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CONTENTS

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Editorial

1. **Are Doctors Victims of Depression in Secret?** _____ 1
Mohsin Masud Jan

Original Articles

2. **Hyperuricemia in Patients Taking Anti-Tuberculosis Drugs Including Pyrazinamide for both Category-1 and Category-2 Tuberculosis, in population of KPK-Pakistan** _____ 2-5
1. Jamaluddin 2. Nizamuddin 3. Abid Shah 4. Waheed Iqbal
3. **Prevalence, Etiology and Management of Hyponatremia in Hospitalized Patients** _____ 6-9
1. Shafiq Cheema 2. Sidra Cheema 3. Aqsa Rahman
4. **Comparison of Negative Appendectomy Rate between Alvorado Score and Adult Appendicitis Score at Allama Iqbal Memorial Teaching Hospital Sialkot** _____ 10-13
1. Adnan Butt 2. Nimra Ikram 3. Kamran Hamid
5. **Comparison of Efficacy of Fosfomycin and Ceftriaxone in the Treatment of Urinary Tract Infections in Children** _____ 14-17
1. Arshia Munir 2. Muhammad Aqeel Khan 3. Muhammad Bilal Khattak 4. Kalimullah Khan
5. Irum Naz
6. **Socioeconomic Status of Patients with End Stage Renal Disease and the Microeconomic Impact of Hemodialysis** _____ 18-22
1. Amer Azhar 2. Mufti Baleegh-ur-Raheem Mahmood 3. Ahmad Zeb Khan 4. Tariq Ikram
7. **Hematological Abnormalities with Low Dose Methotrexate in Rheumatoid Arthritis Patients** _____ 23-26
1. Muhammad Abbas 2. Amir Khan 3. Muhammad Khalid 4. Sajjad Ali Shah 5. Shah Zaib
8. **Immunoexpression of Cytokeratin 20 and Cytokeratin 7 in Colorectal Adenocarcinoma in Association to Histological Grade** _____ 37-31
1. Muhammad Tariq 2. Pervez Mohammad 3. Muhammad Ashraf Salam
9. **Effect of Covering of Head on Phototherapy Induced Hypocalcemia in Full Term Neonates with Jaundice** _____ 32-36
1. Rahida Karim 2. Jahanzeb Khan Afridi 3. Mariam Farooq
10. **Comparison of Fibrinogen Level and Factor VIII in Single and Multiple Vessels Ischemic Heart Disease** _____ 37-41
Ayesha Samad Dogar
11. **Hypoglycemic Episodes among Cirrhotic Patients Presenting with Hepatic Encephalopathy to Tertiary Care Hospital** _____ 42-46
1. Aliena Badshah 2. Wazir Mohammad 3. Iqbal Haider 4. Zahid Ullah Khan Marwat
12. **Pulmonary Recruitment Maneuver: An Effective Way to Reduce Postoperative Pain after Laparoscopic Cholecystectomy** _____ 47-50
1. Muhammad Umar Farooq 2. Farooq Ahmad 3. Faisal Rauf 4. Muhammad Iqbal
13. **Screening of Diabetes and HIV Infection in Newly Diagnosed Pulmonary Tuberculosis Patients,** _____ 51-55
1. Rizwan Hafeez 2. Sajjad Ahmed Khan 3. Azzan Mujahid 4. Abdullah Irshad
14. **Association Between Periconceptional Folic Acid Deficiency and Occurrence of Skeletal Anomalies in Newborns** _____ 56-59
1. Riasat Ali Nehra 2. Noor ul Mobeen 3. Akmal Bhatti 4. Hafsa
15. **Morphometric Analysis of Lower Pole Calyceal Anatomical Factors in Normal Healthy Kidneys and Their Clinical Significance** _____ 60-64
1. Atika Khurshid 2. Waqar Azim Niaz 3. Kamil Shuaat
16. **Assess the Role of Dental Surgeons in Prevention and Early Diagnosis of Oral Cancers** _____ 65-67
1. Sana Zafar 2. Sadia Rashid 3. Danish Javed 4. Muhammad Rizwan
17. **Descriptive Study on Presentation of the Stroke** _____ 68-72
1. Jeando Khan Daidano 2. Nazia Azam Yusufani 3. Ahmed Ali Kanher

Guidelines and Instructions to Authors _____ i

Editorial

Are Doctors Victims of Depression in Secret?

