Int Med* 2012;259:493-519.
7. Ray KK, Cannon CP, Cairns R, DA Morrow et al. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol* 2009;29(3):424-430.
8. Mohamed A, Khalifa A, Atif A, Samia S, et al. Levels of apolipoproteins as risk factors for coronary artery disease. *J Vasc Bras* 2011;10 (4): 293-297.
9. Min L, Qun L, Yong Z, Gang T. ApoB/apoA1 is an effective predictor of coronary heart disease risk in overweight and obesity. *J Biomedical Res* 2011; 25(4): 266-273.
10. Ying X, Qian Y, Jiang Y, et al. Association of the Apolipoprotein B/Apolipoprotein A-I ratio and low-density lipoprotein cholesterol with insulin resistance in a Chinese population with abdominal obesity. *Acta Diabetologica* 2012; 49(6):465-472.
11. Jing F, Yingying M, Jing G, Zhenyu Z, Yingjun L, et al. The value of Apolipoprotein B/ Apolipoprotein A1 ratio for metabolic syndrome diagnosis in a Chinese population: a cross-sectional study. *Lipids in Health and Disease* 2014;13 (81):1-10.
12. Makaridze Z, Giorgadze E, Asatiani K. Association of the apolipoprotein B/apolipoprotein A-1 ratio, metabolic syndrome components, total cholesterol, and low density lipoprotein cholesterol with insulin resistance in the population of Georgia. *Int J Endocrinol* 2014;(8).
13. Sondermeijer BM, Rana JS, Arsenault BJ, Shah PK, Kastelein JJ, et al. Non-HDL cholesterol vs. apo B for risk of coronary heart disease in healthy individuals: the EPIC-norfolk prospective population study. *Eur J Clin Invest* 2013;1009-15.
14. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001;358: 2026-2033.
15. Meisinger C, Loewel H, Mraz W, Koenig W. Prognostic value of apolipoprotein B and A-I in the prediction of myocardial infarction in middle-aged men and women: results from the MONICA/ KORA Augsburg cohort study. *Eur Heart J* 2005; 27:1-8.
16. Dunder K, Lind L, Zethelius B, Berglund L, and Lithell H. Evaluation of a scoring scheme, including proinsulin and the Apolipoprotein B/ Apolipoprotein A1 ratio, for the risk of acute coronary events in middle-aged men: uppsala Longitudinal Study of Adult Men (ULSAM). *The Am Heart J* 2004;148(4):596-601.
17. Leroux G, Lemieux I, Lamarche B, Cantin B, et al. Influence of triglyceride concentration on the relationship between lipoprotein cholesterol and apolipoprotein B and A-I levels. *Metabolism* 2000; 49(1):53-61.
18. Fogelstrand P, Borén J. Retention of atherogenic lipoproteins in the artery wall and its role in atherogenesis; Review. *Nutrition, Metabolism & Cardiovascular Diseases* 2012; 22: 1-7.
19. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, et al. Association of LDL Cholesterol, Non-HDL Cholesterol, and Apolipoprotein B Levels with Risk of Cardiovascular Events among Patients Treated With Statins. A Metaanalysis. *JAMA* 2012;307(12):130213-130209.
20. Grundy SM, Cleeman JJ, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005; 112(17): 2735-2752.
21. Tamang HK, Timsina U, Singh KP, et al. Apo B/Apo A-I Ratio is Statistically A Better Predictor of Cardiovascular Disease (CVD) than Conventional Lipid Profile: A Study from Kathmandu Valley, Nepal. *J Clin Diagnos Res: JCDR* 2014; 8(2):34-36.
22. Lima ML, Carvalho, Graças MD, & Sousa, Oliveira M. Apo B/apo A-I ratio and cardiovascular risk prediction. *Arquivos Brasileiros de Cardiologia* 2007; 88(6):187-190.
23. Athyros VG, Ganotakis ES, Elisaf MS, Liberopoulos EN, Goudevenos IA, Karagiannis A. Prevalence of vascular disease in metabolic syndrome using three proposed definitions. *Int J Cardiol* 2007; 117:204-10.
24. Walldius G and Jungner I. Is there a better marker of cardiovascular risk than LDL cholesterol? Apolipoproteins B and A-I - new risk factors and targets for therapy. *Nutrition, Metabolism and Cardiovascular Diseases* 2007; 17(8): 565-571.
25. Yusuf PS, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the Inter heart study): case-control study. *The Lancet* 2004; 364(9438): 937-952.
26. Belfki H, Ali SB, Bougatef S, et al. The Apolipoprotein B/Apolipoprotein A1 ratio in relation to metabolic syndrome and its components in a sample of the Tunisian population. *Exp Molec Pathol* 2011;91(2):622- 625.
27. Arsenault BJ, Rana JS, Lemieux I, Despres JP, Kastelein JJ, Boekholdt SM, et al. Physical inactivity, abdominal obesity and risk of coronary heart disease in apparently healthy men and women. *Int J Obes* 2010;34(2):340-7.

To Determine the Clinical Pattern and Postoperative Complications of Thyroidectomy

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ABSTRACT

Objective: To assess the postoperative complications in patients underwent thyroidectomy at tertiary care Hospital

Study Design: Prospective case series study

Place and Duration of Study: This study was conducted at the Departments of General Surgery of LUH Hyderabad from October 2014 to September 2015.

Materials and Methods: All the cases with diagnosis were thyroid disorder and underwent thyroidectomy were selected in the study. Cases above 25 years of age were included. Patients were prepared for the surgery after counseling regarding surgical and post-operative complications. All the surgeries were carried out by senior surgeons along with cooperation of the ENT surgeons. After surgeries patients were taken under follow-up and all developed postoperative complication were recorded in the proforma.

Results: Mean age of the patients was 44.50±5.23 years. 31(43.66%) patients were male while 40(56.34%) were female. 100% patients had neck swelling, 8.45% had pain, 9.85% had swallow difficulty and 7.04% had breathing difficulty while others less common complaints were found in 14.08% patients. Regarding post-operative complications, 4.22% patients had transient RNA palsy, 5.63% patients had hypocalcemia, 3.44% had dysphagia, 4.22% had infections, while 1.40% had seroma.

Conclusion: Presentation of neck swelling was in all cases, and most common post operative complications were hypocalcemia, transient RNA palsy and superficial infection, female gender is most common.

Key Words: Thyroidectomy, clinical presentation, postoperative complications

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INTRODUCTION

Term goiter is utilized to represent as enlarge in size of the thyroid gland.^{1,2} Disorders of the thyroid constitute the 2nd most regular endocrine illness taking after DM. Incidence of nodular goiter and the anatomy of thyroid expanded in areas with incessant Iodine Deficiency. It has been archived that the thyroid changes with Iodine Deficiency in the early stages by diffuse hyperplasia, while chronic introduction to iodine deficiency brings about nodular hyperplasia, expanded colloid content and expanded follicular cell height. Surgical removal of the thyroid is a standard amongst the most frequent surgeries performed in iodine 5 to 7 regions inadequately.² All inclusive, the Total Goiter Prevalence (TGP) in the overall population is assessed to be 15.8%, differing between in America 4.7% and in Africa 28.3%. In the 6–12 years children studies reported different prevalence. As well as in southern Sudan 22.3%, in Rajasthan 11.4% Rajasthan, and in India 20.5%.³⁻⁵

In the 6–12 years children another study reported prevalence as in 39.9% in Ethiopia in year 2005, and noticeable goiter in 12.2%.⁶ The predominance of goiter was higher in women than men in various reviews in the world.^{3,5,7} In Pakistan goiter incidence among the general population 16.6% at Baltistan, North East Pakistan. In North incidence in males 20.4%, in women 28.1% and in the south in men as 13.9% and in women is 21.2%.^{8,9} In another Pakistani study reported that 140 cases underwent different surgical techniques of thyroidectomy, out of them 15 found with carcinoma, furthermore out of 105 cases having multinodular goiter showed 7.6% carcinoma.¹⁰ In study conducted in the Nawabshah also found different type of cancer in cases with multinodular goiter 52% in women and 45% in men.¹⁰

Surgical treatment is common treat for neck surgeries. Post-operative complications for example, hypo-parathyroidism and RLNI and bleeding take a big part from all complications.¹¹ However, in the multiple and different complications are reported. Recurrent LN was 1st disclosed and named through the Galen in 2nd century.¹² Higher risk nerve injury is right sided due by its wide ranged anatomical deviations as compare to left side. In the some new studies stated that vocal cord paralysis through iatrogenic injury of RLNI is the commonest event in thyroid surgeries. Though several techniques has been introduced for prevention nerve injury, till now prevalence of the recurrent LNP differ

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between 1.5-14%.¹³ This study has been conducted to evaluate the postoperative complications in patients underwent thyroidectomy at tertiary care Hospital.

MATERIALS AND METHODS

Current prospective case series study has been done in the general surgery department of LUH Hyderabad. Duration was 6 months from November 2014 to May 2015. Cases with age more than 20 years and both genders were incorporated. All the patients with presentation of thyroid disorder were included. After admission complete clinical examination and routine laboratory investigations were done. Surgeries were carried out by senior surgeons. All the patients were discharged from the ward on stable condition, and advised for complete follow-up at OPD of general surgery; follow-up days were selected according to patient's condition. Patients were not come in the follow-up those were excluded from the study. All the postoperative complications during postoperative hospital stay and during follow-up at OPD were entered in the proforma. All data was analyzed in the SPSS version 16.

RESULTS

Mean age of the patients was 44.50+5.23 years. 31(43.66%) patients were male while 40(56.34%) were female. Table 1.

Regarding clinical presentation, 100% patients had neck swelling, 8.45% had pain, 9.85% had swallow difficulty and 7.04% had breathing difficulty while others less common complaints were found in 14.08% patients. Fig:1.

38.02% patients had total thyroidectomy while 61.98% patients had subtotal thyroidectomy. Fig:2

Regarding post-operative complication, 4.22% patients had transient RNA palsy, 5.63% patients had hypocalcemia, 3.44% had dysphagia, 4.22% had infections, while 1.40% had seroma. Table:2.

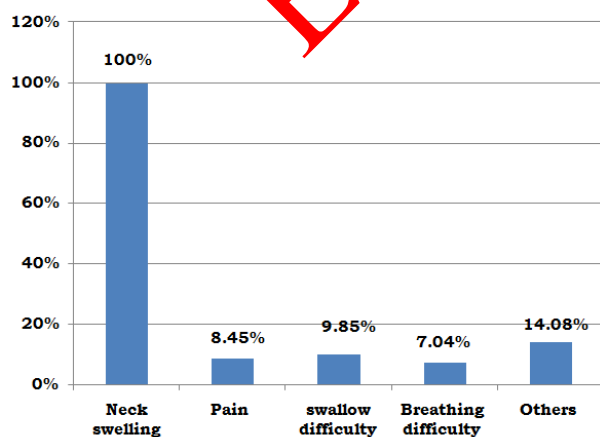


Figure No. 2: Clinical presentation n= 71

Table No.1: Patients according to age and gender distribution n=71

Basic characteristics	Numbers/ Percentage
Age (mean+SD)	44.50+5.23 years
Gender	
Male	31(43.66%)
Female	40(56.34%)

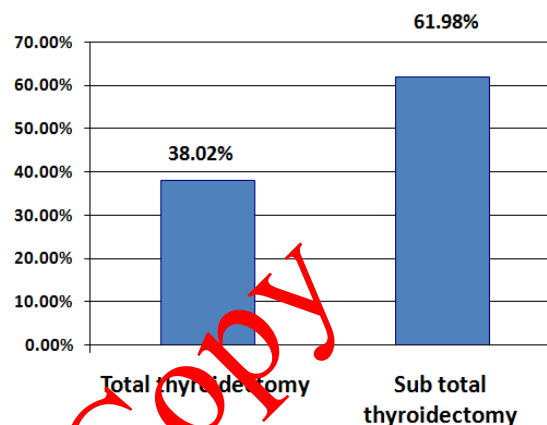


Figure No.2: Type of thyroidectomy n= 71

Table No.2: Postoperative complications after thyroidectomy n=71

Post operative complications	Frequency (%)
RNA palsy	
Transient	03(4.22%)
Permanent	01(1.40%)
Hypocalcemia	04(5.63%)
Dysphagia	01(3.44%)
Infection	03(4.22%)
Haematoma	01(1.40%)
Granuloma	01(1.40%)
Seroma	02(1.40%)

DISCUSSION

This study has been carried out to determine postoperative complications of thyroidectomy. Patient's mean age was 44.50+5.23 years. 31(43.66%) patients were male while 40(56.34%) were female. Comparable findings regarding age and gender were found in the study of Gupta A et al¹⁴as; majority of cases 51% were between age as 21-40 years and females predominated as 77%. In some other series of as Singh P et al.¹⁵ stated mean age 47 years and Islamet al.¹⁶ also found comparable age range. Female's predominance with thyroid disorder may due to presence of estrogen receptors in tissues of the thyroid.¹⁷

In our series according to clinical pattern 100% patients had neck swelling, 8.45% had pain, 9.85% had swallow difficulty and 7.04% had breathing difficulty while

others less common complaints were found in 14.08% patients. In the favor of this study Gupta A et al¹⁴ also reported that all patients were with presentation of neck swelling following by in 3% patients had cervical lymphadenopathy, 1% cases had dysphagia, dyspnea in 1 cases and hoarseness had in 1 cases also. in another study of Prakash A, et al¹⁸ seen comparable findings regarding clinical presentation as well as 95.55% patients was neck swelling. In contrast of our study Sachdeva HS, et al¹⁹ found greater prevalence of dysphagia in 33.33% cases and presentation of dyspnea in 26.66% cases, this may due to our study sample size was very short as compare to that study. While Godinho-Matos L, et al²⁰ found similar clinical presentation as neck swelling in 100% cases, 4% cases with dysphagia, 3% were with dyspnea, 8% pain while hoarseness of voice was found in the 3% cases.

In our series regarding post-operative complications, 4.22% patients had transient RNA palsy, 5.63% patients had hypocalcemia, 3.44% had dysphagia, 4.22% had infections, while 1.40% had seroma. In the comparison of our study Khanzada TW et al²¹ reported that overall postoperative complications were 10.7%, without mortality and further he reported that hypocalcaemia was the major complication of thyroidectomy and minimum rate was found of RLN injury and the bleeding. Prevalence of RLN injury is still not known exactly unknown. While Khanzada TW et al²¹ reported that permanent RLN palsy was in 1.4% cases. Some other studies also found similar findings as our study regarding hypocalcaemia and RLN injury.²²⁻²⁴ In our study infection found in the 4.22% of cases. On other hand Khanzada TW et al²¹ demonstrated infection only in 1 (0.7%) cases. In another study also found similar findings as well as in 2% of the cases. In our study event of postoperative mortality was not made. As well as similar findings were noted in the studies of Lombardi CP et al²² and Khanzada TW et al²¹.

CONCLUSION

Presentation of neck swelling was in all cases, and most common postoperative complications were hypocalcemia, transient RNA palsy and superficial infection, female gender is most common. Few studies showed big prevalence of complication as compare to our study. More big sample studies are needed to determine this difference.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. William NS, Russel RCG, Williams NS, Bulstrode CJK. Thyroid Enlargement. Bailey and Love's Short Practice of Surgery. 26th ed. 2013.p.747-749.
2. Iqbal N, Hussain JR, Riaz A, Zafar U. Risk factors for postoperative complications after Thyroidectomy in simple multinodular goiter. JSZMC 2005;6(2):802-807
3. Mesele M, Degu G, Gebrehiwot H. Prevalence and associated factors of goiter among rural children aged 6-12 years old in Northwest Ethiopia, cross-sectional study. BMC public health 2014;7:14(1):130.
4. Elnour A, Hambraeus L, Eltom M, Dramaix M, Bourdo P. Endemic goiter with iodine sufficiency: a possible role for the consumption of pearl millet in the etiology of endemic goiter. Am J Clin Nutr 2000;71: 59-66.
5. Singh MB, Marwal R, Lakshminarayan J. Assessment of iodine deficiency disorders in school Age children in Jodhpur district of Rajasthan. J Hum Ecol 2010;32(2):79-83.
6. Abuye C, Berhane Y, Akalu G, Getahun Z, Ersumo T. Prevalence of goiter in children 6 to 12 years of age in Ethiopia. Food Nutr Bull 2007;28(4): 391-398.
7. Kamath R, Bhat V, Rao RSP, Das A, Ganesh KS, Kamath A. Prevalence of goiter in rural area of Belgaum District. Ind J Comm Med 2009;34(1): 48-51.
8. Qamar MF, Abbas S. Prevalence and case reports of goiter at district Bahawalpur, Pakistan 2012; 1(1);33-37.
9. Stewart AG. Drifting continents and endemic goiter in northern Pakistan. BMJ 1990;(6738): 1507-1512.
10. Waseem MTW, Khanzada, Samad A, Kumar B. Incidence of thyroid carcinoma in multinodular goiters. Rawal Med J 2010;35(1):65-7.
11. Kerimoglu RS, Gozalan U, Kama NA. Complications of thyroid surgery: Analysis of 1159 cases. IJMMS 2013;1:35-8.
12. Goldenberg D, Randolph GW. Thyroid Surgery: Preventing and Managing Complications. Paolo Miccoli, editor. Willy-Blackwell; 2012.p.117-127.
13. Sarma MK, Kakati K, Sharma K, Goswami SC. Recurrent laryngeal nerve injury (RLNI) in thyroid surgery and its prevention. Int J Res Med Sci 2017; 3(7):1632-6.
14. Gupta A, Jaipal D, Kulhari S, Gupta N. Histopathological study of thyroid lesions and correlation with ultrasonography and thyroid profile in western zone of Rajasthan, India. Int J Res Med Sci 2016;4(4):1204-8.
15. Singh P, Chopra R, Calton N, Kapoor R. Diagnostic Accuracy of Fine Needle Aspiration Cytology of Thyroid lesions. J Cytol 2000; 17(3):135-9.
16. Islam R, Ekramuddaula AFM, Alam MS, Kabir MS, Hossain D, Alauddin M. Frequency & pattern

- of malignancy in solitary thyroid nodule. Bangladesh J Otorhinolaryngol 2009;15(1):1-5.
17. Krukowski ZH. The thyroid gland and thyroglossal tract. In: Williams NS, Bulstrode CJK, O'Connell PR, editors. Baily & Love's short practice of surgery. 24th ed. London: Hodder education;2004.p.776-804.
 18. Psarras A, Papadopoulos SN, Livadas D, Pharmakiotis AD, Koutras DA. The single thyroid nodule. Br J Surg 1972;59(7):545-8.
 19. Prakash A, Moulik BK, Sharma LK, Kapur M, Poddar PK. Carcinoma of thyroid gland. A clinical study. Ind J Surg 1974;43:409-16.
 20. Godinho-Matos L, Kocjan G, Kurtz A. Contribution of fine needle aspiration cytology to diagnosis and management of thyroid disease. J Clin Pathol 1992;45:391-5.
 21. Khanzada TW, Samad A, Memon W, Kumar B. Post thyroidectomy complications: the Hyderabad experience. J Ayub Med Coll Abbottabad 2010; 22(1):65-8.
 22. Lombardi CP, Raffaelli M, De Crea C, Traini E, Oraganao L, Sollazzi L, et al. Complications in thyroid surgery. Minerva Chir 2007;62:395-408.
 23. Bron LP, O'Brien CJ. Total thyroidectomy for clinically benign disease of the thyroid gland. Br J Surg 2004;91:569-74.
 24. Younes N, Robinson B, Delbridge L. The aetiology, investigation and management of surgical disorders of the thyroid gland. A NZ J Surg 1996;66:481-90.
 25. Dionigi G, Rovera F, Boni L, Castano P, Dionigi R. Surgical site infections after thyroidectomy. Surg Infect 2006;7Suppl 2:S117-20.