Mohsin Masud Jan

Editor

Doctors get sad, like anyone else. So how do doctors cope when sad days turn into weeks, even months? Are there unique factors that lead to physician depression? Are doctors different from the general population in the way in which they respond to depression? What treatments do doctors seek or avoid?

Here's what many depressed doctors do: Nothing. Or they try things that don't help.

First let us take a look at what exactly describes depression in itself. Depression (major depressive disorder) is a common and serious medical illness that negatively affects how you feel, the way you think and how you act. Fortunately, it is also treatable. Depression causes feelings of sadness and/or a loss of interest in activities once enjoyed. It can lead to a variety of emotional and physical problems and can decrease a person's ability to function at work and at home.

Depression symptoms can vary from mild to severe and can include:

- o Feeling sad or having a depressed mood
- o Loss of interest or pleasure in activities once enjoyed
- o Changes in appetite— weight loss or gain unrelated to dieting
- o Trouble sleeping or sleeping too much
- o Loss of energy or increased fatigue
- o Increase in purposeless physical activity (e.g., hand-wringing or pacing) or slowed movements and speech (actions observable by others)
- o Feeling worthless or guilty
- o Difficulty thinking, concentrating or making decisions
- o Thoughts of death or suicide

Symptoms must last at least two weeks for a diagnosis of depression.

Also, medical conditions (e.g., thyroid problems, a brain tumor or vitamin deficiency) can mimic symptoms of depression so it is important to rule out general medical causes.

Depression affects an estimated one in 15 adults (6.7%) in any given year. And one in six people (16.6%) will experience depression at some time in their life. Depression can strike at any time, but on average, first appears during the late teens to mid-20s. Women are more likely than men to experience depression. Some studies show that one-third of women will experience a major depressive episode in their lifetime.

Now let us go through a few of the most common risk factors for depression.

- 1) A failing marriage. A relationship on the rocks is destabilizing for anyone, yet physicians are more likely to lose marriages to spousal neglect. Doctors don't have predictable 40-hour work weeks. With erratic schedules requiring weekend and evening call, physicians routinely miss family events, kids' activities, and holidays.
- 2) Social isolation. Loneliness may lead to depression in anyone, and physicians are at high risk for social isolation. Frequent moves during training and working 80+ hour work weeks leave little time for friends or family. Even when not working, doctors are talking about medicine, thinking about patients, studying for board exams, or gathering continuing medical education credits.
- 3) Being a physician is an independent risk factor for social isolation in itself.
- 4) Death of a spouse. Physicians are uniquely affected by the loss of a life partner, because they have had less time to develop a support system than the general population. The death of a spouse can be a particularly devastating event for male physicians, who appear to be at higher risk for depression because they often rely on their marital partners

for emotional support and are more challenged to ask for help or be vulnerable with friends or colleagues compared with female physicians.

- 5) Financial distress. Although doctors have greater earning capacity than the general population, they often save less and spend more on student loans, cars, and homes, owing to family and cultural expectations. Many physicians are financially preyed upon by unethical employers, other professionals, even friends and family who believe that "all doctors are wealthy." Physicians can also make poor financial decisions, further exacerbating their inability to build a nest egg until much later in life than most. Some still have student loan debt into their 50s or 60s and have saved little for retirement.
- 6) Childhood trauma. Early sexual, emotional, and physical abuse increase the risk for depression for all.
- 7) Family history of depression. Both nonphysicians and physicians whose parents suffer from depression are at increased risk of developing depression.
- 8) Retirement. A major life event, such as retirement, can lead to depression in many people—yet when one's identity is wrapped so tightly around a career, as it is for a doctor, the depression may be far worse.

Now, when encountered with such an obstacle in life, What Do Depressed Doctors Do? Do they just go to the doctor? Most don't. Many doctors do nothing. Medical training teaches us to "suck it up," so help-seeking is not a well-honed skill among doctors. Many lack self-awareness that they are suffering from depression. And those who do take action rely on several Self-treatment Strategies

- 1) Self-distraction.
- 2) Self-soothing. Cooking and overeating may transiently ease depressive symptoms. Dark chocolate is favored, followed by other sugary snacks, such as donuts and pastries at nurses' stations and clinic break rooms.
- 3) Self-care. Some docs are chronically sleep-deprived, so sleeping in or relaxing on vacation is their go-to self-care strategy. Obsessive exercise is also extremely popular among doctors. Beware: Cross Fit, running marathons, or power lifting, although great for depression, may turn into an addiction and lead to injury.
- 4) Others read self-help books, pray, meditate, do yoga, sing, dance, listen to music, or play with kids/pets. Some docs keep a stash of thank-you cards from patients that they read when depressed. Remembering grateful patients is a form of self-affirmation that rebuilds confidence and self-esteem.
- 5) Taking up new Hobbies. Many physicians throw themselves into obsessive crafting to treat depression.
- 6) Emotional release. Physicians have disclosed crying under their desks between patients, closet crying, and crying themselves to sleep in the call room.
- 7) And finally Self-prescribing. Whereas some docs write their own prescriptions, others steal drug samples from their office or buy them on the Internet so that there's no record.

Sadly, many doctors continue to suffer with untreated or poorly treated depression, owing to fear of seeking treatment in a medical environment that stigmatizes and punishes physicians with mental health issues. In fact, many physicians experience occupationally induced depression, and those who have non-career-related risk factors for depression seem more likely to suffer from depression than the general population, owing to the tremendous self-sacrifice required of our doctors.

Hyperuricemia in Patients Taking Anti-Tuberculosis Drugs Including Pyrazinamide for both Category-1 and Category-2 Tuberculosis, in Population of KPK-Pakistan

Jamaluddin¹, Nizamuddin², Abid Shah² and Waheed Iqbal²

ABSTRACT

Objective: To document hyperuricemia in patients taking Anti-Tuberculosis Therapy (ATT) including Pyrazinamide (PZA) in both CAT-1 and CAT-2 Patients.

Study Design: An open labeled & single centered longitudinal study.

Place and Duration of Study: This study was conducted at the Khyber Medical College (KMC) & Khyber Teaching Hospital, Peshawar from December 2016 to May 2017.

Materials and Methods: Sixty patients with pulmonary tuberculosis were enrolled. Patients were assigned into 2-groups (30 patients in each group), including group-A as CAT-1 patients, who were taking ATT for the first time and group-B as CAT-2, who presented with recurrent tuberculosis and were put on ATT for the second time. Standard ATT was given to group-A and Streptomycin was added to standard ATT in group-B for the first 02-months and uric acid (UA) level was done before the initiation of therapy, at the end of two-month intensive regimen and 02-months after the stopping Pyrazinamide. The primary target was to find out hyperuricemia in both groups.

Results: In CAT-1 patients, uric acid was increased to 6.44 ± 0.91 after two months aggressive regimen, and with discontinuation of pyrazinamide in CAT-1 patients for two month the uric acid falls again to 4.71 ± 0.83 . Similarly, in CAT-2 patients, uric acid was increased to 6.64 ± 0.91 with two months therapy which downgrade to 5 ± 1.15 after two months of stopping pyrazinamide. There is significantly increase in uric acid level with two months of ATT in both groups (p -value=0.01). There is 100% recovery in female patient in Cat-1 as compared to Cat-2 female patients (91.6%), similarly 94.77% males improved in Cat-1 as compared to Cat-2 males whose recovery is 86.67%.

Conclusion: ATT including PZA can cause significant hyperuricemia, in both CAT-1 and CAT-2 patients. This raised in uric acid level is reversible with discontinuation of PZA, but may persist in some of CAT-2 patients.

Key Words: Hyperuricemia, Anti tuberculosis drugs, Pyrazinamide, CAT-1 and CAT-2.

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INTRODUCTION

Tuberculosis is infectious disease, which is caused by Mycobacterium Tuberculosis. It is very common in the developing countries including Pakistan, but it is also increasing in the developed countries due to HIV-AIDS. Globally, 10.4 million new cases were reported in 2016. About 10% are them are co-infected by HIV infection. It is the ninth common cause of death worldwide and the first amongst the infectious disease. Pakistan is at number five amongst 22 countries with high incidence of tuberculosis. Annually, about 480,000 people are infected and around 70,000 people die due tuberculosis^{1,2}.