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Vitamin D Deficiency in Breast Cancer Patients and its Association with Histopathological Tumor Characteristics

Sadaf Fatima, Asma Rafique and Fatima Tehsin

Vitamin D Deficiency
in Breast Cancer
Patients and
Histopathological
Tumor

ABSTRACT

Objective: To determine the prevalence of vitamin D deficiency in women with breast carcinoma and to determine the association of vitamin D levels with histopathological tumor characteristics.

Study Design: Observational Study.

Place and Duration of Study: This study was conducted at the Oncology Department, Nishtar Medical College / Hospital Multan from April 2016 to October 2016.

Materials and Methods: Ninety female patients with diagnosis of breast cancer on histopathology reporting were selected. A specialized Proforma was used to get information about their personal life e.g. marital status, menopause history, age, BMI, educational status and daily life style. Vitamin D levels were measured in all females. Information regarding tumor grade, stage, type of carcinoma and hormonal receptor status was extracted from pathology, histology and hematology reports of patients.

Results: The mean age of study participants was 46.64 ± 10.64 Years. All of the participants were married. 48 (53.3%) patients were in post-menopausal period. 74 (82.2%) were urban residents. Mean vitamin D levels in study participants were 17.78 ± 14.66 ng/ml. There were 56 (62.2%) patients with deficient vitamin D levels, 18 (20.0%) with sub-optimal and 16 (17.8%) patients with optimal vitamin D levels. We did not found any strong association of vitamin D levels with tumor grades, stage and expression of tumor ER and HER-2 receptors. However in our study, tumor ER receptors expression was significantly high in patients with deficient and optimal vitamin D levels as compared to the patients with suboptimal vitamin D levels.

Conclusion: There is high prevalence of vitamin D deficiency in breast cancer patients. We did not found any association of vitamin D levels with tumor characteristics.

Key Words: Breast Cancer, Vitamin D, menopausal state

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INTRODUCTION

Breast cancer is a leading cause of death in women globally.¹ In Pakistan every 5th women with cancer have diagnosis of breast cancer. Literature have suggested that vitamin D levels are inversely related with the development of many types of epithelial cancers including the breast cancer.³ It has also been shown that sun-light exposure significantly reduces the risk of breast cancer by 25% to 65%, because sun-light is a direct source of vitamin D production.^{4,5} About 90% of total body vitamin D is produced by skin in response to ultra-violet B sun-light radiations, while remaining 10% is obtained from different dietary sources.

In spite of maintaining bone and mineral homeostasis vitamin D has also its role in carcinogenesis. It exerts

its anti-proliferative properties by binding to specific vitamin D receptors present in many cells and tissues of the body. Some human genes also contain vitamin D sensitive DNA sequences that are very important for proper cell proliferation, differentiation as well as angiogenesis.^{6,7} Deficient levels of vitamin D impair these activities resulting in abnormal cell growth, impaired angiogenesis and thus cancer development. Vitamin D receptors are also present in nuclei of human breast cells and it is hypothesized that polymorphism of these vitamin D receptor genes increases the likelihood of breast cancer in women.^{8,9}

Vitamin D is metabolized to 25-hydroxyvitamin D (25OHD) in the liver, 25OHD levels are used to measure Vitamin D levels in the body. Recent data have documented increased risk of reoccurrence of breast cancer and death in women with deficient levels of vitamin D and in those who have early diagnosis of breast cancer.¹⁰⁻¹² Little data have been from Pakistan and also from East Asia regarding prevalence of vitamin D deficiency in female patients with breast carcinoma. So in present study we evaluated the prevalence of vitamin D deficiency in women with breast carcinoma and to determine the association of vitamin D levels with histopathological tumor characteristics.

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MATERIALS AND METHODS

This observational study was conducted in oncology ward of Nishtar Hospital Multan (NHM). Ninety female patients with diagnosis of breast cancer on histopathology reporting were selected in a period of seven months from April 2016 to October 2016. Patients of breast cancer who have received any type of vitamin D supplementation from last one year were excluded from analysis. This study had approval from IRB of hospital.

A specialized Proforma was used to get information about their personal life e.g. marital status, menopause history, age, BMI, educational status and daily life style. Blood samples for vitamin D levels were taken in anti-coagulant free tubes from all participants and 25-OHD levels were measured using chemiluminescence technique using Abbott architect immunodiagnosics system manufactured by Abbott laboratories USA. 25-OHD levels < 20 ng/ml were labelled as deficient, 20-30 ng/ml as suboptimal and >30 were considered as optimal vitamin D levels. Information regarding tumor grade, stage, type of carcinoma and hormonal receptor status was extracted from pathology, histology and hematology reports of patients.

Analysis was done using computer software SPSS v23. Chi-square test was used to see the association between vitamin D levels status and stage of tumor, grade of cancer and hormonal receptor status. Mean vitamin D levels between pre-menopausal and post-menopausal women were compared using independent sample t-test.

RESULTS

Ninety female patients with diagnosis of breast cancer were recruited for this study. The mean age of study participants was 46.64 ± 10.64 Years. All of the participants were married. 42 (46.7%) were with pre-menopausal status and 48 (53.3%) were with post-menopausal status. 74 (82.2%) were urban residents. 66 (73.3%) patients were poor and only 2 (2.2%) patients were rich. 56 (62.2%) females were illiterate. Positive family history of breast cancer was found in 35.6% patients. 84 (93.3%) females were house wives. Mean vitamin D levels in study participants were 17.78 ± 14.66 ng/ml. There were 56 (62.2%) patients with deficient vitamin D levels, 18 (20.0%) with sub-optimal and 16 (17.8%) patients with optimal vitamin D levels.

Regarding association of vitamin D with tumor characteristics, there were 60.7% patients with deficient vitamin D levels who have Tumor Grade I, while most of the patients with sub-optimal and optimal vitamin D levels (66.7% and 62.5% respectively) were with tumor grade II. But this difference was not statistically significant (p-value 0.10).

Regarding stages of tumor, most of the patients with deficient vitamin D levels (50.0%) were with tumor stage III, there were 24.0% patients with suboptimal vitamin D levels in tumor stage III and 62.5% with optimal vitamin D levels (p-value 0.67).

Over expression of tumor estrogen receptor (ER) was found in 71.4% patients with deficient vitamin D levels, in 44.4% patients with sub-optimal vitamin D levels and in 87.5% patients with optimal vitamin D levels with p-value 0.54. Over-expression of progesterone receptors (PR) was found 67.9% patients with deficient levels, in 55.6% patients with sub-optimal and 75.0% patients with optimal vitamin D levels with insignificant p-value of 0.54. over-expression of HER-2 receptor was found in 46.4% patients with deficient vitamin D levels, in 55.6% patients with sub-optimal and in 50.0% patients with optimal vitamin D levels (p-value 0.79).

Table No.1: Baseline Characteristics of Patients.

Variable	Value
Age	46.64 $\pm$ 10.64
BMI	27.21 $\pm$ 6.67
Marital Status	
Married(%)	90 (100)
Unmarried(%)	0 (0.0)
Menopause State	
Pre-menopausal(%)	42 (46.7)
Post-menopausal(%)	48 (53.3)
Residential Status	
Rural(%)	16 (17.8)
Urban(%)	74 (82.2)
Socio-economic Status	
Poor(%)	66 (73.3)
Middle Income(%)	22 (24.4)
Rich(%)	2 (2.2)
Educational Level	
Illiterate(%)	56 (62.2)
Literate(%)	34 (37.8)
Family History of Breast Cancer	
Yes(%)	32 (35.6)
No(%)	58 (64.4)
Occupational Status	
House Wife(%)	84 (93.3)
Working Women(%)	6 (6.7)
Vitamin D Levels	17.78 $\pm$ 14.66
Vitamin D status	
Deficient(%)	56 (62.2)
Sub-optimal(%)	18 (20.0)
Optimal(%)	16 (17.8)

Tumor metastasis was found in 4 (7.1%) patients with deficient vitamin D levels, and in 12.5% patients with optimal vitamin D levels but there was no patients with suboptimal vitamin D levels with insignificant difference p-value 0.61.

We also compared mean vitamin D levels in post and pre-menopausal females and we did not found any significant difference in mean vitamin d levels between these patients; mean vitamin D levels 16.00 ± 14.04 ng/ml and 19.33 ± 15.14 respectively. Mean vitamin D levels were little high in pre-menopausal females with p-value 0.28 (table 3).

Table No.2: Association of Vitamin D status with Tumor Characteristics.

		Vitamin D Status			P-value
		Deficient (<20 ng/ml) N= 56	Sub-optimal (20-29.9 ng/ml) N=18	Optimal (>30 ng/ml) N=16	
Grades of Tumor	Grade I (%)	34 (60.7)	6 (33.3)	6 (37.5)	0.10
	Grade II (%)	20 (35.7)	12 (66.7)	10 (62.5)	
	Grade III (%)	2 (3.6)	0 (0.0)	0 (0.0)	
Stages of Tumor	Stage I (%)	10 (17.9)	2 (11.1)	2 (12.5)	0.67
	Stage II (%)	6 (10.7)	2 (11.1)	0 (0.0)	
	Stage III (%)	28 (50.0)	12 (24.0)	10 (62.5)	
	Stage IV (%)	12 (21.4)	2 (11.1)	4 (25.0)	
Tumor Estrogen Receptor (ER)	Positive (%)	40 (71.4)	8 (44.4)	14 (87.5)	0.02
	Negative (%)	16 (28.6)	10 (55.6)	2 (12.5)	
Tumor Progesterone Receptor (PR)	Positive (%)	38 (67.9)	10 (55.6)	12 (75.0)	0.54
	Negative (%)	16 (28.6)	8 (44.4)	4 (25.0)	
Tumor epidermal growth factor receptor-2 (HER-2)	Positive (%)	26 (46.4)	10 (55.6)	8 (50.0)	0.79
	Negative (%)	30 (53.6)	8 (44.4)	8 (50.0)	
Extent of Disease Spread	Early stage (%)	8 (14.3)	4 (22.2)	2 (12.5)	0.61
	Locally advanced (%)	44 (78.6)	14 (77.8)	12 (75.0)	
	Metastasis (%)	4 (7.1)	0 (0.0)	2 (12.5)	

Table No.3: Comparison of vitamin D levels between pre-menopausal and post-menopausal women.

	Vitamin D Levels		P-value
	Mean	Standard Deviation	
Pre-menopausal women	19.33	15.14	0.28
Post-menopausal Women	16.00	14.04	

DISCUSSION

Vitamin D deficiency have now become a major public health issue. In Pakistan the reported prevalence of vitamin D deficiency have been reported to be from 70 to 97% more than twice the incidence reported from western countries.¹³ A study published from Denmark have revealed that immigrants from Pakistan have very low vitamin D levels.¹⁴ In our study, the mean vitamin D levels were 17.78 ± 14.65 ng/ml. In the study by Imtiaz et al. mean vitamin D levels in breast cancer women were 9.6 ± 5 ng/ml.¹⁵ The levels reported by them were very less as compared to our study. Napoli et al. reported mean vitamin D levels in breast cancer women were 13.4 ± 0.5 ng/ml.¹⁶ Many other investigators have also found decreased vitamin D levels in breast cancer patients.^{10,17,18}

In our study, there were 62.2% patients with deficient vitamin D levels, 20.0% with sub-optimal vitamin D levels and 17.8% patients with optimal vitamin D levels. In the study by Imtiaz et al. there were 99% patients with deficient or sub-optimal vitamin D levels and only 1.0% patients with optimal vitamin D levels. In a study by Acevedo et al. 70.47% female having breast cancer with deficient vitamin D levels, 22.85% patients with sub-optimal vitamin D levels and 6.7%

patients with optimal vitamin D levels.¹⁹ These results were similar to the results of our study.

In our study, most of women (82.2%) who presented with breast cancer were living in urban areas. Another study conducted in Pakistan have also found a high prevalence (91.7%) of urban population who present with breast cancer.²⁰

In our study, mean vitamin D levels were little less in post-menopausal women as compared to pre-menopausal women. Other studies have also revealed similar results. Vrieling et al. concluded that low vitamin D levels is associated with higher risk of metastasis and poor survival in BC patients.²¹ In our study, there were 6 patients with metastasis, out of which 4 patients were with deficient vitamin D levels.

In our study, we did not found any strong association of vitamin D levels with tumor grades, stage and expression of tumor PR and HER-2 receptors. However in our study, tumor ER receptors expression was significantly high in patients in deficient and optimal vitamin D levels as compared to the patients with suboptimal vitamin D levels. Imtiaz et al. also did not found any significant association of vitamin D levels with tumor characteristics.¹⁵ However, Thanasitthichai et al found significant association of vitamin D levels with clinic-pathological features of patients with breast cancer. Hatse et al. found significant association of vitamin D levels with improved operative outcomes.²² Recent meta-analysis reports have also concluded improved survival in patients with high levels of vitamin D.^{23,24}

CONCLUSION

There is high prevalence of vitamin D deficiency in breast cancer patients. We did not found any

association of vitamin D levels with tumor characteristics.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66(1):7-30.
2. Gilani G, Kamal S, Akhter A. A differential study of breast cancer patients in Punjab, Pakistan. *J Pak Med Assoc* 2003;53(10):478-81.
3. Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for cancer prevention: global perspective. *Ann Epidemiol* 2009;19(7):468-83.
4. John EM, Schwartz GG, Dreon DM, Koo J. Vitamin D and breast cancer risk: the Nhanes I epidemiologic follow-up study, 1971–1975 to 1992. *Cancer Epidemiol Prev Biomarkers* 1999; 8(5):399-406.
5. Ness RA, Miller DD, Wei L. The role of vitamin D in cancer prevention. *Chinese J Natural Med* 2015;13(7):481-97.
6. de Lyra EC, da Silva IA, Katayama MLH, Brentani MM, Nonogaki S, Góes JCS, et al. 25 (OH) D 3 and 1, 25 (OH) 2 D 3 serum concentration and breast tissue expression of 1 α -hydroxylase, 24-hydroxylase and Vitamin D receptor in women with and without breast cancer. *J Steroid Biochem Mol Biol* 2006; 100(4):184-92.
7. Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss A, Wilson RG, et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. *Eur J Cancer* 2005;41(8):1164-9.
8. Zhang K, Song L. Association between vitamin D receptor gene polymorphisms and breast cancer risk: a meta-analysis of 39 studies. *PLoS One* 2014;9(4):e96125.
9. Reimers LL, Crew KD, Eadshaw PT, Santella RM, Steck SE, Slesnick T, et al. Vitamin D-related gene polymorphisms, plasma 25-hydroxyvitamin D, and breast cancer risk. *Cancer Causes Control* 2015;26(2):187-203.
10. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N. Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. *J Clin Oncol* 2009;27(23):3757-63.
11. Huss L, Butt S, Borgquist S, Almquist M, Malm J, Manjer J. Serum levels of vitamin D, parathyroid hormone and calcium in relation to survival following breast cancer. *Cancer Causes Control* 2014;25(9):1131-40.
12. Rose AA, Elser C, Ennis M, Goodwin PJ. Blood levels of vitamin D and early stage breast cancer prognosis: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013;141(3):331-9.
13. Iqbal R, Khan AH. Possible causes of vitamin D deficiency (VDD) in Pakistani population residing in Pakistan. *J Pak Med Assoc* 2010;60(1):1-2.
14. Andersen R, Mølgaard C, Skovgaard LT, Brot C, Cashman K, Jakobsen J, et al. Pakistani immigrant children and adults in Denmark have severely low vitamin D status. *Eur J Clin Nutr* 2008;62(5):625-34.
15. Imtiaz S, Siddiqui N, Raza SA, Loya A, Muhammad A. Vitamin D deficiency in newly diagnosed breast cancer patients. *Indian J Endocrin Metab* 2012;16(3):409.
16. Napoli N, Vattikuti S, Ma C, Rastelli A, Rayani A, Donepudi R, et al. High prevalence of low vitamin D and musculoskeletal complaints in women with breast cancer. *Breast J* 2010; 16(6):609-16.
17. Thanasitthichai S, Chaiwerawattana A, Prasitthipayong A. Association of vitamin D level with clinicopathological features in breast cancer. *Asian Pac J Cancer Prev* 2015;16(12):4881-83.
18. Neuhausen ML, Sorensen B, Hollis BW, Ambis A, Ulrich CM, McTiernan A, et al. Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors. *Am J Clin Nutr* 2008;88(1): 133-9.
19. Acevedo F, Pérez V, Pérez-Sepúlveda A, Forenzano P, Artigas R, Medina L, et al. High prevalence of vitamin D deficiency in women with breast cancer: The first Chilean study. *Breast* 2016;29:39-43.
20. Imtiaz S, Siddiqui N. Vitamin-d status at breast cancer diagnosis: correlation with social and environmental factors and dietary intake. *J Ayub Med Coll Abbottabad* 2014;26(2):186-90.
21. Vrieling A, Hein R, Abbas S, Schneeweiss A, Flesch-Janys D, Chang-Claude J. Serum 25-hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. *Breast Cancer Res* 2011;13(4):R74.
22. Hatse S, Lambrechts D, Verstuyf A, Smeets A, Brouwers B, Vanderpe T, et al. Vitamin D status at breast cancer diagnosis: correlation with tumor characteristics, disease outcome and genetic determinants of vitamin D insufficiency. *Carcinogenesis* 2012;bgs187.
23. Kim Y, Je Y. Vitamin D intake, blood 25 (OH) D levels, and breast cancer risk or mortality: a meta-analysis. *Br J Cancer* 2014;110(11):2772-84.
24. Mohr SB, Gorham ED, Kim J, Hofflich H, Garland CF. Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. *Anticancer Res* 2014;34(3):1163-6.

An Experience of Treatment Outcome in Acute Appendicitis with Antibiotics and Appendectomy at a Tertiary Care Hospital

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ABSTRACT

Objective: The present study was designed with an objective to assess the outcomes of antibiotics as primary treatment versus appendectomy in uncomplicated acute appendicitis (UAA).

Study Design: Observational study

Place and Duration of Study: This study was conducted at the Department of Surgery, PUMHSW Nawabshah from 2014 to April 2016.

Materials and Methods: A sample of 227 diagnosed cases of acute appendicitis of both genders, age 16 - 60 years, clinical history and clinical signs of appendicitis with positive findings on Ultrasonography and increased leukocyte counts were the inclusion criteria. Study subjects were divided into group A and B on the basis of modified Alvarado score. Patients <4 score Alvarado score was exclusion criterion. Data was analyzed on SPSS 22.0 ($P \leq 0.05$).

Results: During of pain and analgesic consumption was significantly higher in the group B as compared to group A in initial 2 days after surgery ($p=0.001$). However, the intensity of pain started decreasing after 2 days in group A and 4 days in group B, and this difference disappeared at one-month follow up. Hospital stay was lengthy in group B and surgical site infections were comparatively higher in group A patients. Mean cost therapy was expensive in group B compared to group A.

Conclusion: The present study concludes the antibiotic therapy as safe and effective alternate to appendectomy in uncomplicated acute appendicitis with low recurrence rate and cost.

Key Words: Acute appendicitis, Appendectomy, Antibiotic treatment

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INTRODUCTION

The trail blazing innovations through rigorous researches have put a medicine as an ever changing science with new understanding in pathophysiology of disease and new trends of evidence – based treatments to achieve the complete cure with minimal most time and costs. Nevertheless, the etiology of acute appendicitis is yet poorly understood and hence over the century, it has been thought that acute appendicitis invariably progress to perforation.^{1, 2} Hence this misperceived dogma has continuously been instigating and making appendectomy as the most preferred and common traditional treatment vis-à-vis, about 300,000 appendectomies are performed in United State each year, drawing off extreme health care system¹.

AA has a common occurrence with life time incidence of approximately 9%.³ While 20% of patients with complicated and 80% with UAA having great diathesis of resolution,⁴ and this vast majority of patients presenting with UAA have propelled, both surgeons and public to shift the traditional surgical approach towards non-operative management.^{5,6} In this regard nearly one – quarter of surgeons in Ireland routinely treat patients of UAA non-operatively.⁷ In recent years, the management approach of UAA has been changing with antibiotic therapy⁸ and many randomized control trials have inferenced the vignette that antibiotic management is an efficacious treatment with lower complications than surgical intervention.⁹ While the important question in comparing the two treatment option needs the answer with the fact that, “Does antibiotic treatment draw substantial certainty of security, can antibiotic embrace subsequent morbidities”. And in this context, acute appendicitis have been divided in complicated (associated with abscess or phlegmon) and uncomplicated. While the complicated appendicitis almost always needs surgery, UAA needs to be strictly scrutinized for surgical or non- surgical treatment.¹⁰ While the use of Alvarado scoring system with high quality ultra-sonography have

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depicted a sufficiently high accuracy in treatment decision.¹¹⁻¹⁴ Many published meta-analyses on this topic¹⁵⁻¹⁷ have concluded that antibiotics first strategy of treatment is probably a safe approach, but the definitive conclusions about its effectiveness compared with appendectomy cannot be made. All of the studies have focused on analysis of the clinical outcomes.^{15,17} But it remains to be determined whether the benefits of avoiding an operation with the antibiotics-first approach will outweigh the burden to the patient related to future appendicitis episodes, more days of antibiotic therapy, lingering symptoms, and uncertain sense of security affecting quality of life. The present study was designed with an objective to assess the outcomes of antibiotics as primary treatment versus appendectomy in uncomplicated acute appendicitis (UAA).

MATERIALS AND METHODS

A sample of 227 patients of both genders from 16 to 60 years in age having no H/O previous episode of appendicitis, surgery or co-morbidities presented with typical history and clinical signs of appendicitis with positive findings on Ultrasonography and increased leukocytes (WBC) levels on two occasions within 24 hours at our surgical unit one from April 2014 to April 2016, were enrolled in this Observational study - randomized and quasi-randomized prospective study. Patients of complicated appendicitis with an appendicolith, perforation, abscess or phlegmon were excluded. All patients gave written informed consent to participate in this study. Study population was divided into two A and B groups on the basis of modified Alvarado score, and patients below 4 score of Alvarado were not included. Group A: Alvarado-score 5-7 were allocated with antibiotics and observation and Group B: Alvarado-score 8 - 10 underwent Surgery. After keeping NPO, Intravenous fluids, antibiotics (ciprofloxacin 500mg x 2) plus metronidazole (500mg x 8hmlly) and analgesics with diclofenac sodium (50-75mg I/V daily) were administered for two days to group A. Daily follow up of these patients were done with clinical examination, fever and CBC. Patient resistant and refractive to antibiotherapy with worsening symptoms confirmed on US were taken to appendectomy. Patient with clinical improvement confirmed on CBC and US were discharged on third day and received oral treatment with ciprofloxacin (500mg) twice a day and metronidazole (400mg) thrice a day for 07 days. All the appendixes of patients converted (cross over) in surgery were examined for Histopathology. With prophylactic antibiotics-Cephalosporin 3rd generation I/V 30 minutes before the start of incision. Patients underwent standard open appendectomy through Mc Burney right lower quadrant muscle-splitting incision. Post-operative antibiotics were given in all patients for 2 days. All resected Appendixes were biopsied. Appendicitis was termed

with histological evidence of transmural neutrophil invasion at the muscular layer of appendix. Duration of pain, hospital stay, wound infection, recurrence, costs, adhesions / incisional hernia and non- working days were studied for analyzing outcome. Routine follow up was taken on days 15, 30, 90 180 and 360. The study was approved by ethics committee. Informed written consent was signed by patients or legal attendant. Data analysis was performed on statistical package for social science (SPSS) 22.0 for windows was used to have statical evaluation ANOVA and chi-square test with subset Fisher's exact test were used and $P \leq 0.05$ was considered as statically significant.

RESULTS

Under screening through strict inclusion and exclusion criteria, 227 patients were found eligible for randomized recruitment in two different groups A and B. While after having Alvarado score (8-10), CBC and Ultrasound report, 120 patients were assigned in group B for instant appendectomies. While remaining 107 patients having Alvarado score (5-7) were randomized to group A. Further 11 and 18 patients were lost in follow up from group A and B leaving behind 96 and 102 patients respectively in each cohort available for objective analysis of this study. The demographics base line characteristics of group A and B are shown in following Table 1.

Table No. 1: Demographic characteristics of study subjects

Particulars	Group A		Group B	
	Male	Female	Male	Female
Sex	61	35	60	42
Male Female ratio				
Age range	16 – 60	20 – 55	16 - 58	20 -50
Median age	26	24	27	26
Median, pain score on NRS (0-10)	4	5	7	8
No. of patients discharged satisfactory	57	29	60	42

During of pain and analgesic consumption were significantly higher in the group B as compared to group A in initial 2 days after surgery. However, the intensity of pain started decreasing after 2 days in group A and 4 days in group B, and this difference disappeared at one-month follow up and no significant difference in pain score was noted in subsequent follow up in both groups. However, the mean number of days

in which patient felt abdominal pain was 5 in group A and 8 in group B.

Table No.2: Findings in groups of study subjects

	Male	Female
No. of patients, worsened in symptoms during hospital stay.	04	06
Conversion to surgery / cross-over during hospital stay	04	06
cross-over during follow up	04	07
Range of hospital stay	1 - 15	1 - 20
Mean length of hospital stay	3 ± 1	4 ± 1
Adverse effects on antibiotics / Diasshan	02	04
No. of days not worked by patients (Mean)	03	04
Recurrent appendicitis	06	10
Total cross – over from antibiotics to surgery	08	13
Negative appendectomies	02	03
Wound infection	02	03
Mortality	00	00

Table No.3: Treatment outcomes comparing Group A and B

Particulars	Group A		Group B	
	Male	Female	Male	Female
Duration of pain in hours	22±15.7	20±10.5	36±15.10	37±16.5
Median, pain score on NRS (0-10)	4	5	7	8
Hospital Stay days (mean)	4±1	5±1	3.3±0.5	4.1±1.4
Wound infection	02	03	5	6
Costs	7000	7000	10,000	24,000
Adhesions / incisional hernia				2
No. of days not worked during illness (median)	06 (6-12)	07 (6-17)	14 (12-20)	20 (14-21)
Conversion to surgery	08	13	60	42
Negative appendectomies	02	03	07	09

There was higher length of stay in group B as comparison to group A in general. But the length of stay including re-admission was higher in patients of group A, who underwent for appendectomy after failure of antibiotic treatment. Surgical site infections were comparatively higher in group A patients underwent for appendectomy after failure of antibiotic treatment in comparison to group B patient who instantly underwent appendectomy. However, 07 patients of group B

developed more severe wound infections. Among these 4 had delayed healing by secondary intention and 3 developed incisional hernia as complication in follow up period. So the complication rate was 0% and 3% in group A and B respectively. The mean cost of therapy was Rs. 7,000/- in the antibiotic / non-operative (A) group, including all lab and Ultrasonologic investigations and recurrent admission without operation. While all expenses of surgical material, anesthesia drugs, analgesics, antibiotics, dressings amounting about 22,000/- in group B. In this study the length of days not worked by patients during illness in group A was significantly low in comparison to group B. (median 6 days versus 18 days in group A & B respectively). From group A, 21(22%) patients have not responded to antibiotic therapy. In this study, 24% (5/21 patients) and 15.6% (16/102 patient) negative appendectomies were encountered in group A and Group B.

DISCUSSION

Unfortunately, the exact pathophysiology of appendicitis is not entirely clear, but major reason is obstruction of lumen^{18, 19}. Clinically, appendicitis may present in different ways while some studies report that non-complicated and complicated (perforated) appendicitis are different entities and that in many cases acute appendicitis may resolve spontaneously.²⁰ Consequently, treatment option of acute appendicitis should be based on either complicated or uncomplicated²¹. Despite the fact that surgical appendectomy is the standard treatment of acute appendicitis, but several investigators have studied the conservative antibiotic treatment with good results.^{22, 23} For this reason UAA with conservative antibiotic treatment was become a very attractive alternate to surgery.²⁴ While the use of Alvarado scoring system with Ultrasonography is help full in detection of complicated or UAA.²⁵ Hence, this study reflects the outcomes of antibiotic treatment versus appendectomy in UAA. Although we were not sure about effectiveness of antibiotic first strategy in comparison to appendectomy for UAA before start of study, but we found that 83 of (86.45%) of 96 patients were success fully treated with antibiotic therapy and this corresponding to studies of Hansson et al and Barry VC et al.^{26, 24} However, despite success of antibiotics for more advanced infections it has not yet been accepted as a standard treatment for UAA.²⁷ In comparison, the treatment efficacy rate for appendectomy, this study found that 86 (84%) of 102 patients were successfully treated, and this inference is nearly similar to studies shown in table no. 4 ranged between 85 and 100% with overall efficacy rate 88%^{28, 29}. The number of patients who developed post-operative complications like incisional hernia was significantly higher) in the surgery group B as shown in table no. 3, the relative

number of surgical site infection was more in percentage in group A (antibiotic treated) patients, which somehow corresponding to three studies as referred fine studies of table No. 4 plus Malik AA et al¹⁹. In perspective to objective of comparison between two modalities of treatment, this study finds the antibiotic treatment with longer hospital stay due to intra venous antibiotics and monitoring of patient to ensure safety before discharge. These results are corresponding to studies of Williams IM et al¹⁵. We have found a significant reduction in overall costs for group A in comparison to group B. and this in government hospital, which even otherwise indicates that antibiotic treatment achieves significant cost-saving and is most suitable and affordable option of treatment for our downtrodden major strata of society, so we can predict this treatment for every UAA for outpatient setting as the common practice in near future. So for the number of days not worked during these two types of treatments, this study finds that patients treated with antibiotics were associated with significant less days not worked as compared with appendectomy (6-12 versus 12-21) and this corresponds to study of Salminen as shown in table-4. While in group A the failure of antibiotic treatment was (22%) among them again there was 05 patients (5%) with negative appendectomies, which otherwise concludes as (22 - 5 = 17%) failure or recurrence with of treatment. Again, there were 16(16.6%) patients with negative appendectomies in group B. Hence if we combine both groups A & B patients it comes to be 198 study population having negative appendectomies of 21, which makes about (11%). This otherwise expresses the goodness of antibiotics, which we lost with negative appendectomies with poor pre-operative detection by Alvarado and ultrasounds, these findings are very relative with many studies suggested that each year over 300,000 appendicitis are performed in United State with 15% negative appendectomies.

CONCLUSION

The present study reports, with unapproving quality of diagnosis for UAA by using Alvarado scoring system in addition to Ultrasonography and complete blood counts, it can be n successfully treated with antibiotics and rate of negative appendectomies may be decreased. Antibiotic therapy is safe and effective alternative to appendectomy in UAA, with reasonably low recurrence rate and cost.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Leung TT, Dixon E, Gill M, Mador BD, Moulton KM, Kaplan GG, et al. Bowel obstruction following appendectomy: what is the true incidence?. *Annals Surg* 2009; 250(1):51-3.
2. Fitz R. Perforating inflammation of vermiform appendix. *Am J Med Sci* 1886;92:321-46.
3. Anderson JE, Bickler SW, Chang DC, Talamini MA. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995–2009. *World J Surg* 2012;36(12):2787-94.
4. Andersson RE, Hugander A, Thulin AJ. Diagnostic accuracy and perforation rate in appendicitis: association with age and sex of the patient and with appendicectomy rate. *Eur J Surg Acta Chirurgica* 1992;158(1):37-41.
5. Flum DR. Clinical practice: Acute appendicitis—Appendectomy or the “antibiotics first” strategy. *N Engl J Med* 2015; 2015(372):1937-43.
6. Kolata G. Antibiotics resurface as alternative to removing appendix. *The New York Times* 2015. Accessed November 24, 2015.
7. Kelly ME, Khan A, Ur Rehman J. A National evaluation of the conservative management of uncomplicated acute appendicitis: How common is this and what are the issues? *Dig Surg* 2015; 32: 321-330.
8. Di Saverio S, Sibilio A, Giorgini E, Biscardi A, Villani S, Coccolini F, et al. The NOTA Study (Non Operative Treatment for Acute Appendicitis): Prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. *Annals Surg* 2014; 260(1):109-17.
9. Can Appendicitis be treated with antibiotics? Retraction muddies the water. Published 2011. Accessed June 2, 2015.
10. Theilen LH, Mellnick VM, Longman RE, Tuuli MG, Odibo AO, Macones GA, et al. Utility of magnetic resonance imaging for suspected appendicitis in pregnant women. *Am J Obstet Gynecol* 2015;212(3):345-e1.
11. Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. *BMC Med* 2011 Dec 28;9(1):139.
12. Alvarado A. A practical score for the early diagnosis of acute appendicitis. *Annals Emerg Med* 1986;15(5):557-64.
13. Jones RP, Jeffrey RB, Shah BR, Desser TS, Rosenberg J, Olcott EW. Journal Club: the Alvarado score as a method for reducing the number of CT studies when appendiceal ultrasound fails to visualize the appendix in adults. *Am J Roentgenol* 2015; 204(3):519-26.
14. Tan WJ, Pek W, Kabir T, Goh YC, Chan WH, Wong WK, et al. Alvarado score: a guide to

- computed tomography utilization in appendicitis. *ANZ J Surg* 2013; 83(10):748-52.
15. Wilms IM, de Hoog DE, de Visser DC, Janzing HM. Appendectomy versus antibiotic treatment for acute appendicitis. *The Cochrane Library* 2011;(9): 23-7.
 16. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ* 2012; 344:e2156.
 17. Mason RJ, Moazzez A, Sohn H, Katkhouda N. Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surgical Infect* 2012;13(2):74-84.
 18. Ditillo MF, Dziura JD, Rabinovici R. Is it safe to delay appendectomy in adults with acute appendicitis?. *Annals Surg* 2006;244(5):656-60.
 19. Malik AA, Bari SU. Retracted article: Conservative Management of Acute Appendicitis. *J Gastrointestinal Surg* 2009;13(5):966-70.
 20. Singh JP, Mariadason JG. Role of the faecolith in modern-day appendicitis. *Annals Royal Coll Surgeons Engl* 2013;95(1):48-51.
 21. Andersson RE, Schien M. Antibiotics as first-line therapy for acute appendicitis: evidence for change in clinical practice. *World J Surg* 2012;36(9): 2037-2038.
 22. Eriksson S, Granström L. Randomized controlled trial of appendectomy versus antibiotic therapy for acute appendicitis. *Bri J Surg* 1995;82(2): 166-9.
 23. Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA* 2015;313(23):2340-8.
 24. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, et al. Amoxicillin plus clavulanic acid versus appendectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *The Lancet* 2011;377(9777):1573-9.
 25. Mason RJ. Appendicitis: is surgery the best option?. *The Lancet* 2011;377(9777):1545-6.
 26. Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendectomy as primary treatment of acute appendicitis in unselected patients. *Bri J Surg* 2009;96(5):473-81.
 27. Humes DJ, Simpson J. Acute appendicitis. *BMJ: Bri Med J* 2006;333(7567):530.
 28. Styrd J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg* 2006;30(6):1033.
 29. Cuschieri J, Florence M, Flum DR, Jurkovich GJ, Linn P, Steele SR, et al. SCOAP collaborative. Negative appendectomy and imaging accuracy in the Washington state surgical care and outcomes assessment program. *Annals Surg* 2008; 248(4): 557-63.
 30. Flum DR, Koepsell T. The clinical and economic correlates of misdiagnosed appendicitis: nationwide analysis. *Archives Surg* 2002; 137(7): 799-804.