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The number of new cases and recurrent cases is alarming and may be more, as most of the cases are not reported. It is a treatable disease and timely diagnosis followed by complete course of ATT can prevent mortality of the patient and spread of infection in the community. Anti tuberculosis drugs are given for six months including 2-months as intensive phase and 4-months as maintenance phase. In the intensive phase, we are using four drugs for CAT-1 patients, including Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. Streptomycin is added to all these drugs for the first two months in case of CAT-2 patients. Most of the treatment failure occurs due to poor compliance with the therapy. Poor compliance is due to longer duration of treatment and multiple adverse effects caused by all ATT³. Hyperuricemia is one of the most important adverse effects, which occurs with Pyrazinamide (PZA) and to some extent with ethambutol. Streptomycin can impair renal function and can further increase it in case of CAT-2 patients. Pyrazinamide is a bacteriostatic drug, which may be bactericidal at high concentration. It is one of the most important amongst the first line ATT drugs, which is recommended in the intensive

phase for both CAT-1 and CAT-2 patients. It is converted in the body into its active metabolite, pyrazinoic acid. Hyperuricemia occurs due to impaired excretion of uric acid in the proximal tubules of the kidney due PZA metabolite, pyrazinoic acid.

In the human body, uric acid is produced by purine metabolism. Most of the mammals metabolise it to allantoin and allantoic acid with the help of uricase, which is easily water-soluble and easily excreted in urine. In contrast to most other mammals, humans don't have sufficient enzyme level of uricase, due to which there is rapid accumulation of uric acid in the serum. It precipitates in the form of urate crystal, leading to the clinical manifestation of gout and urolithiasis. Very high-level uric acid can lead to acute kidney injury in the form of acute renal failure. In human body, approximately 70% of uric acid is excreted via kidneys, while the rest passes into the gastrointestinal tract, where it is oxidized to allantoin, allantoic acid and urea. Uricase and other enzymes, which are present in the normal intestinal flora, do this⁴.

Hyperuricemia is usually defined as a serum uric acid (SUA) level greater than 7.0 mg/dl in male and SUA level greater than 6.5mg/dl in females. It is a very important metabolic condition, which "may be caused by increased urate production (over producers) or decreased renal urate excretion (under excretors)"⁵. Usually, it is caused by under excretion. In most of the patients, it is usually asymptomatic, but elevated levels of uric acid can cause crystal deposition in many organs of the body including skin, joints and kidney. This can lead to gout, skin tophi, kidney urate stones and urolithiasis⁶.

In case of tuberculosis, asymptomatic hyperuricemia occur in the first two months of intensive therapy. PZA is considered to be the most notorious in all ATT for this adverse effect in all adult and children^{7,8}. Most of the ATT causing some degree of renal stress and affect the renal excretion of many metabolic waste products including urate. This can increase the effects of PZA and thus accumulation of uric acid occurs more quickly in case of giving all anti tuberculosis drugs. Streptomycin, which is given in case of CAT-2 tuberculosis can also impair the renal function and thus can further increase the urate level⁹.

There are a number of documented studies, conducted at both national and international level to document this association. In this study, we have focused to compare the level of hyperuricemia in both CAT-1 and CAT-2 patients, taking ATT including PZA. We have conducted this study to evaluate this association in the population of Khyber Pukhtoonkhwa.

MATERIALS AND METHODS

This single center & longitudinal study was conducted in the KMC & Teaching Hospital, Peshawars starting from December 2016 to May 2017. The sample size was calculated with the help of WHO-online calculator. Ethical committee approval was taken in advance and after informed consent, 60 patients having pulmonary

tuberculosis were enrolled. All these patients were divided into 2 groups, labeled as group-A as CAT-1 cases, who, group-B as recurrent CAT-2 cases. All the demographic and clinical information like age, sex, ethnicity and treatment strategy were obtained from the patients. All patients in CAT-1 were put on four drugs including Isoniazid, Rifampicin, Ethambutol and Pyrazinamide, while streptomycin was added to these drugs in case of CAT-2 cases. Serum uric acid level was recorded initially, at the end of two month of therapy and after two month of the discontinuation of pyrazinamide.