Effects of Smoking on Systemic Blood Pressure, Serum Cholesterol and Serum Bilirubin in Medical Students

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ABSTRACT

Objective: To determine the effects of smoking on systemic blood pressure, serum cholesterol and serum bilirubin in medical students.

Study Design: Case control study

Place & Duration: This study was conducted at the Liaquat University of Medical and Health Sciences Hospital from June 2014 to November 2014.

Materials and Methods: A sample of 100 medical students was divided into 50 smokers and 50 non-smokers. Age, weight, smoking duration, blood pressure, serum cholesterol and serum bilirubin were collected in a pre structured proforma. Data was analyzed by statistical package SPSS 22.0.

Results: Duration, cigarettes smoked and pack year of cigarette smoked were noted as 3.85 ± 3.96 years, 10.25 ± 3.57 and 1.7 ± 0.56 respectively ($p=0.0001$). Mean systolic and diastolic BP in smokers and non-smokers noted as 143.9 ± 12.67 and 135.1 ± 15.24 ($p=0.002$), 75.6 ± 9.72 and 67.9 ± 6.06 mmHg ($p=0.0001$) respectively. Similarly serum bilirubin and cholesterol were noted as 0.99 ± 0.27 and 1.13 ± 0.20 ($p=0.005$), 156.5 ± 18.6 and 119.3 ± 22.70 mg/dl ($p=0.0001$) respectively.

Conclusion: The present study reports high systemic blood pressure and serum cholesterol and low serum bilirubin in the smokers. Preventive strategies must be implemented to quit the smoking by youngsters.

Key Words: Smoking, Blood pressure, Cholesterol, Bilirubin, Medical students

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INTRODUCTION

Tobacco cigarette smoking is one of the preventable causes of mortality and morbidity the World over. If smoking quit is encouraged it may reduce the mortality. A previous study reported that the tobacco related deaths will multiply many time over next 3-5 decades if it is not discouraged.¹ Morbid effects of cigarette smoking are well documented, with evidence of a decrease in life. Previous studies reported that the smokers die ten years than non-smokers.^{2,3} Tobacco smoking is a addicting habit and people crave for it once they have begun. In particular, when the youngsters are addicted, then it will be very dangerous for the health due to more life and more exposure to tobacco smoke.⁴ Tobacco smoke has association with the cardiovascular diseases (CVD) which is a leading cause of death globally.⁵

Mortality due to CVD related now accounts for one-third cases globally. It is leading cause of death in both developing and developed countries.⁶ Both tobacco smoking and CVD are eminently preventable conditions. Systemic high blood pressure is termed as the 'systemic hypertension' which is a increasing globally. Hypertension is preventable cause of CVD by multiple strategies as quitting tobacco smoking and physical activity.^{7,8} Systemic hypertension damages the target organs which include the; heart, eye, brain, and kidneys. Proper preventive measures and removal of risk factors such as tobacco smoking may greatly help to reduce the burden of health problems.⁹ Vascular disorders of heart, brain and kidney are also associated even with the suboptimal blood pressure (BP).¹⁰ A previous study reported vascular injury may occur even with suboptimal systolic BP >115 mmHg.⁶ Several studies¹¹⁻¹³ have established the association of tobacco cigarette smoking, hyperlipidemia and systemic high blood pressure. The present study was conceived keeping in view the significance of cigarette smoking is increasing in the youngsters, in particular the medical students. Medical students smoke cigarette as time pass, social taboos, alleviate exam anxiety and as a symbol social dignity.¹¹⁻¹³ As the medical students are future of health care providers, there is dire need to highlight the issue of smoking with special reference to high blood pressure and blood lipids. These maladies are

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preventable cause of mortality. The present study is first type of its design which highlights the neglected social problem of cigarette smoking young medical students. The present study analyzed the health hazards of cigarette smoking with special reference to systemic blood pressure and serum cholesterol.

MATERIALS AND METHODS

This case control study was conducted in Liaquat University of Medical and Health Sciences Hospital from June 2014 to November 2014. The subjects were the medical students who voluntarily provided the information in the pre designed proforma. Study was launched after ethical clearance from Institutional Ethical Committee. A sample of 100 medical students was divided into 50 smokers and 50 non-smokers. Age, weight, smoking duration, blood pressure, serum cholesterol and serum bilirubin were collected in a pre structured proforma. Age of 19- 26 years and male subjects were the inclusion criterion. Subjects with history of family systemic hypertension, diabetes mellitus, hyperlipidemia, female students and coronary artery disease were excluded. Also subjects taking multivitamin, anti oxidant pills, and drugs were excluded. Study protocol was explained and data confidentially was secured. Students were informed that the data will be confidential and will never be disclosed in public even after study is published. Personal and family history, systemic blood pressure, body weight and blood sampling was performed under standard protocol. Nonsmoker was defined as one who never smoked cigarettes. An occasional smoker was excluded also. Voluntary subjects were asked to sign proforma and consent form. Cigarette smoke as "Pack years" was calculated as "No. of cigarettes smoked per day $\times$ No. of years smoked/20".¹⁴ Systemic blood pressure was measured according to JNC criteria VII; first by auscultatory method followed by sphygmomanometer. 5 – 10 minutes rest was mandatory for each participant before recording blood pressure. Data was collected on a predesigned proforma. Consent forms were designed for volunteers and were kept confidential. Statistical analysis was done by statistical software SPSS 22.0 version (IBM Corporation, USA) for windows. Continuous and categorical data variables were analyzed by student's t test and Chi square test respectively. All data analysis was performed at 95% ($P \leq 0.05$).

RESULTS

Demography and biochemical findings of study subjects are shown in table 1. Age and body weight between two groups were similar ($p > 0.05$). Mean $\pm$ SD duration, cigarettes smoked and pack year of cigarette smoked were noted as 3.85 ± 3.96 years, 10.25 ± 3.57 and 1.7 ± 0.56 respectively ($p = 0.0001$).

Table No.1: Demography and biochemical findings of study subjects

	Smokers (n=50) Mean $\pm$ SD	Non-smokers (n=50) Mean $\pm$ SD	P-value
Age (years)	24.7 $\pm$ 2.45	24.8 $\pm$ 2.30	0.86
Body weight (kg)	68.9 $\pm$ 7.30	68.5 $\pm$ 4.54	0.74
Systolic BP (mmHg)	143.9 $\pm$ 12.67	135.1 $\pm$ 15.24	0.002
Diastolic BP (mmHg)	75.6 $\pm$ 9.72	67.9 $\pm$ 6.06	0.0001
Serum Bilirubin (mg/dl)	0.99 $\pm$ 0.27	1.13 $\pm$ 0.20	0.005
Serum Cholesterol (mg/dl)	156.5 $\pm$ 18.6	119.3 $\pm$ 22.70	0.0001

Mean systolic and diastolic BP in smokers and non-smokers reveals significant differences noted as 143.9 ± 12.67 and 135.1 ± 15.24 , 75.6 ± 9.72 and 67.9 ± 6.06 mmHg respectively ($p = 0.002$ and 0.0001). Similarly serum bilirubin and cholesterol were noted as 0.99 ± 0.27 and 1.13 ± 0.20 ($p = 0.005$), 156.5 ± 18.6 and 119.3 ± 22.70 mg/dl ($p = 0.0001$) respectively.

DISCUSSION

The present research is the first study which highlights the health hazards of cigarette smoking in medical students. The present study is of public health significance as it includes the young social class of medical students who will take the responsibility of health care provider in the future. As the medical curriculum is stressful, the examination anxiety and worries drag the students to alleviate by one or other means such as cigarette smoking which is easily available. Taste craving behavior and wrong friendship are other causes of cigarette smoking in medical students. The present study could recruit only fifty smokers. Mean age shows, majority belonged to third decade of life. Mean $\pm$ SD duration, cigarettes smoked and pack year of cigarette smoked were noted as 3.85 ± 3.96 years, 10.25 ± 3.57 and 1.7 ± 0.56 respectively ($p = 0.0001$). The findings are in agreement with a recent study of Jena et al¹⁵ and others.¹⁶⁻¹⁸ Mean systolic and diastolic BP in smokers and non-smokers reveals significant differences noted as 143.9 ± 12.67 and 135.1 ± 15.24 , 75.6 ± 9.72 and 67.9 ± 6.06 mmHg respectively ($p = 0.002$ and 0.0001). This shows the smokers were having high mean systolic and diastolic BP, the findings are in agreement with previous studies.¹⁶⁻¹⁸ This shows the smokers were having high mean systolic and diastolic BP, the findings are in agreement with previous studies.¹⁵⁻¹⁸ Several studies¹⁵⁻¹⁸ have been conducted

to find the association of cigarette smoking and high blood pressure, but controversial results have been reported. Some of previous studies¹⁵⁻¹⁸ reported strong association of cigarette smoking and high systemic blood pressure; the findings are in keeping with present study. While other studies¹⁹⁻²¹ reported no such association, this is controversial and inconsistent with present and previous studies¹⁵⁻²⁰. The present study reports raised systolic and diastolic BP in smokers ($p=0.05$) as shown in table 1. Highly controversial results are reported by previous studies,²²⁻²⁴ which reported the cigarette smoking decreases the systemic blood pressure. This is highly controversial and paradoxical and might be due to technical errors in biostatistical analysis, different social population, different geographical areas and researcher bias. Previous studies reported that the rise in systemic blood pressure may be due to the nicotine mediated stimulation of sympathetic stimulation through cholinergic and adrenergic receptors.^{25,26} Cigarette smoking increases the arterial stiffness, and increases the chances of atherogenesis, thrombo-embolism, ischemic cardiac disease and coronary crisis.^{27,28} Serum bilirubin was found decreased in smokers this is consistent with previous studies.^{29,30} It is known that the serum bilirubin is a natural plasma anti oxidant which is consumed by free radical stress as in cigarette smokers. Blood cholesterol was raised in smokers this is consistent with previous studies.^{31,32}

The present study has certain limitations such as; first- cause effect relationship cannot be ascertained due to study design, second – different race and ethnicity and third- medical students are always exposed to mental stress, hence the findings should be cautiously interpreted for the general populations.

CONCLUSION

The present study reports high systemic blood pressure and serum cholesterol and low serum bilirubin in the smokers. Preventive strategies must be implemented to quit the smoking by youngsters.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Calo WA, Ortiz AP, Suarez E, Guzman M, Perez CM. Association of cigarette smoking and metabolic syndrome in a Puerto Rican adult population. *J Immigr Minor Health* 2013;15(4): 810-816.
2. Li S, Yun M, Fernandez C, Xu J, Srinivasan SR, Chen W, et al. Cigarette smoking exacerbates the adverse effects of age and metabolic syndrome on subclinical atherosclerosis: the Bogalusa Heart Study. *PLoS One* 2014; 9(5):e96368.
3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
4. Ferrante M, Saulle R, Ledda C, Pappalardo R, Fallico R, La Torre G, et al. Prevalence of smoking habits, attitudes, knowledge and beliefs among Health Professional School students: A cross sectional study. *Ann Ist Super Sanita* 2013;49: 143-9.
5. Pahlavan PS, Frøbert O. Clinical findings and educational status in chest pain patients admitted to an emergency department. Report from a three month survey at Be'sat hospital, Teheran, Iran. *Ital Heart J* 2004;5:762-6.
6. World Health Organization. The World Health Report 2002; Risk to Health 2002. Geneva: World Health Organization, 2001.
7. Singh RB, Suh ML, Singh VP, Chaithiraphan S, Laothavorn P, Singh RG, et al. Hypertension and stroke in Asia: Prevalence, control and strategies in developing countries for prevention. *J Hum Hypertens* 2000;14:749-63.
8. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part I: General considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001;104:2746-53.
9. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: Overview of randomised drug trials in their epidemiological context. *Lancet* 1990;335:827-38.
10. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke and coronary disease. Part 1: Prolonged difference in blood pressure: Prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765- 74.
11. Al-Khalifa II, Mohammed SM, Ali ZM. Cigarette Smoking as a Relative Risk Factor for Metabolic Syndrome. *J Endocrinol Metab* 2016;6(6):178-182.
12. Jamshidi L, Seif A, Vazinigheysar H. Comparison of Indicators of Metabolic Syndrome in Iranian Smokers. *Zahedan J Res Med Sci* 2014;16(1): 55-58.
13. Kaur J. Assessment and Screening of the Risk Factors in Metabolic Syndrome. *Med Sci* 2014; 2:140-152.
14. Bornaards CM, Twisk JW, Snel J, Van Mechelen W, Kemper HC. Is calculating pack years retrospectively a valid method to estimate life-time tobacco smoking? A comparison

- between prospectively calculated pack years and retrospectively calculated pack years. *Addiction* 2001;96:1653-61.
15. Jena SK, Purohit KC. Smoking status and its effect on blood pressure: A study on medical students. *CHRISMED J Health Res* 2017; 4:14-8.
 16. Aronow WS, Dendinger J, Rokaw SN. Heart rate and carbon monoxide level after smoking high-, low-, and non-nicotine cigarettes. A study in male patients with angina pectoris. *Ann Int Med* 1971; 74:697-702.
 17. Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking associated hemodynamic and metabolic events. *N Engl J Med* 1976;295:573-7.
 18. Elliott JM, Simpson FO. Cigarettes and accelerated hypertension. *N Z Med J* 1980;91:447-9.
 19. Lang T, Bureau JF, Degoulet P, Salah H, Benattar C. Blood pressure, coffee, tea and tobacco consumption: An epidemiological study in Algiers. *Eur Heart J* 1983;4:602-7.
 20. Simons LA, Simons J, Jones AS. The interactions of body weight, age, cigarette smoking and hormone usage with blood pressure and plasma lipids in an Australian community. *Aust N Z J Med* 1984;14:215-21.
 21. Okubo Y, Miyamoto T, Suwazono Y, Kobayashi E, Nogawa K. An association between smoking habits and blood pressure in normotensive Japanese men. *J Hum Hypertens* 2002;16:91-6.
 22. Imamura H, Tanaka K, Hirae C, Furugami T, Yoshimura Y, Uchida K, et al. Relationship of cigarette smoking to blood pressure and serum lipids and lipoproteins in men. *Clin Exp Pharmacol Physiol* 1996;23:397-402.
 23. Benowitz NL, Sharp DS. Inverse relation between serum cotinine concentration and blood pressure in cigarette smokers. *Circulation* 1989;80:1309-12.
 24. Goldbourt U, Medalie JH. Characteristics of smokers, non-smokers and ex-smokers among 10,000 adult males in Israel. II. Physiologic, biochemical and genetic characteristics. *Am J Epidemiol* 1977;105:75-86.
 25. Adamopoulos D, van de Borne P, Argacha JF. New insights into the sympathetic, endothelial and coronary effects of nicotine. *Clin Exp Pharmacol Physiol* 2008;35:458-63.
 26. Haass M, Kübler W. Nicotine and sympathetic neurotransmission. *Cardiovasc Drugs Ther* 1997; 10:657-65.
 27. O'Rourke M, Frohlich ED. Pulse pressure: Is this a clinically useful risk factor? *Hypertension* 1999;34: 372-4.
 28. Wood DM, Mould MS, Ong SB, Baker EH. Pack year smoking histories: What about patients who use loose tobacco? *Tob Control* 2005;14:141-2.
 29. Lim JE, Kim H, Jee SH. Combined effects of Smoking and Bilirubin Levels on the Risk of Lung Cancer in Korea: The Severance Cohort Study. *PLoS One* 2014; 9(8): e103972.
 30. Jo J, Kim H, Yun JE, Lee KJ, Jee SH. Cigarette Smoking and Serum Bilirubin Subtypes in Healthy Korean Men: The Korea Medical Institute Study. *J Prev Med Public Health* 2012;45(2):105-112.
 31. Patel K, Prajapati P, Sanghavi S, Goplani V. A study on effects of cigarette smoking on blood cholesterol in young population of Ahmedabad. *Int'l J Basic Appl Physiol* 2014; 3(1):129-33.
 32. Sheno AS, Kadam V, Ghanekar J. Effect of Smoking on Serum Lipid Levels: A Hospitalbased Study. *MGM J Med Sci* 2015;2(1):1315.

Association of Iron Deficiency Anemia with Preterm Labor

Iron Deficiency Anemia
with Preterm LaborSibghah Usman¹, Aneela Shaheen², Rao Muhammad Haris Hameed³ and Ahsanullah M Mirbahar⁴

ABSTRACT

Objective: To investigate the association of iron deficiency anemia as a cause of preterm labour.

Study Design: Descriptive/cross sectional study

Place and Duration of Study: This study was conducted at the Department of Obstetrics and Gynaecology, Nishtar Hospital Multan from July 2016 to December 2016

Materials and Methods: After approval from ethical committee of hospital, informed consent was taken from patients and data was entered and analyzed with computer software SPSS version 20. All numerical data was presented as mean and Standard Deviation and categorical data was presented as frequency and percentages. P Value of 0.05 was considered as significant.

Results: Total patients included in this study were 196 (100%), all were females, in which 138 (70.4%) were house wives and 58 (29.6%) were working ladies. Mean Hb of the patients was 8.06 ± 1.42 , mean of serum Ferritin was 12.90 ± 2.62 , mean of delivery time was 34.78 ± 2.35 , mean of BMI was 29.85 ± 1.67 , mean of parity was 3.24 ± 1.37 , mean of gravidity was 3.15 ± 1.23 . Out of 196 (100%) it was observed that 128 (65.3%) were facing the condition of pre-term labor and 68 (37.7%) delivered normally.

Conclusion: Anaemia in pregnancy was found to be associated with increased risk for preterm labour.

Key Words: Haemoglobin, anemia, preterm birth, Hemoglobin, Parity

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INTRODUCTION

Out of the numerous causes of perinatal mortality and morbidity, preterm birth is one of the most frequent underlying factor worldwide¹. Maternal anemia and preterm birth goes hand in hand with each other in various studies done for the purpose of documenting their association². Chinese studies done for documenting the association between anemia and preterm birth are erratic, inconsistent and variable. Studies have given a notion and are now pointing to the fact that the strength of association of anemia and preterm birth may fluctuate vary based primarily on the time of gestation at the onset of anemia and duration of gestation till the persistence of anemia³. Spontaneous preterm labour, preterm premature rupture of membranes (PROM) and medically indicated preterm birth are subtypes of preterm birth, inspite of knowing

this fact rarely a study is performed for judging the relation of anemia and specific subtype of preterm birth to determine individual burden of each subtype on the association of preterm birth and anemia⁴. Any study for this purpose might blow the whole concept of any association between anemia and preterm labour, if only an individual subtype show increased risk contrary to other subtypes⁵. This type of study embody the potential of throwing light on hidden etiologies and underlying mechanisms for preterm labour which are still waiting to be discovered⁵.

Multiple pathways including maternal infection, hypoxia and aerophilous stress are the suspected culprits for preterm labour being quoted over and over as major underlying biological pathways⁶. There is possibility of increase susceptibility of mother toward infections and also increase stress on both fetus and mother due to chorionic hypoxia caused by iron deficiency anemia. Activation of maternal or fetal hypothalamic-pituitary-adrenal axis resulting from cascade following active immune response to combat infection leads to initiation of preterm labour⁷. Oxidative stress harming erythrocytes and fetoplacental unit add the final stone to the adverse possibilities of iron deficiency anemia⁸.

Our hypothesis is based on the possibility of increased risk of preterm labour due to maternal anemia which may lead to the discovery of the hidden mechanism and causes of preterm labour.

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MATERIALS AND METHODS

After approval from ethical committee of hospital, informed consent was taken from patients before including patient's data in research and they were ensured about their confidentiality. Patient's telephonic contacts and addresses were taken. Blood was collected with all septic precaution in CBC vial for hemoglobin count. Gestational age, in completed weeks, was estimated based on the last menstrual period. Preterm birth was defined as live births delivered before 37 completed weeks. Pregnant women with preterm labor of age 25 to 35 years were included in the study. Any other cause which can induce preterm labor (twins or infections diagnosed radiologically and complete urine examination respectively) were excluded from the study. All the data entered and analyzed using computer software SPSS version 10. Mean and standard deviation was calculated for quantitative variables like age, hemoglobin count and gestational age. Frequency and percentage were calculated for qualitative variables like preterm birth and outcome (iron deficiency anemia) Yes/No. Effect modifier like age, gravidity and parity was controlled by stratification of data. Post stratification multiple regression test was applied. A p value 0.05 was considered statistically significant.

RESULTS

Total subjects included in this study were one hundred and ninety six 196 (100%), all were females, in which 138 (70.4%) were house wives and 58 (29.6%) were working ladies. Mean of Hb of the subjects was 8.06 ± 1.42 , mean of serum Ferritin was 12.90 ± 2.62 , mean of delivery time was 34.78 ± 2.35 , mean of BMI was 29.85 ± 1.67 , mean of parity 3.24 ± 1.37 , mean of gravidity was 3.15 ± 1.23 . It was observed that out of these 196 subjects, 128 (65.3%) were facing the condition of pre-term labor and 68 (34.7%) delivered normally (Table-1-2).

Table No.1: Demographic Variables

Characteristics	Mean	Std. Deviation
Hb	8.061	1.416
Serum Ferritin	12.903	2.626
Time of delivery	34.785	2.350
BMI	29.852	1.674
Parity	3.244	1.377
Gravidity	3.158	1.232

In this study, the outcome variable was pre-term labor. We applied the logistic regression to find the predictors for preterm labor, it was noted that serum Ferritin and gravidity were significant with pre-term labor and time of delivery, Hb, BMI, Parity and occupation of women were not. Odds ratios also described this trend. Others measures of association such as Concordant Discordant

showed the association but Goodman-Kruskal Gamma not showed the association (Table-3-4).

The logistic regression equation was as;

Pre-term labor = $3.587 - 0.1693 \text{ Hb} + 0.1732 \text{ Serum Ferritin} - 0.07691 \text{ Time of delivery} - 0.06083 \text{ BMI} + 0.03033 \text{ Parity} + 0.2822 \text{ Gravidity}$

Table No.2: Women Occupation and Preterm Birth

Women occupation.		
Characteristics	Frequency	Percent (%)
House wife	138	70.4 %
Working Lady	58	29.6 %
Preterm Birth		
Yes	128	65.3 %
No	68	34.7 %

Table No.3: Multiple Regressions for association

Term	Coef	SE Coef	P-value
Constant	3.25	3.90	0.019
Hb	-0.1693	0.113	0.130
Serum Ferritin	0.1732	0.0636	0.005
Time of Delivery	-0.0769	0.0669	0.250
BMI	-0.0608	0.0934	0.514
Parity	0.030	0.115	0.791
Gravidity	0.282	0.138	0.035
Occupation	0.361	0.368	0.322

Table No.4: Odds Ratios for Continuous Predictors

	Odds Ratio	95% CI
Hb	0.8443	(0.6770, 1.0528)
Serum Ferritin	1.1891	(1.0497, 1.3470)
Time of Delivery	0.9260	(0.8122, 1.0557)
BMI	0.9410	(0.7835, 1.1301)
Parity	1.0308	(0.8231, 1.2909)
Gravidity	1.3261	(1.0127, 1.7365)

Pairs	Number	Percent
Concordant	5843	67.1
Discordant	2813	32.3
P-value of Goodman-Kruskal Gamma		0.35

DISCUSSION

Erratic results of multiple studies done to find out the correlation between maternal anemia and preterm birth could be explained by analyzing anemia as an adverse and cumulative exposure. Like any other adverse agent, resulting adverse effect response could vary with the

time of exposure and also extent of exposure. This explanation paves the way for the certain possibility of different correlation of anemia to the outcome of pregnancy and preterm birth depending upon the time of gestation at the time of anemia i.e showing strong co-relation at early gestation compared to late gestational age. Also, Heterogeneous subtypes of preterm birth are not usually observed and considered in each study done on preterm labour,⁹ leading to difficulty in finding out any co-relation among etiologically distinct endpoints¹⁰. Even in previous Chinese studies, only minute level of attention has been paid to study anemia as a risk factor for preterm birth clinical subtypes¹¹. Only spontaneous preterm births are usually focused in most studies. In our study, meticulous study design was used to overpower these limitations and to explore any existing relation between physiological haemo-dilution and preterm birth.

In our study, early trimester anemia was related to moderately increased risk of preterm birth. This association could not be attributed to any random happening. Though mainly restricted to spontaneous preterm labour, anemia in third trimester gestation was related to decrease incidences of preterm birth in all of its subtypes. There is no relation between anemia and medically indicated preterm birth. Our findings make a valid point by addressing the effect of exposure window of anemia and different risk profile for various different preterm birth subtypes.

Results of our study coincide with a meta-analysis showing increased risk of preterm birth in patient who develop anemia in early gestation. It also shows that there is an inverse relation between anemia developing at late gestation to preterm birth. Preterm birth clinical subtypes were neglected in all four Chinese studies emphasizing only on association and relation of anemia with preterm births giving suprious and confused results¹¹. Some researchers reported association of high risk of preterm birth to anemia in the early trimester, while others show no relation among them¹². Only severe anemia (Hb<7 g/dl) in the third trimester was related to a slightly high risk for preterm birth in last study observation.¹³ Antecedently, Associations between maternal anemia and preterm birth clinical subtypes was only reported by five studies¹³. Dichotomized of pregnant women into two groups of anemic or non-anemic was done in most studies using single cut-off point, remaining categorized them with several cut-off points using different values of Hb.¹³ Reliability of spline analysis is more than continuous exposure data.¹⁴ In our study, non-linear effects were taken in to account by flexible spine transformation using Hb concentrations as a continuous variable. Association of anemia varies with every subtype of preterm birth, showing the divergent nature of this relation. Increase risk of spontaneous preterm labour was seen to be related with early gestation anemia and

also with anemia present throughout the gestation in contrast to reduced risk of preterm labour with mid or late pregnancy anemia. Iron deficiency leads to anemia emergence in the form of pre-existing or early onset anemia which could prevail just the early period of pregnancy or throughout the pregnancy. Hypoxia, aerophilous stress, maternal infection and triggering of the spontaneous onset of preterm labour are the potential consequences of iron deficiency anemia.

Physiological haemo-dilution during pregnancy on reaching its rock bottom (lowest value) might be able to hide the true association between anemia and preterm birth, was the cause of apprehension for researchers of previous studies¹⁵. Till now, no study is done to find out the association between physiological anemia occurring secondary to haemodilution and preterm birth. We used 1st trimester hemoglobin level as the baseline and Hb reduction across trimesters to mimic haemo-dilution in our study. Our study shows that haemo-dilution was related with reduced risk for preterm birth. That fact my friend might be the justification for the reciprocal relationship of the late trimester anemia and preterm birth.

Chinese cohort had a fairly low (4.7%) overall preterm birth rate with the main contribution from its spontaneous preterm labour (77%) subtype. Consistency of this rate is observed in various cohort done in this region. However, the obstetrical interventions rate at preterm and term gestations was 11.6 and 16.7% in our study. Most industrialised societies have much higher rate of intervention than our population due to impending fetal compromise.¹ Probably, these inconsistencies in threshold for intervention in practice of both culture could have played a significant role in our study findings. In our setting, we used 1st day of last menstrual period to calculate the gestational age. So, patient ability to remember her last menstrual date and other errors associated with menstrual geological dating might have altered a little bit of our clinical findings. The association of preterm birth and anemia in 1st trimester was likely related to iron deficiency, with little or no effect of iron supplementation because iron supplements were prescribed after the diagnosis of anemia. Nevertheless, women in their late gestation were more susceptible to take iron supplement as treatment advice and a lot of medical attention for anemia. The reciprocal association between late gestation anemia and spontaneous preterm labour, in addition to the effects of conventional physiological haemo-dilution,¹⁶ might be representing an artifact because of advantageous medical interventions. The effect of prevention, early diagnosis and prompt treatment of maternal anemia on trimming the rates of spontaneous preterm labour and preterm promenade needs further investigation and research.

CONCLUSION

Maternal anemia in pregnancy is in strong relation with increased risk of preterm labour in contrast to adequate physiological haemo-dilution during pregnancy which is associated with reduced risk of preterm birth. Prevention, early diagnosis and aggressive treatment of maternal anemia may be a broadway for intervention, and a topic worthy of further investigation.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bulletin of the World Health Organization* 2010;88(1):31-8.
2. Ebrahim SH, Kulkarni R, Parker C, Atrash HK. Blood Disorders Among Women: Implications for Preconception Care. *Am J Preventive Med* 2010;38(4S):S459-67.
3. Lee AI, Okam MM. Anemia in pregnancy. *Hematol Oncol Clin North Am* 2011;25(2):241-59.
4. Voskaridou E, Balassopoulou A, Boutou E. Pregnancy in beta-thalassemia intermedia: 20-year experience of a Greek thalassemia center. *Eur J Haematol* 2014 ;93(6):492-9.
5. Janz TG, Johnson RL, Rubenstein SD. Anemia in the emergency department: evaluation and treatment. *Emerg Med Practice* 2014;15(11):1-15.
6. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, et al. Lancet Nutrition Interventions Review, Group; Maternal and Child Nutrition Study. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *Eur J Haematol* 2013;382(9890):452-77.
7. Qaseem A, Humphrey LL, Fitterman N, Starkey M, Shekelle P. Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. *Annals Int Med* 2013;159(11):770-9.
8. Thereso O. Anemia vs iron deficiency increased risk of preterm delivery in a prospective study. *Am J Clin Nutr* 1992;55:985-8.
9. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. *J Matern Fetal Neonatal Med* 2006;19:773-82.
10. Savitz DA, Blackmore CA, Thorp JM. Epidemiologic characteristics of preterm delivery: aetiologic heterogeneity. *Am J Obstet Gynecol* 1991;164:467-71.
11. Wang J, Ren A, Ye R, Zheng J, Li S, Liu J, et al. Study on the third trimester hemoglobin concentrations and the risk of low birth weight and preterm delivery. *Zhonghua Liu Xing Bing XueZaZhi* 2007;18:15-18.
12. Zhou L, Yang W, Hu J, Deng C, Tao X, Stoltzfus R. Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China. *Am J Epidemiol* 1998; 48:992-1006.
13. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol* 1996;87:163-68.
14. Adams MM, Sarno AP, Harlass FE, Rawlings JS, Read JA. Risk-factors for preterm delivery in a healthy cohort. *Epidemiology* 1995;6:525-32.
15. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. *Am J Clin Nutr* 2005;81:S1218-22.
16. Xiong X, Buekens P, Fraser WD, Guo Z. Anemia during pregnancy in a Chinese population. *Int J Gynecol Obstet* 2003;83:159-64.

The Effect of Aspirin on Mortality in Tuberculous Meningitis

Muhammad Amin¹, Malik Muhammad Naeem¹ and Arif Raza²

ABSTRACT

Objective: To evaluate the effect of aspirin on mortality occurring within 2 months of starting treatment in tuberculous meningitis (TBM) stage III patients in patients 1-15 years of age.

Study design: A randomized open label placebo controlled trial

Place and Duration of study: The study was conducted at Pediatric unit II B.V.H. from March 2015 to September 2015.

Materials and Methods: A total of 162 patients of 1-15 years of age with TBM stage III were included in the study. Patients were divided in Group A (Aspirin group having 81 patients) and Group B (Placebo group having 81 patients). Outcome was noted in terms of mortality in both groups. All patients were treated with 4 antitubercular drug RHZE regimen (rifampicin 15mg/kg, isoniazid 10mg/kg, pyrazinamide 25mg/kg and ethambutol 15mg/kg) per oral daily for 2 months followed by RH (rifampicin 15mg/kg, isoniazid 10mg/kg) for 10 months along with corticosteroid (prednisolone 1-2mg/kg) per oral daily for 4 weeks and tapered in next 4 weeks. Oral aspirin was given to only group A patient at 60mg/kg per day divided 12 hourly starting with the first dose of antitubercular therapy.

Results: Out of a total of 162 children, there were 79 (48.8%) male and 83 (51.2%) female. Majority of the children, 106 (65.4%) were from 6 to 10 years of age. Miliary TB was found in 31 (19.1%) children. Presence of severe wasting was found amongst 40 (24.7%). Overall mortality was noted in 43 (26.5%) children. When both groups were divided, all the variable were found not to be statistically significant (p value > 0.05).

Conclusion: In children with TBM stage III, aspirin resulted in reduction in mortality but did not achieve statistically significance

Key Words: Aspirin, Mortality, Tuberculous Meningitis

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INTRODUCTION

Tuberculosis (TB) is a global health issue. One third of the world population is infected with *Mycobacterium tuberculosis*; each year 9 million people develop disease and about 95% of the world's cases of TB occur in South East Asia, sub-Saharan Africa and Western Pacific. TB is the second leading killer after human immunodeficiency virus with annually about 2 million deaths; 10% of whom are younger than 15 years old. About 98% of those deaths occur in the developing countries of Asia and Africa¹. In Pakistan approximately 5.7 million people suffer from TB, with 260,000 new cases occurring every year². The exact population of children with TB in Pakistan is unknown³. Tuberculous meningitis (TBM) is the most severe manifestation of tuberculosis in term of high mortality and morbidity⁴.

Pathological manifestations of TBM are exudates, tuberculoma, hydrocephalus and stroke. Cerebrovascular complications of TBM that typically occur as multiple or bilateral lesions in the territories of middle cerebral artery perforating vessels are termed as tuberculous vasculopathy⁵. Vessel pathology appears to be a consequence of its immersion in the local inflammatory exudates leading to luminal thrombosis. There is some evidence that vasospasm may mediate stroke early in the course of disease and proliferative intimal disease in later strokes.

The worst outcome of TBM is mainly due to the delay in diagnosis and mostly patient present at stage III⁶. Corticosteroids with antitubercular therapy were thought to reduce mortality and morbidity but their role in reducing strokes has not been proven. Aspirin also reduces mortality and its role in reducing stroke in TBM needs further studies⁷. One study is available with aspirin that showed reduction in stroke 24.2% compared to placebo group 43.3% and mortality 21.7% compared to placebo group 43.3%⁸.

I wanted to the role of aspirin in reducing mortality in TBM in children as the available study includes both children and adults as no study was conducted previously on aspirin in Pakistan. TBM is not uncommon in Pakistan so we should try to search new drugs to improve the outcome.