Statistical Analysis; SPSS version 16.0 was used for analysis of all the data including frequencies, percentages. Independent sample T-test was applied to determine the difference between the means of two groups with 95% of confidence level, and significant p-value of ≤ 0.05 . The Graph was constructed using Microsoft Excel 2013. All the findings were presented in graphs and tables.

RESULTS

The study consists of 60 patients, which were classified into two groups of 30 in each individual. CAT-1 were treatment naïve patient while in CAT-2 those patients were included who were put on ATT for the 2nd time. In CAT-1, 19 (63.3%) were males while 11 (36.7%) were females, the UA at start of anti-tubercular therapy, at two months and after two months of stopping ATT was 4.67 ± 0.72 , 6.44 ± 0.91 and 4.71 ± 0.83 respectively. All the values are summarized in table 1.

Similarly, in CAT-2 patients, male vs female ratio was 19 (56.7%) and 13 (43.3%) respectively. Uric acid was 4.67 ± 0.74 at start of therapy and was upsurges to 6.64 ± 0.91 with two months therapy which downgrade to 5 ± 1.15 after two months of stopping pyrazinamide. All the data is summarized in table 2.

Table No. 1: CAT-1 patients

		Frequency	Mean	SD
Age		30	48.53	9.96
Gender	Males	19(63.3%)	-	-
	Females	11(36.7%)	-	
Uric Acid at start		30	4.67	0.72
Uric Acid at 2 months		30	6.44	0.91
Uric Acid after 2 months of stopping therapy		30	4.71	0.83

Table No. 2: CAT-2 patients

Variables		Frequency	Mean	SD
Age		30	48.43	11.57
Gender	Males	17(56.7%)	-	-
	Females	13(43.3%)	-	
Uric Acid at start		30	4.67	0.74
Uric Acid at 2 months		30	6.64	0.19
Uric Acid after 2 months of stopping therapy		30	5.0	1.15

Table No. 3: Improvement of males and females between two groups after stopping therapy

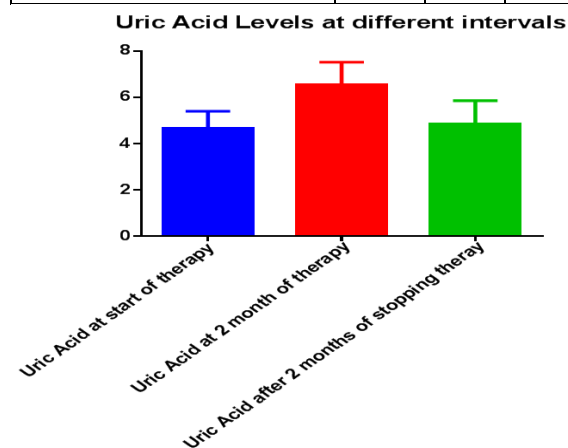
Females			
Variables	Uric Acid (2.4-6)	Uric Acid above 6	Improvement
ATT 1 st time	11	0	100 %
ATT 2 nd time	12	1	91.6 %
Total	23	1	
Males			
Variables	Uric Acid (3.4-7)	Uric Acid above 7	Improvement
ATT 1 st time	19	1	94.77 %
ATT 2 nd time	15	2	86.67 %
Total	33	3	

Table No. 4: Differences between means of uric acid between two groups

		Mean	SD	T	P. value	95% CI
UA-1	ATT 1 st time	4.6700	.72595	-.035	0.972	-0.38-0.37
	ATT 2 nd time	4.6767	.74124			
UA-2	ATT 1 st time	6.4467	.91264	-.759	0.451	-0.70-0.31
	ATT 2 nd time	6.6400	1.05458			
UA-3	ATT 1 st time	4.7167	.83173	-1.091	0.280	-0.80-0.23
	ATT 2 nd time	5.0000	1.15460			

Table No. 5: Test for association

	Mean	SD	p-value
Uric Acid at start	4.67	0.72	0.01
Uric Acid After 2 months	6.54	0.98	

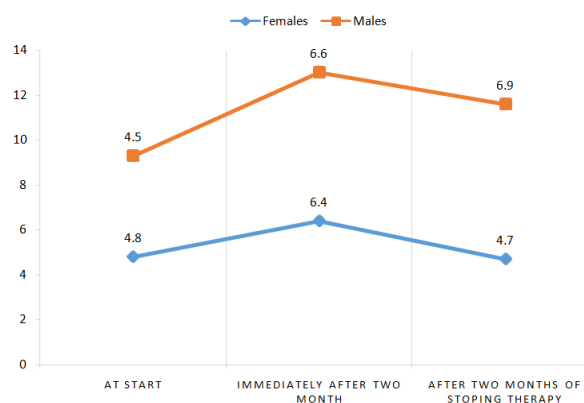
**Figure No. 1: Uric Acid levels at different intervals**

Although there no significant differences between the UA levels at different intervals of both groups (summarized in table 4.0) but there is significant increase of UA levels (4.67 ± 0.72) at start of the therapy and after two months of the therapy (UA levels

= 6.4 ± 0.91 in Cat-1 and UA levels = 6.6 ± 1.05) with p-value 0.01 as shown in table 5.

After stopping of ATT therapy, there is 100% recovery of females patient in CAT-1 as compared to CAT-2 females patients (91.6%), similarly 94.77% males improved in CAT-1 as compared to CAT-2 males whose recovery is 86.67% as shown in table 3.

The overall UA levels are graphically shown in figure 1.0 while the comparison of upsurges in UA level between males and females is graphically in figure 2.0.

URIC ACID LEVEL WITH DRUG THERAPY**Figure No. 2: Uric Acid levels between males and females in both groups**

DISCUSSION

Tuberculosis is a dreadful chronic infectious disease, targeting mostly the poor and under privileged communities in the world. But at the same time, it is a potentially curable disease with a very good outcome, if timely diagnosed and treated. Anti-tuberculosis medication is recommended for six months including first 2-months as intensive phase and last 4-months as maintenance phase. In the intensive phase, along with other ATT, pyrazinamide is given. Its metabolites can cause decrease excretion of uric acid by the kidney and thus can lead to hyperuricemia.

In our study, we have two groups as CAT-1 and CAT-2. In CAT-1, the UA was 4.67 ± 0.72 , 6.44 ± 0.91 and 4.71 ± 0.83 at the start, at two months and after two months of stopping ATT respectively. Similarly, in CAT-2 patients, UA was 4.67 ± 0.74 at start of therapy and was upsurges to 6.64 ± 0.91 with two months therapy which downgrade to 5 ± 1.15 after two months of stopping pyrazinamide. In our study, after stopping of ATT therapy, there was 100% recovery of female patient in CAT-1 as compared to CAT-2 female patients (91.6%). Similarly 94.77% male improved in CAT-1 as compared to CAT-2 male whose recovery was 86.67%.

The findings of our study are also closed to the findings of another study conducted by Mahantesh A et al, at Bangalore. It was observed “that mean serum uric acid at 0th week was 5.1 mg/dl, which increased to 6.8 mg/dl and 6.6 mg/dl at 2nd and 8th week, respectively”. Among all these patients, “48.72% patients showed 25-

50% increase in the uric acid level, while 41.02% patients showed an increase in serum uric acid level beyond normal range (>7 mg/dl)". Similarly, there were non-significant increased in UA levels in 41.02% patients from 2nd and 8th week¹⁰.

The finding of our study are also close to the finding of another study, conducted by Louthrenoo W et al, "showing a little higher results at second week, with a significant increase in uric acid level (9.78 ± 3.21 mg/dL, $P < 0.001$)". In all these patients, these changes persisted for the whole second month, but returned to the baseline value at the end of fourth month. Over all, only 13 patients (81.25%) had developed hyperuricemia¹¹.

The findings of our study are also close to the finding of another study, conducted by Pokam BD et al, showing that "hyperuricemia was observed in 56/96 (58.3%) of the studied group as compared with four of 32 (12.5%) in the control group ($p < 0.001$)". It was also observed in this study that treatment duration was significantly associated with hyperuricemia ($p = 0.0016$), while gender has a very little effects ($p = 0.1275$)¹².