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MATERIALS AND METHODS

This was a randomized controlled study, conducted in Pediatric unit II B.V.H. Bahawalpur from March 2015 to September 2015. Non probability consecutive sampling technique was used. All the patients of 1-15 years of age with TBM stage III were included. These criterias were confirmed by history, examination and investigations (Complete blood count (CBC) with platelets count, Prothrombin time (PT), Activated partial thromboplastin time (APTT), Bleeding time (BT), Liver function test (LFT's), renal function test (RFT's) and CT brain). Patients were excluded from the study who were on antitubercular treatment (by history), had bleeding diathesis (by history, examination and with platelets count, PT, APTT and BT), aspirin allergy (by history), liver disease (by history, examination and LFT's), kidney failure (by history, examination and RFT's) or subarachnoid hemorrhage (by examination and CT brain). The study was approved by the Institutional Ethical Committee. Children with TBM admitting in the ward through accident and emergency fulfilling the inclusion criteria were selected. Informed consent was taken from the parents / guardian. Randomization was done by lottery method into group A (aspirin) and B (placebo). Demographic data as well as brief history and examination was documented on Performa (annex A). All patients were treated with 4 antitubercular drug RHZE regimen (rifampicin 15mg/kg, isoniazid 10mg/kg, pyrazinamide 25mg/kg and ethambutol 15mg/kg) per oral daily for 2 months followed by 1H (rifampicin 15mg/kg, isoniazid 10mg/kg) for 10 months along with corticosteroid (prednisolone 1-2mg/kg) per oral daily for 4 weeks and tapered in next 4 weeks. Oral aspirin was given to only group A patient at 80mg/kg per day divided 12 hourly starting with the first dose of antitubercular therapy. All the data was entered on a pre-designed Performa (annex A) for each patient. The collected data was analyzed by SPSS version 10. Mean and standard deviation were calculated for quantitative variables like age. Frequency and percentage were calculated for qualitative variables like outcome (mortality). Effect modifiers were controlled by stratification of age (1-5years, 6-10 years, and 11-15 years) sex, associated miliary tuberculosis (defined as millet like 1-5mm seeding of TB bacilli in the lung, as evident on chest x-ray), and patient with severe wasting (defined as a weight-for-length less than minus three SD). Chi square test was applied to compare the quantitative data (sex, mortality, presence of miliary TB, presence of severe wasting) and p value ≤ 0.05 were taken as statistically significant.

RESULTS

Out of a total of 162 children, there were 79 (48.8%) male and 83 (51.2%) female. Mean age was 7.3 years

with standard deviation of 3.07 years. Majority of the children, 106 (65.4%) were from 6 to 10 years of age while 37 (22.8%) 1 to 5 years and 19 (11.7%) 11 to 15 years of age. Miliary TB was found in 31 (19.1%) children. Presence of severe wasting was found amongst 40 (24.7%). Overall mortality was noted in 43 (26.5%) children. (Figure No.1)

When both groups were divided, there were 18 (22.2%) children from 1 to 5 years in Group A whereas 19 (23.6%) in Group B, 53 (65.4%) from 6 to 10 years in Group A and same in Group B, while 10 (12.3%) from 11 to 15 years and 9 (11.1%) in Group B. After applying chi square, no statistical significance (p value = 0.961) was found between the both groups (Table No.1)

There were 37 (45.7%) male in Group A and 42 (51.9%) in Group B whereas 44 (54.3%) female in Group A and 39 (48.1%) in Group B. No statistical significance (p value = 0.432) was found between both the groups. (Table No.2)

Table No.1: Comparison of age between both the groups

Age (Years)	Groups		Total	P value
	A	B		
1-5	18 (22.2%)	19 (23.6%)	37 (22.8%)	0.961
6-10	53 (65.4%)	53 (65.4%)	106 (36.6%)	
11-15	10 (12.3%)	9 (11.1%)	19 (11.7%)	
Total	81 (50%)	81 (50%)	162 (100%)	

Table No.2: Distribution of Gender between both the groups

Gender	Groups		Total	P value
	A	B		
Male	37 (45.7%)	42 (51.9%)	79 (48.8%)	0.432
Female	44 (54.3%)	39 (48.1%)	83 (51.2%)	
Total	81	81	162	

Table No.3: Comparison of miliary TB, presence of severe wasting and mortality between both the groups

	Group A	Group B	P value
Miliary TB	17 (21.0%)	14 (17.3%)	0.549
Presence of Severe Wasting	18 (22.2%)	22 (27.2%)	0.466
Mortality	18 (22.2%)	25 (30.9%)	0.213

As far as presence of miliary TB between the both groups is concerned, it was found 17 (21.0%) in Group A and 14 (17.3%) in Group B with an insignificant p value of 0.549. (Table No.3)

Presence of severe wasting was found in 18 (22.2%) children in Group A and 22 (27.2%) in Group B with an insignificant p value of 0.466. (Table No.3)

There were 18 (22.2%) children who died in Group while 25 (30.9%) in Group B. No statistical significance for mortality between the both groups was found as p value turned out to be 0.213. (Table No.3)

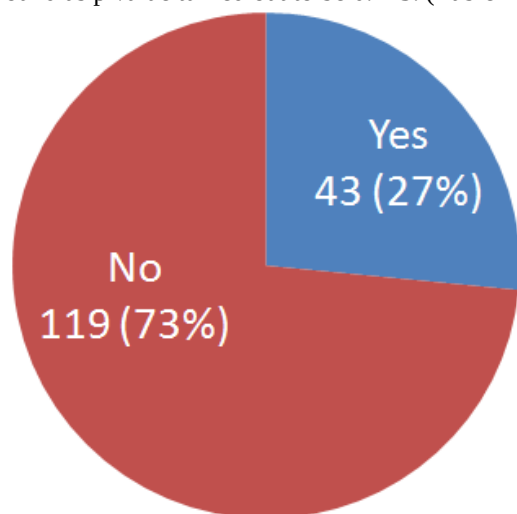


Figure No.1: Overall Mortality

DISCUSSION

The recommended first-line treatment agents for all forms of CNS tuberculosis are Isoniazid, Rifampicin, Pyrazinamide and Ethambutol taken daily either individually or in combination form.¹⁰ Patients are usually treated for a minimum of 10 months. Therapy is extended to at least 12 months in those who fail to respond, or if treatment interruptions have occurred for any reason. Isoniazid penetrates the CSF freely and has potent early bactericidal activity. At standard doses isoniazid achieves CSF levels 10-15 times the minimum inhibitory concentration of *M. tuberculosis*.^{11,12}

In current study, miliary TB was found in 17 (21.0%) children in Group A and 14 (17.3%) in Group B. Miliary TB could be an indicator for TBM in the countries with high prevalence of TB.¹³ Concomitant miliary tuberculosis should bring TBM to mind in cases with an unknown origin. Female predominance, longer symptom duration, higher protein level in CSF may be remarkable in patients with TBM accompanied with miliary TB.^{14,15}

Not many studies have evaluated the impact of aspirin on outcome of patients with TBM. In the present study, mortality was reduced in children who received aspirin (22.2%) as compared to those who were given placebo (30.9%). Although, there was reduction in terms of mortality in children who used aspirin but these results were not statistically significant (p value = 0.213).

Two recent studies have examined the possible benefits of aspirin in TBM treatment. The first study was a randomized controlled trial of aspirin versus placebo in 118 Indian adults.⁸ Aspirin was associated with a non-significant reduction in stroke at 3 months, and a significant reduction in mortality (21.7 versus 43.4%, $P = 0.02$). The effects of aspirin are difficult to interpret, however, as prednisolone was also given to some patients such as those with severe disease at baseline, or those whose clinical condition worsened during treatment. The second study was a randomized controlled trial with three parallel arms (low- and high-dose aspirin and placebo) in South African children.^{16,17} Aspirin had no impact on morbidity (hemiparesis and developmental outcome) or mortality. Aspirin was well tolerated, but one death occurred and was probably related to aspirin. Outcomes in the high-dose aspirin group compared favourably with the other treatment groups despite younger age and more severe neurological involvement.¹⁸ Aspirin has also been found to be associated with 19.1% absolute risk reduction in ischemic stroke and 22% absolute risk reduction in mortality of TBM.⁸ The observed reduction in the frequency of stroke may be due to antiplatelet and antithrombotic effects of aspirin.^{19,20}

CONCLUSION

In children with TBM stage III, aspirin resulted in reduction in mortality but did not achieve statistically significance. Further studies with large sample size could ensure better understanding and outcome for the role of aspirin in children with TBM.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. World Health organization. Global tuberculosis report 2014. Geneva: World Health organization; 2014.
2. Codlin AJ, Khowaja S, Chen Z, Rahbar MH, Qadeer E, Ara I, et al. Short report: Gender differences in tuberculosis notification in Pakistan. *Am J Trop Med Hyg* 2011;85(3):514-7.
3. Pakistan Paediatric Association. Guidelines for diagnosis and management of tuberculosis in children. 1st ed. Lahore: Pakistan Paediatric Association; 2006.
4. Chiang SS, Khan FA, Milstein MB, Tolman AW, Benedetti A, Starke JR, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; 14(10):947-57.
5. Kalita J, Nair PP, Misra UK. Predictors of stroke and its significance in the outcome of tuberculous meningitis. *J Stroke Cerebrovasc Dis* 2009;18(4): 251-8.

6. Iype T, Chacko S, Raghavan S, Mathew R, Mohan M. Preliminary report of directly observed treatment, short course in tuberculous meningitis. *Ann Indian Acad Neurol* 2010;13(1):57-60
7. Misra UK, Kalita J, Maurya PK. Stroke in tuberculous meningitis. *J Neurol Sci* 2011;303(1-2):22-30.
8. Misra UK, Kalita J, Nair PP. Role of aspirin in tuberculous meningitis: a randomized open label placebo controlled trial. *J Neurol Sci* 2010;293(1-2).
9. Starke JR, Tuberculosis. In: Jensen HB, Baltimore RS, editors. *Pediatric infectious diseases: principles and practices*. Philadelphia: WB Saunders; 2002.p. 396-419.
10. Rieder HL, Snider DE, Cauthen GM. Extrapulmonary tuberculosis in the United States. *Am Rev Respir Dis* 1990;141:347-351.
11. Kaojarearn S, Supmonchai K, Phuapradit P, Mokkhavesa C, Krittiyanunt S. Effect of steroids on cerebrospinal fluid penetration of antituberculous drugs in tuberculous meningitis. *Clin Pharmacol Ther* 1991;49:6-12.
12. Starke JR. Pediatric tuberculosis: time for a new approach. *Tuberculosis (Edinb)* 2003;83:208-12.
13. Donald PR, Schaaf HS, Schoeman JF. Tuberculous meningitis and miliary tuberculosis: the Rich focus revisited. *J Infect* 2005;50:193-5.
14. Donald PR, Schaaf HS, Schoeman JF. Tuberculous meningitis and miliary tuberculosis: the Rich focus revisited. *J Infect* 2005;50:193- 5.
15. Marais BJ, Gie RP, Schaaf HS, Hesselning AC, Enarson DA, Beyers N. The spectrum of childhood tuberculosis in a highly endemic area. *Int J Tuberc Lung Dis* 2006;10:732-8.
16. Schoeman JF, Janse van Rensburg A, Laubscher JA, Springer P. The role of aspirin in childhood tuberculous meningitis. *J Child Neurol* 2011;26: 956-62.
17. Starke JR. Pediatric tuberculosis: time for a new approach. *Tuberculosis (Edinb)* 2003;83:208-12.
18. Yaramis A, Gurkan F, Elevli M, Soker M, Haspolat K, Kirbas G, et al. Central nervous system tuberculosis in children: a review of 214 cases. *Pediatrics* 1998;102:E49.
19. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986. *Int J Tuberc Lung Dis* 1999;3: S231-79.
20. World Health Organization. *Treatment of tuberculosis, guidelines for national programmes*. Geneva: World Health Organization; 2003. WHO/CDS/TB/2003.313.

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Frequency of Nail Clubbing in Patients with Various Presentation of Tuberculosis

Kanwal Abbas Bhatti¹, Soniha Aslam² and Kuldeep Kumar³

ABSTRACT

Objective: This study is designed to evaluate the frequency of TB patients presenting with digital clubbing because of different complications of TB.

Study Design: Observational study.

Place and Duration of Study: This study was conducted in the Institute of Chest diseases at Kotri, Sindh Pakistan from January 2016 to December 2016.

Materials and Methods: A total of 50 patients admitted through the outpatient department, presenting with the different complications of tuberculosis, treated and untreated both were included in the study. Patients with comorbidities like cardiovascular and diabetes were excluded. After consent detailed history was taken and complete physical examination was performed with necessary laboratory investigations and also radiological findings conformed by senior consultants. Demographic data, radiological findings and clubbing were tabulated and analyzed

Results: During study period 50 patients were enrolled in study out of which 42 (84%) males and females 08(12%) between age group 15-30 years 15(30%), 31-45 years 11(22%) and in age group of 46-60 include 24(48%). Most of the patients 35(70%) belong to rural areas while 15(30%) from urban areas. In 22(44%) patient there was family history of TB while 28(56%) had not any history of TB. Smoking habits was observed in 34(68%) while 16(32%) never smoked. Majority of patients belonged to lower economic class 43(86%), while 07(14%) belongs to middle class also.

Conclusion: The global TB community cannot afford to continue ignoring this facet of TB care and control and needs to act with urgency to address what is likely to be a huge public health burden.

Key Words: Nail Clubbing, Patients, Tuberculosis

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INTRODUCTION

Tuberculosis (TB) constitutes a major public health challenge due to worsening of the health services in developing countries like our, prompt measures with increased investment in intervention strategies may prevent this situation from worsen in future. Epidemiological data available for Pakistan is not up to mark. In Pakistan around 43,000 people diagnosed with TB with estimated death rate about 70,000 deaths every year. Based on Burden of Disease estimates, TB represents 5% of the total DALYs (disability adjusted life years) which indicates that the burden of tuberculosis in Pakistan is substantially higher than the world. Different taboos regarding tuberculosis, malpractice, poor compliance of patients due to illiteracy and unawareness, failure of DOT (direct

observation therapy), MDR (multiple drug resistance) which is major issue both in effectiveness and cost wise.

Despite of several awareness programs through several Medias still patients in our set up instead of being presenting during early onset due to ethical, economical, myths and so many hindrances make them unable to seek medical advice. By the passage of time under similar circumstance of risk factors patients not only develops complications but they also be carriers to the others. Various complications usually reflected in radiography and by digital clubbing.

Digital clubbing is one of the oldest known sign in clinical practices dates back to Hippocrates. Clubbing is defined as focal bulbous enlargement of the terminal phalanx of the fingers and/or toes due to proliferation of connective tissue in both anteroposterior and lateral diameter of the nails. In most instances it is asymptomatic/ idiopathic, but it may be best predictors of some life threatening morbidities like lung cancer, idiopathic pulmonary fibrosis.^{1,2}

Clubbing is associated with various clinical conditions, most commonly associated with lung disease like neoplastic lung disease; non-neoplastic lung diseases include bronchiectasis, lung abscess, interstitial lung disease, fibrosis and empyema. Other causes include cyanotic heart diseases, infective endocarditis,

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inflammatory bowel disease, coeliac disease and primary biliary cirrhosis. Pathophysiology suggestive of clubbing is hyper vascularization at distal phalanx. In pulmonary circulation platelet precursors fail to become fragmented into platelets and easily trapped in the peripheral vasculature, releasing platelet-derived growth factor and vascular endothelial growth factor which promote vascularity leading to clubbing.^{3,4}

Clubbing may be present in one of five stages/grades

1. **No visible clubbing.** Fluctuation and softening of the nail bed only. No visible changes of nails.
2. **Mild clubbing.** Loss of the normal $<165^\circ$ angle (Lovibond angle) between the nail bed and the nail fold. Schamorth's window is obliterated. Clubbing is not obvious at a glance.
3. **Moderate clubbing.** Increased convexity of the nail fold. Clubbing is apparent at a glance.
4. **Gross clubbing.** Thickening of the whole distal phalanx (resembling a drumstick)
5. **Hypertrophicosteoarthropathy.** Shiny aspect and striation of the nail and skin with longitudinal striations.⁵

Assessment of nail clubbing: Clubbing can be assessed by physical examination with some uncertainty in mild cases with different signs. Digital cameras and computerized analysis in modern setup is utilized with more accuracy.⁶

Different signs of clubbing:

Profile sign or Lovibond's angle: It is defined by the angle made by nail as it exists from the proximal nail fold. In normal subjects, profile angle is usually less than 180° angle more than 180° is suggestive of clubbing.

Hyponychial angle: It is measured by drawing a line from distal digital crease to the cuticle and another line from the cuticle to hyponychium which is the thickened stratum corneum of epidermis lying under the free edge of the nail. Normal hyponychial angle is less than 192° . As hyponychial angle is independent of age, sex, height, and weight of the patient so mostly acceptable criteria.^{7,8}

Phalangeal depth ratio: It is the ratio of digit's depth measured at the junction between skin and nail bed at distal interphalangeal joint usually measured at the index finger. Normally the depth at distal interphalangeal joint is more than the depth at nail bed. In clubbing fingers, connective tissue deposition expands the pulp in the terminal phalanx and the ratio becomes reversed. This ratio is also independent of age, sex, and ethnicity of population. A Phalangeal depth ratio of over 1 is indicative of clubbing. It can be measured by a caliper or a digital photograph. While performing this measurement with calipers; it should be ensured that the calipers must not compress the tissues during measurement.⁹

Digital index: It is the sum of NB: DIP ratio of circumference at nail bed with circumference at distal

interphalangeal joint for all 10 fingers. A digital index of 10.2 or higher is indicative of clubbing. Digital index is more specific for clubbing.

Schamroth sign: This sign is elicited by placing the dorsal surfaces of terminal phalanges of corresponding right and left fingers together. Normal fingers create a diamond-shaped window when the dorsal surfaces of terminal phalanges of similar fingers are opposed to each other. In patients with clubbing this diamond-shaped window gets obliterated.^{10, 11, 12}

This study is designed to evaluate the frequency of TB patients presenting with digital clubbing because of different complications of TB.

MATERIALS AND METHODS

This observational study was conducted in the Institute of Chest diseases at Kotri, Sindh Pakistan from January 2016 to December 2016. Patients presenting with the different complications of tuberculosis, treated and untreated both were included in the study. Patients with comorbidities like cardiovascular and diabetes were excluded. A total of 50 patients admitted through the outpatient department. After consent detailed history was taken and complete physical examination was performed with necessary laboratory investigations and also radiological findings conformed by senior consultants. Demographic data, radiological findings and clubbing were tabulated and analyzed.

In our setup diagnosis of clubbing was made by clinical signs. Clubbing was evaluated by profile angle (PA), hyponychial angle (HA) of index fingers and the ratio of distal phalangeal depth to interphalangeal depth (DPD/IPD) of index fingers and was graded accordingly.¹³

RESULTS

During study period 50 patients were enrolled in study out of which 42 (84%) males and females 08(12%) between age group 15-30 years 15(30%), 31-45 years 11(22%) and in age group of 46-60 include 24(48%). Most of the patients 35(70%) belong to rural areas while 15(30%) from urban areas. In 22(44%) patient there was family history of TB while 28(56%) had not any history of TB. Smoking habits was observed in 34(68%) while 16(32%) never smoked. Majority of patients belonged to lower economic class 43(86%) while 07(14%) belongs to middle class also. Regarding weight of patients 48(96%) had weight more 45 Kg and 02(06%) had weigh less than 45 Kg shown in table 1.

Radiological findings of all TB were confirmed by senior consultants. Unilateral lung involvement in 12 (24%) males and 02 (04%) females while bilateral lung in males 38 (76%) and 02 (04%) females. Upper lung field involved in 42(84%) males and in 02 (24%) females. Middle lung field in 42(84%) and lower lung field in 34(68%) no females had middle or lower lung field involvement. Consolidation seen in 18 (36%)

males and 01 (02%) female. Bronchiectasis found in 14(28%) males and 02(24%) females. Cavitation observed in 30 (60%) males while no female show cavitory lesion on x-ray chest. Pleural effusion seen in 17 (34%) males and pneumothorax 02(04%) males, no female shows these both changes. Fibrosis was obvious in 22 (44%) males and 04 (24%) females and empyema in 03 (06%) males only shown in table 2.

Table No.1: Demographics of TB patients n=50

Age in years	15-30	31-45	46-60
	15(30%)	24(48%)	11(22%)
Gender	Male	Females	
	42(84%)	08(10%)	
Residence	Rural	Urban	
	35(70%)	15(30%)	
Family history of TB	Yes	No	
	22(44%)	28(56%)	
Smoking Habit	Yes	No	
	34(68%)	16(32%)	
Socioeconomic status	Upper	Middle	Lower
	00	07(14%)	43(86%)
Body Weight	>45 Kg	<45 Kg	
	38(76%)	12(24%)	

Table No.2: Radiographic Findings

X- ray pattern	Number	%	Number	%
	Males		Females	
Unilateral lung field	12	(24%)	02	(04%)
Bilateral lung fields	38	(76%)	02	(04%)
Upper lung field	42	(84%)	02	(2%)
Middle lung field	42	(84%)		
Lower lung field	34	(68%)		
Consolidation	18	(36%)	01	(02%)
Bronchiectasis	14	(28%)	02	(24%)
Cavitation	30	(60%)		
Pleural effusion	17	(34%)		
Pneumothorax	02	(04%)		
Fibrosis	22	(44%)	04	(24%)
Empyema	03	(06%)	00	(00%)

Table No.3: Digital clubbing

Nail Clubbing	Bronchiectasis 34.2%		Fibrosis 52.6%		Empyema 7.8%	
	Male	Female	Male	Female	Male	Female
Grade 1	00	00	00	00	00	00
Grade 2	00	00	00	00	00	00
Grade 3	06	01	09	01	02	00
Grade 4	04	02	08	02	01	00
Grade 5	00	00	00	00	00	00

Table 3 is showing clubbing associated with various complication of TB. Out of 50 patients 38 (76%) shows clubbing, in bronchiectasis 34.2%, 52.6% in fibrosis and 7.8% in Empyema. In Bronchiectasis total 13 cases with 06 males in grade 3 and 04 in grade 4 and females 01 in grade 3 while 02 in grade 4. In Fibrosis total 20 cases with 09 males in grade 3 and 08 in grade 4 and females 01 in grade 3 while 02 in grade 4. In empyema total 03 cases with 02 males in grade 3 and 01 in grade 4 while no female shows clubbing

DISCUSSION

TB in its various forms remains a killer disease in our part of the world which is probably due to hygienic practices and late diagnosis leading to spread of disease, development of complication may bring patients to visit the physician for the first time. Different complication of tuberculosis found associated with digital clubbing as common and significant clinical manifestation needs proper investigations for evaluation of underlying pathology.

As compared to a developed country, where TB is common among elderly, it is a disease of young in a developing country. Seventy five percent (75%) of tuberculosis cases occur in age group of 15–59 years, the most economically productive sector of society. It was true in this study, as 30% in 15-30 years age group, 48% of patients were in the age group of 31-45 years and 11% of patients were in the age group of 46-60 years.^{12, 15}

Of the 50 patients 08 patients (16%) were females and 42 patients (84%) were males which is unrelated with studies conducted by Akhtar T and Ahmed M who found the ratio of females more than males that is 57% females and 43% males, this difference may be due to change in sample size or study duration.^{16, 17}

In this study majority of patient 70% belongs to rural areas deprived of necessary facilities of healthy living like clean drinking water and sanitation, 68% were smokers and 86% belongs to lower socio economic class, these findings are more or less similar with the study of Jagdeesh and Metha who found more than half 39 (65.0%) were having rural background, (33.3%) smokers and 60% patient belong to lower socioeconomic status. Weight loss was the presenting symptom in 53.84% of patients while in this study 24% patients had weight less than 45 Kg.^{15, 18}

Pulmonary TB is associated with various long term lung complications like fibrosis, bronchiectasis, pleural effusion, and empyema. This study reveals unilateral lung involvement in (28%) while bilateral lung in(80%)while study conducted by M. Khattak shows unilateral upper lung field 46%, bilateral upper lung fields 22%. Upper lung field involved in 42(84%) males and in 02 (24%) females. Middle lung field in 42(84%) and lower lung field in 34(68%) no females had middle or lower lung field involvement. Lower lung field 7%, cavitation in 25% observed by Khattak Consolidation seen in 18 (36%) males and 01 (02%) female. Bronchiectasis found in 52% while cavitation

observed in 60% on x-ray chest. Pleural effusion seen in 34% and pneumothorax 04% shows these both changes. Fibrosis was obvious in 68% and empyema in 06%. And study conducted by Jeremiah and Bruce shows emphysematous change in (36%), bronchiectasis (40%), bronchovascular distortion (56%) cases, more or less similar findings were observed in this study with some differences in sample size and setup.^{15,19, 20}

Out of 50 patients 38 (76%) shows clubbing, in bronchiectasis 34.2%, 52.6% in fibrosis and 7.8% in Empyema. In Bronchiectasis total 13 cases with 06 males in grade 3 and 04 in grade 4 and females 01 in grade 3 while 02 in grade 4. In Fibrosis total 20 cases with 09 males in grade 3 and 08 in grade 4 and females 01 in grade 3 while 02 in grade 4. In empyema total 03 cases with 02 males in grade 3 and 01 in grade 4 while no female shows clubbing.

Nicotra and Barker found the frequency of digital clubbing (28.3%), while studies from endemic areas of TB have shown a 30% frequency of clubbing amongst smear-positive TB patients even much higher frequency of digital clubbing (82%) is found in study conducted in India like this in which 76% cases present with clubbing justifying the patients from endemic areas presenting associations of clubbing with severity of disease.^{21, 22, 23}

CONCLUSION

Exploring mechanisms to address the long term complications that follow treatment of pulmonary TB is long overdue and will significantly contribute to the quality of care for TB patients. In many PTB patients successful completion of TB treatment or bacteriological cure is not the end of the need for care. Systematic generation of data is needed to develop approaches for the pre-vention, care and treatment of patients with post TB chronic lung disease. The global TB community cannot afford to continue ignoring this facet of TB care and control and needs to act with urgency to address what is likely to be a huge public health burden

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

- Hippocrates. Hippocrates. 1st ed. London: Loeb Classical Library, No. 148, William Heinemann ltd; 1923. Prognostic;p.7–55. Available from: <http://www.archive.org/details/hippocrates02hippuoft>.
- Dickinson CJ. Lung diseases associated with digital clubbing. *Clin Exp Rheumatol* 1992; 10 (Suppl 7):23-5.
- McKinney J, Jacobs W, Bloom B. Persisting problems in tuberculosis. In: *Emerging Infections*, NY Academic press;1998.p. 51-146.
- Khan KS. Setting health care priorities in Pakistan, *J Pak Med Assoc* 1995;45: 222-27.
- Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? *JAMA* 2001;286:341–7
- Spicknall KE, Zirwas MJ, English JC 3rd. Clubbing: an update on diagnosis, differential diagnosis, pathophysiology, and clinical relevance. *J Am Acad Dermatol* 2005;52(6):1020-8.
- Sarkar M, Mahesh DM, Madabhavi I. Digital clubbing. *Lung India: Official Organ of Indian Chest Society* 2012;29(4):354-362.
- Altman RD, Tenenbaum J. Hypertrophic osteoarthropathy. In: Kelly WN, Harris ED, Ruddy S, editors. *Textbook of Rheumatology*. 5th ed. Philadelphia: WB Saunders Company; 1997.p. 1514–20.
- Hanssen-flaschen J, Nordberg J. Clubbing and hypertrophic osteoarthropathy. *Clin Chest Med* 1987;8:287–98.
- Lovibond JL. Diagnosis of clubbed fingers. *Lancet* 1938;1:363-4.
- Regan GM, Tagg B, Thomson ML. Subjective assessment and objective measurement of finger clubbing. *Lancet* 1977; 1(7489):530-2.
- Khanna BK, Khare KS. Clubbing in pulmonary tuberculosis. *Ind J Tub* 1986; 33:11.
- Vazquez-Abad D, Eneida C, Martinez-Lavin M. Digital clubbing: a numerical assessment of the deformity. *J Rheumatol* 1989;16:518-20
- Moreira JS, Hass M, Moreira ALS, Fleck JF, Camargo JJP. Reversal of digital clubbing in surgically treated lung cancer patients. *J Bras Pneumol* 2008;34(7):481-489.
- Khattak MI, Ihsanullah, Muhammad A, Khan N, Zaman M. Frequency of sputum positive AFB cases among patients of pulmonary tuberculosis in tertiary care hospitals of northern Pakistan. *J Ayub Med Coll Abbottabad* 2010;22(2).
- Akhtar T, Imran M. Management of TB by practitioners of Peshawar. *J Pak Med Assoc* 1994; 44(12):280–2.
- Ahmed M, Aziz S. Pattern of TB in general practices. *J Pak Med Assoc* 1998;48(6):183–4.
- Jagadeesh T, Metha S, Salah HA. A Study to Evaluate the Role of Electrocardiographic Changes in Chronic Obstructive Pulmonary Disease. *J Evolution Med Dent Sci* 2015; 4(15) ; 2561-2567
- Shah M, Reed C .Complications of tuberculosis. *Curr Opin Infect Dis* 2014;27(5):403–10
- Chakaya J, Kirenga B, Getahun H. Long term complications after completion of pulmonary tuberculosis treatment: A quest for a public health approach. *J Clin Tuberculosis and Other Mycobacterial Dis* 2016;3:10–12
- Nicotra MB, Rivera M, Dale AM, et al: Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. *Chest* 1995; 108:955- 961.
- Barker AF. Bronchiectasis. *N Eng J Med* 2002; 346:1393-1393.
- Khanna BK, Khare KS. Clubbing in pulmonary tuberculosis. *Ind J Tub* 1986; 33:11.

Complications, Associations and Outcome in Children with Congenital Chloride Diarrhoea

Iqtadar Seerat and Muhammad Arshad Alvi

ABSTRACT

Objective: To determine the complications and associations of congenital chloride diarrhoea to improve prognosis.

Study Design: Observational / descriptive study.

Place and Duration of Study: This study was conducted at the Paediatric Gastroenterology, Hepatology & Nutrition, King Faisal Specialist Hospital & Research Centre, Jeddah, Kingdom of Saudi Arabia from September, 2003- September, 2016

Materials and Methods: A total of 19 confirmed cases of children with congenital chloride diarrhoea between birth and 14 years of age were included in this study. The data was collected from the ICIS used in hospital power chart system. The data was presented in form of a pie chart and a table.

Results: Out of these 19 cases we found 12(63%) patients with failure to thrive, 12(63%) patients with motor developmental delay, 12 (63%) patients with short stature, 13(68.4%) patients with renal abnormalities, 6(31.5%) with vitamin D deficiency, 3(15.7%) with iron deficiency anaemia, 2(10.4%) with congenital heart disease (Transposition of great arteries & Ventricular septal defect) and 1 case of colitis (5.2%).

Conclusion: Due to various associations and complications of congenital chloride diarrhoea we conclude that early diagnosis and regular follow up with multidisciplinary team comprising Paediatric Gastroenterologist, Nephrologist, Endocrinologist, General Paediatrician for developmental assessment and Dietician are required to improve prognosis.

Key Words: Congenital Chloride Diarrhoea (CLD), multidisciplinary team, complications, associations

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INTRODUCTION

Congenital chloride diarrhoea (CLD) is an autosomal recessive disease caused by mutations in the SLC26A3 gene. It is characterized by secretory watery diarrhoea of prenatal onset with high faecal chloride concentration and metabolic alkalosis.^{1,2,3} Due to the loss of the SLC26A3 mediated transport in the surface epithelium of the ileum and colon there is an impairment of active chloride/bicarbonate exchange which ultimately results in hyponatraemia, hypokalaemia, hypochloraemia and metabolic alkalosis. The intra-uterine diarrhoea leads to polyhydramnios and premature birth.⁴ If not treated adequately most patients will die due to severe dehydration within the 1st few months of life.

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The diagnosis is established when faecal chloride concentration exceeds 90 mmol/l after correction of dehydration. Congenital chloride diarrhoea should be treated with full oral replacement of sodium and potassium salts to achieve normal growth and avoid renal damage. In the literature there is mentioning of a variety of complications and associations in relation with congenital chloride diarrhoea. In this study we focused on this important aspect of disease. In our all 19 cases the genetic testing revealed a novel homozygous mutation in exon 5 of the SLC26A3 gene that encodes the protein regulating chloride bicarbonate absorption in distal ileum and colon.⁵

MATERIALS AND METHODS

A total of 19 confirmed cases of children with congenital chloride diarrhoea between birth and 14 years of age were included in this observational study. The study was carried out for the time period from September, 2003- September, 2016. The data was collected from the ICIS used in hospital power chart system. The data was presented in form of a pie chart and a table.

RESULTS

The table 1 shows the salient features in history and also embarks on important clinical manifestations in

our group of patients. The figure 1 reveals the number of complications and associations which our patients have come across over a period of time. Out of these 19 cases we found 12 patients (63%) were failure to thrive (weight below the 5th centile), 12 patients (63%) with motor developmental delay, 12 (63%) patients with short stature, 13 patients (68.4%) with renal abnormalities, 6 patients (31.5%) with vitamin D deficiency, 3 patients (15.7%) with iron deficiency anaemia and 2 patients (10.4%) with congenital heart disease (Transposition of great arteries & Ventricular septal defect) and 1 patient (5.2%) with colitis.

In total of 19 patients 13 developed renal abnormalities like end stage renal disease, nephrocalcinosis, increased echogenicity of both kidneys and renal stones. The renal abnormalities were picked up with help of renal ultrasound scans.

Table No.1: History and Presentation

Salient Features	Number of patients
Premature Birth	6
Polyhydramnios	8
Family History	6
Abdominal distension	14
Diarrhoea	19
Electrolyte Imbalance	19
Dehydration	19

■ Renal abnormalities ■ Failure to thrive ■ Short stature ■ Developmental delay
■ Vitamin D deficiency ■ Iron deficiency anaemia ■ Congenital heart disease ■ Colitis



Figure No.1: Number of complications and associations observed in 19 patients with congenital chloride diarrhoea

DISCUSSION

After the two American cases partly of Italian descent more than 250 cases with CLD have been reported worldwide. The incidence of CLD was established to be 1/14,000 in Kuwait compared to that of Finland 1/43,000. This high incidence in Kuwait and Middle East may be due to the multigenerational practice of consanguineous marriages and the autosomal recessive manner of inheritance of the disease.^{5,6}

In our group of patients we were able to pick up complications and associations like failure to thrive, motor developmental delay, short stature, vitamin D deficiency, iron deficiency anaemia, renal abnormalities, colitis and congenital heart disease. Congenital chloride diarrhoea seems to be associated

with an increased risk for intestinal inflammation. In the Finnish series, at least 3 patients have a diagnosis of unspecified colitis or crohn's disease.^{7,8}

As down regulation of SLC26A3 emerges in the inflamed colonic mucosa a link between intestinal inflammation and the primary defect of CLD is possible. In our 19 patients only one child developed rectal bleeding for which he has had both upper GI endoscopy and colonoscopy.

The colonoscopy showed small discreet ulcers and inflammation in left colon. The biopsies from the affected area confirmed colitis. The upper GI endoscopy was unremarkable. After appropriate treatment his symptoms of colitis have settled. Although a slightly increased risk for gastrointestinal malignancies among the carriers of SLC26A3 has been proposed but in our small study no malignancies were found.⁹

In this study we found 2 cases of congenital heart disease with transposition of great arteries and ventricular septal defect, therefore it is worth targeting and screening this group of patients for congenital heart disease with help of echocardiography.

The nutritional status of patients should be improved with the help of a dietician as they are prone to have recurrent episodes of dehydration during which the oral intake decreases. Due to lack of nutrition and calories children lose weight and also exhibit manifestations of nutritional deficiencies like iron, vitamin D. In our twin centre (King Faisal Specialist Hospital & Research Centre) Riyadh, children with congenital chloride diarrhoea requiring renal transplant are given nutrition through gastrostomy to overcome malnutrition.

Although the overall long-term outcome in the Finnish series of CLD is favourable, the relatively high incidence (28%) of chronic renal disease underlines the importance of early diagnosis, adequate salt substitution and regular follow-up of CLD.¹⁰ In our study 68.4% children with congenital chloride diarrhoea were found to have renal manifestations. This is mainly due to inclusion of echogenic kidneys (53.85%) which were picked up on serial renal ultrasound scans.

In the literature many other associations in relation with congenital chloride diarrhoea like hernia, subfertility, cystic fibrosis etc. are reported.^{11,12,13,14,15} In our group of patients no other significant complications or associations were observed. We treat our patients with oral sodium chloride, potassium chloride salts and omeprazole. We also emphasise on the importance of keeping good compliance with medications to improve the long term prognosis.¹⁶

CONCLUSION

We conclude that early diagnosis and regular follow up with multidisciplinary team are required for prevention of complications to improve prognosis.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Makela S, Kere J, Holmberg C, et al. SLC26A3 mutations in congenital chloride diarrhea. *Hum Mutat* 2002;20:425–38.
2. Holmberg C, Perheentupa J. Congenital Na⁺ diarrhea: a new type of secretory diarrhea. *J Pediatr* 1985; 106: 56–61.
3. Darrow DC. Congenital alkalosis with diarrhea. *J Pediatr* 1945;26:519–32.
4. Groli C, Zucca S, Cesaretti A. Congenital chloridorrhea: antenatal ultrasonographic appearance. *J Clin Ultrasound* 1986;14: 293–5.
5. Holmberg C, Perheentupa J, Launiala K, Hallman N. Congenital chloride diarrhea. Clinical analysis of 21 Finnish patients. *Arch Dis Child.* 1977; 52:255–267.
6. Hoglund P, Auranen M, Socha J, et al. Genetic background of congenital chloride diarrhea in high-incidence populations: Finland, Poland, Saudi Arabia and Kuwait. *Am J Hum Genet* 1998;63: 760–8.
7. Yang H, Jiang W, Furth EE, et al. Intestinal inflammation reduces expression of DRA, a transporter responsible for congenital chloride diarrhea. *Am J Physiol* 1998;275(6 Pt 1): G1445–53.
8. Lohi H, Makela S, Pulkkinen K, et al. Upregulation of CFTR expression but not SLC26A3 and SLC9A3 in ulcerative colitis. *Am J Physiol Gastrointest Liver Physiol* 2002; 283: G567–75.
9. Hemminki A, Hoglund P, Pukkala E, et al. Intestinal cancer in patients with a germ line mutation in the down-regulated in adenoma (DRA) gene. *Oncogene* 1998;16:681–4.
10. Holmberg C, Perheentupa J, Pasternack A. The renal lesions in congenital chloride diarrhea. *J Pediatr* 1997;91:738–743.
11. Maisonet L. Inguinal hernia. *Pediatr Rev* 2003;24: 34–5.
12. Haila S, Saarialho-Kere U, Karjalainen-Lindsberg ML, et al. The congenital chloride diarrhea gene is expressed in seminal vesicle, sweat gland, inflammatory colon epithelium, and in some dysplastic colon cells. *Histochem Cell Biol* 2000; 113: 279–86.
13. Ko SB, Zeng W, Dorwart MR, et al. Gating of CFTR by the STAS domain of SLC26 transporters. *Nat Cell Bio* 2004;6:55–57.
14. Hihnala S, Kujala M, Toppari J, et al. Expression of SLC26A3, CFTR and NHE3 in the human male reproductive tract: role in male subfertility caused by congenital chloride diarrhoea. *Mol Hum Reprod* 2006;12:107–11.
15. Hoglund P, Hihnala S, Kujala M, et al. Disruption of the SLC26A3-mediated anion transport is associated with male subfertility. *Fertil Steril* 2006; 87: 232–5.
16. Hihnala S, Hoglund P, Lammi L, et al. Long-term clinical outcome in patients with congenital chloride diarrhea. *J Pediatr Gastroenterol Nutr* 2006;42:369–75.

Histopathological Analysis of Renal Tissue to Evaluate the Effects of Proton Pump Inhibitors at Cellular Level

Muhammad Javed¹, Amna Mubeen¹ and Nusrat Manzoor²

ABSTRACT

Objective: To evaluate the cytopathological effects of proton pump inhibitors on renal tissue in different doses by using an animal model

Study Design: Randomized control trial.

Place and duration of study: This study was conducted at Post Graduate Medical Institute Lahore for a period of 4 weeks.

Materials and Methods: The sample size was 60 mice. The sampling technique was Simple Random Sampling. The mice were obtained from National Institute of Health Islamabad. The animals were kept in labeled cages under standard environmental conditions. Animals were divided into three groups. One group served as control and the other two served as treated groups. Micrometry was done to evaluate the effects of drug.

Results: It was observed on study of histological sections that proton pump inhibitors induce toxic effects on cells of uriniferous tubules of kidney. The tubular cells showed varying degree of tubular atrophy.

Conclusion: The observations of the study revealed that it damages the uriniferous tubules by causing their atrophy leading to renal insufficiency. It is desired that these result will generate awareness about the careful use of the proton pump inhibitors by the people and the clinicians.

Key Words: Cytopathology, Renal toxicity, Atrophy

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INTRODUCTION

Proton pump inhibitors are a group of drugs which have the main function of prominent and long lasting decrease in the production of gastric acid. The primary role in the disorders of gastrointestinal tract is played by the altered gastric acid secretion. Acidic environment exerts a negative effect on the homeostasis. ¹Therefore an intragastric pH above 6 is maintained by the use of acid inhibitors. Proton pump inhibitors act on the gastric H⁺/K⁺ ATPase pump to achieve this target. Within this class of drugs, there is no clear difference of efficiency in their function. ^{2,3} For the purpose of study, the drug used was Omeprazole which belongs to the class of proton pump inhibitors. It was introduced in 1989. It is available as capsule and powder form. Its introduction led to the self directed use of the proton pump inhibitors. They are considered as safe medicines but nowadays, people are using them on long term basis. This has attracted the attention to evaluate their adverse effects. ^{4,5}

The use of proton pump inhibitors as treatment for the gastrointestinal disorders is associated with the development of renal impairment. It is evident in almost 15% of the cases of acute renal failure. Drugs are commonly associated with kidney injury. Mostly drugs exert nephrotoxic effects by various mechanism including altered glomerular hemodynamics, micro-angiopathy and tubular cell injury. ^{6,7} Tubulointerstitial diseases of the kidney may be primary in nature involving tubules basically. Secondary form of disease involves the glomeruli or the blood vessels. Variable drugs can cause this condition but symptoms and the findings will be different according to the drug used. ^{8,9} Almost one quarter of the cardiac output undergoes circulation through the renal vasculature so the structural cells of the kidney are at risk of exposure to the toxic effects of the drugs. Medicine induced toxic effects are often encountered possibly because of primary role of the kidneys in the filtration of plasma. ^{10,11} As a result, renal tubular cells bear significant amount of drug and also its metabolites which can damage the renal tissue. Acute renal damage is manifested as edema and infiltration of inflammatory cells. If the process of damage continues then pathology is observed as tubular necrosis, tubular atrophy with dilatation of lumen and basement membrane disruption. ^{12,13,14}

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MATERIALS AND METHODS

A total of 60 mice were obtained from the National Institute of Health Islamabad. They were divided into three equal groups by random number table. One group served as control, whereas other groups were used as treated group. The animals were handled according to international and ethical guidelines for the animal care. They were kept in separate cages which were labeled. Omeprazole used in this experiment was a product of GETZ Pharmaceuticals with the brand name of RISEK having Omeprazole as 20 mg and 40 mg. Equivalent animal dose of omeprazole was calculated. It was dissolved in distilled water and given orally to the animals of treated group. Controls were given same quantity of normal saline at the same time. Animals were sacrificed after 4 weeks of drug administration. Kidneys were dissected out and tissue blocks prepared. Slides were stained for histological study. The duration of administration is chosen according to the previous studies which reflect the nephrotoxic effects of drug.¹⁵ Micrometry was done with the help of oculomicrometer to measure the size of tubular cells. It was attached to the microscope eyepiece. The stage micrometer was placed on the microscope slide stage. The microscope was adjusted and the cell size of the uriniferous tubules was measured in different fields of vision. Mean size was recorded.¹⁶

RESULTS

The observations of the study were recorded using the MS word and Excel data sheet. The data was entered

and analyzed statistically using MedCal for Windows, version 12.5.0.0 (MedCal Software, Ostend, Belgium). ANOVA (Analysis of Variance) test and t- test were used to calculate the quantitative difference between the groups.

Table No.1: Table showing detail of animal groups

Group	Status	Dose	Duration of therapy
1	Control	Normal saline	4 weeks
2	Experimental	20 mg	4 weeks
3	Experimental	40 mg	4 weeks

Table No.2: Comparison of the cell size of uriniferous tubules

Kidney Tubules	Group 1 n=20 mean $\pm$ SD	Group 2 n=20 mean $\pm$ SD	Group 3 n=20 mean $\pm$ SD
Proximal convoluted tubule	15.50 $\pm$ 0.54	14.25 $\pm$ 0.60	13.30 $\pm$ 2.50
Distal convoluted tubule	15.00 $\pm$ 0.56	14.28 $\pm$ 0.75	13.55 $\pm$ 0.74
Collecting ducts	15.00 $\pm$ 0.56	14.28 $\pm$ 0.75	13.55 $\pm$ 0.74

n = number of animals

The interpretation of the p- value was done as follows.

p > 0.05 difference insignificant

*p < 0.05 difference significant

**p < 0.05 difference considerably significant

***p < 0.01 difference highly significant

Table No.3: Significance (p- value) of cell size difference using t- test

Group	Proximal convoluted tubule		Distal convoluted tubule		Collecting ducts	
	Mean difference	p- value	Mean difference	p- value	Mean difference	p- value
Control Vs G2	1.25	0.017*	0.7250	0.011*	1.13	<0.001***
Control Vs G3	2.20	<0.001***	1.4500	<0.001***	1.95	<0.001***

Table No.4: Comparison of the nucleus size of uriniferous tubules

Kidney Tubules	Group 1 n=20 mean $\pm$ SD	Group 2 n=20 mean $\pm$ SD	Group 3 n=20 mean $\pm$ SD
Proximal convoluted tubule	5.8 $\pm$ 0.5	4.5 $\pm$ 0.9	4.0 $\pm$ 0.7
Distal convoluted tubule	5.75 $\pm$ 0.5	4.55 $\pm$ 0.84	3.85 $\pm$ 0.73
Collecting ducts	5.78 $\pm$ 0.47	4.25 $\pm$ 0.66	3.65 $\pm$ 0.52

n = number of animals

Table No.5: Significance (p- value) of nucleus size difference using t- test

Group	Proximal convoluted tubule		Distal convoluted tubule		Collecting ducts	
	Mean difference	p- value	Mean difference	p- value	Mean difference	p- value
Control Vs G2	1.255	0.001***	1.200	0.001***	1.525	<0.001***
Control Vs G3	1.825	<0.001***	1.900	<0.001***	2.125	<0.001***

DISCUSSION

Proton Pump Inhibitors are commonly utilized for the treatment of gastrointestinal disorders. Omeprazole

belongs to this group of drugs. They are known as proton pump inhibitors because they act by inhibiting the H/K ATPase pumps found in the lining cells of the stomach that make gastric acid.^{17,18} Literature review

shows that risks are present with their use like *Clostridium difficile* associated diarrhea, community acquired pneumonia and antiplatelet therapy. In this study, dose related cytopathological effects of proton Pump Inhibitors on the uriniferous tubules were studied. The adverse effects were studied in different groups of animals. These groups were treated with omeprazole and compared with the animals of control group. Acute kidney injury was observed in treated animals. Most of the previous studies are in favor of adverse effects of proton pump inhibitors on kidney.^{19, 20}

It was found that proton pumps are also located in uriniferous tubules of kidney which are sensitive to them. It binds to these pumps and selectively inhibits the H/K ATPase pumps showing that omeprazole has organ specificity. So an immunological basis is suspected for the renal effects of proton pump inhibitors.^{21, 22} The drug binds to the tubular basement membrane component and acts as happen causing the formation of antimembrane antibodies. Endothelial cell activation by the inflammatory mediators promotes leukocyte infiltration. This inflammatory process commonly leads to the tubular damage and acute kidney injury.²³

The renal tubules of the animals treated with drug showed tubular atrophy as compared to the animals of control group which was evident by the significant results. Numerous other studies also reported a positive relationship between their use and acute kidney injury. The most common etiology of kidney damage is drug induced disease, which underlie almost 60-70% of cases. Proton Pump Inhibitors are among the commonly responsible ones and they are gaining attention now as a cause of acute renal damage because of their widespread and continuous use.^{24, 25}

CONCLUSION

Omeprazole belongs to the class of Proton Pump Inhibitors. It is commonly used for the relief of gastrointestinal disorders. The present study was conducted to evaluate the adverse effects on the renal tissue when administered in different doses. The observations of the study revealed that it damages the uriniferous tubules by causing their atrophy leading to renal insufficiency. It is desired that these result will generate awareness about the careful use of the proton pump inhibitors by the people and the clinicians.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Baldwin RM, Ohlsson S, Pedesen RS, Mwinyi J, Ingelman-Sundberg M, Eliasson E, et al. Increased Omeprazole metabolism in carriers of the CYP2C19*17 allele; A pharmacokinetics study in healthy volunteers. *Br J Clin Pharmacol* 2008;65(5):767-774.
2. Boussey K, Smet DJ, Cock DP, Velde VS, Mehuys E, Paepe P, et al. Pharmacokinetics of two formulations of omeprazole administered through a gastrostomy tube in patients with severe neuro developmental problems. *Br J Clin Pharmacol* 2011;72(6):990-996.
3. Devendran A, Uppugunduri SC, Sundaram, R, Gopal D, Krishnamoorthy, Chandrasekaram A. Relative copy number variation of CYP2C19 in south Indian population. *Mol Biol Int* 2012; 643856.
4. Ezquerro PR, Morillas SL, Martinez LJ, Fernandez, GD, Tembleque MG, Avarez AS, Sanz ML. Anaphylaxis to omeprazole. Cross reactivity with other proton pump inhibitors. *Allergol Immunopathol* 2011;39(54): 01.
5. Halbritter J, Mayer C, Rasche FM, Amann K, Lindner TH. Interstitial Nephritis *Internist* 2009; 50(9):1111-25.
6. Holzer P. Acid sensing by visceral afferent neurons. *Acta Physiol* 2011;201(1): 63-75.
7. Heidelbaugh JJ, Kim HA, Chang R, Walker CP. Overutilization of proton pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol* 2012;5(4): 219-232.
8. Iida A, Kaneko H, Iwaki YK, Tokudome K, Iawa S. Inhibition of gastric perception of mild distension by Omeprazole. *World J Gastroenterol* 2012;18(39):5576-5580.
9. James Y, Lau Wai K, Leung Justin CY, Wu Francis KL, Chan Vincent WS, Wong Philip WY, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med* 2007; 356:1631-1640.
10. Li J, Shentu ZJ, Wu L, Dou J, Xu Q, Zhou H, Wu G, et al. Relative bioavailability and pharmacokinetic comparison of two different enteric formulations of Omeprazole. *J Zhejiang Univ Sci B* 2012;13(5):348-355.
11. Lobera T, Navarro B, Pozo D, Gonzalez I, Blasco A, Escudero R. Nine cases of Omeprazole allergy. Cross reactivity between proton pump inhibitors. *J Investig Allergol Clin Immunol* 2009;19(1): 57-60.
12. Leonard CE, Freeman CP, Newcomb CW, Reese PP, Herlim M, et al. Proton pump inhibitors and traditional nonsteroidal anti-inflammatory drugs and the risk of acute interstitial nephritis. *Pharmacoevidenciol Drug Saf* 2012;21(11): 1155-72.
13. Mann PC, Vahle J, Keenan CM, Baker JF, Bradley AE, Goodman DJ. International harmonization of toxicologic pathology nomenclature: an overview and review of basic principles. *Toxicol Pathol* 2012;40(4):7-13.

14. Monzani A, Oderda G. Delayed release oral suspension of omeprazole for the treatment of erosive esophagitis and gastro esophageal reflux disease in pediatric patients, a review. *Clinical and Experi Gastroenterol* 2010;3:17-25.
15. Michael D, Drepper Spaher L, Frossard LJ. Clopidogrel and proton pump inhibitors- where do we stand in 2012. *World J Gastroenterol* 2012; 18(18): 2161-2171.
16. Michelle L, Gumz I, Megan M, Greenlee Brain D, Wingo SC. The renal H⁺ -K⁺-ATPases: physiology, regulation and structure. *Am J Physiol Renal Physiol* 2010;298(1):12-21.
17. Perazella MA, Markowitz GS. Drug induced acute interstitial nephritis. *Nat Rev Neph.*, 6(8): 461-70.
18. Rose, C., Baker, T. and Nicholas, T., 2004. Drug induced tubule-interstitial nephritis secondary to proton pump inhibitors. Experience from a single UK renal unit. *Nephrol Dial Transplant* 2010;19: 1441-6.
19. Romano C, Chiaro A, Comito D, Loddo L, Ferrau V. Proton pump inhibitors in pediatrics: Evaluation of Efficiency in GERD Therapy. *Curr Clin Pharmacol* 2011;6(1):41-7.
20. Sujin RM, Subin RM, Mahesh R, Vinolyia J. The effect of Anti Diabetics in Kidney of Rats. *Ethnobotanical Leaflets* 2009;13:689-701.
21. Shin MJ, Sachs G. Pharmacology of proton pump inhibitors. *Curr Gastroenterol Rep* 2008;10(6): 528-534.
22. Shi S, Klotz U. Proton pumps inhibitors: an update of their clinical use and pharmacokinetics. *Europ J Clin Pharm* 2008;64(10):935-951.
23. Sach G, Shin JM, Hunt R. Novel Approaches to inhibition of gastric acid secretion. *Curr Gastroenterol Rep* 2010;12(6):437-447.
24. Tamura T, Sakaeda T, Kadoyama K, Okuno Y. Omeprazole and Esomeprazole-associated Hyomagnesaemia: Data mining of public version of the FDA adverse event reporting system. *Int J Med Sci* 2012;9(5): 322-326.
25. Tsuzuki T, Okada H, Kawhara Y, Takennaka R, Nasu J, Ishioka H, et al. Proton pump inhibitor step-down therapy for GERD: A multi-center study in Japan. *World J Gastroenterol* 2011;17(11): 1480-1487.

Corrigendum

Name of author in the article titled "Predict the Possibility of Esophageal Varices in HCV Patients on the Basis of Fibro Scan Scoring System" printed in Med Forum volume 2017;28(2) at pages 138-141 has been typographically written as Dr. Haris Alvi which may now be read as "Dr. Haris Alvi."

Editor

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When appropriate may be included.

ACKNOWLEDGMENTS

List of all contributors who do not meet the criteria for Authorship, such as a person who provided purely technical help, writing assistance or department chair who provided only general support. Financial & Material support should be acknowledged.

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