These finding of our study are closed to the finding of another study, conducted by Inayat N et al, showing that the serum uric acid in all patients (n=46) was increased progressively and significant surge was observed in 43% (20/46) of patients at the end of 2-months intensive therapy. In this study, there was progressive significant increase in uric acid level from 0 to week 2, 6, 8, but a sharp increase in the levels of serum uric was observed in weeks 2 and 6, where the levels increased from 2.6 mg/dl to 7.2 mg/dl. This level remained stable between week 6 and 8, where a very small change (7.2 mg/dl -7.4 mg/dl) was observed. Although in our study, there is no such significant differences between the UA levels at different intervals of both groups but there is significant increase of UA levels (4.67 ± 0.72) at start of the therapy and after two months of the therapy (UA levels = 6.4 ± 0.91 in Cat-1 and UA levels = 6.6 ± 1.05) with p-value 0.01¹³.

Based on the result observed in this study show that significant hyperuricemia can occurs during intensive phase of anti tuberculosis treatment, especially in CAT-2 patients. However these are usually mild and self-limiting and do not need to stop the ATT. But severe symptomatic hyperuricemia may need a treat while keeping the ATT continuous.

CONCLUSION

The serum uric acid increases with anti-tuberculosis therapy, especially in CAT-2 patients. Though, it usually improved spontaneously without any intervention, but its level need to be closely monitored in tuberculosis patients and should be treated accordingly if symptoms appear.

Author's Contribution:

Concept & Design of Study: Jamaluddin

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Revisiting Critically: Nizamuddin, Abid Shah
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Prevalence, Etiology and Management of Hyponatremia in Hospitalized Patients

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ABSTRACT

Objective: The objective was to alleviate cerebral edema, not to correct sodium. So give to only severely symptomatic patients.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the National Hospital and Medical Center, Lahore, Pakistan over 90 days period from October 1, 2016 till December 31, 2016.

Materials and Methods: Total of 108 (4.2%) patients out of 2560 patients had hyponatremia defined as serum sodium level of less than 135 mmol/L. There were 60 (55.5%) male patients and 48 (44.4%) female patients, Average age was 56 years.

Results: Severe hyponatremia (defined as $\text{Na}^+ < 120$ mmol/L) was detected in 24 patients (22.2%). The largest group of hyponatraemic patients were euvolemic [48 (44.4%)], followed by hypervolemic [32 (29.6%)] and hypovolemia [28 (25.9%)]. Out of total 108, thirty (27.7%) patients fulfilled the criteria for syndrome of inappropriate anti diuretic hormone (SIADH). During the hospital stay, 4/108 (3.7 %) hyponatraemic patients died. None of the deaths were secondary to hyponatremia. Tolvaptan (a V2RA) was not given to any patient and only 4/108 (3.7%) received 3% saline. At discharge, 84/108 (77.7%) had serum sodium more than 135 mmol/L.

Conclusion: Hyponatremia is common in hospitalized patients of Pakistan. Euvolemic hyponatremia was the most common type, a significant number of which was secondary to SIADH. Management of hyponatremia is challenging but we were able to manage hyponatremia in most of our patients despite non-availability of 3% saline or V2 receptor antagonists.

Key Words: Euvolemic, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion.

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INTRODUCTION

Hyponatremia is very common in hospitalized patients worldwide. The prevalence varies in different studies and range from 5-30 %¹⁻³. The etiology also varies in different clinical settings and patient population. Euvolemic hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH) being the most common cause in hospitalized patients in most studies¹⁻². Management of hyponatremia has always challenged clinicians and nephrologists. Newer agents are changing the way we manage hyponatremia. Lack of V2 receptor antagonists and scarcity of hypertonic saline is making the management even more difficult in hospitalized patients in Pakistan. No data is available on prevalence, etiology and management related to hyponatremia in hospitalized patients in Pakistan.

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We did this cross sectional study to determine the prevalence, etiological factors and management of hyponatremia in a private hospital of Lahore, Pakistan. We also reviewed the literature to discuss available options for the management of different types and degrees of hyponatremia in hospitalized setting.

MATERIALS AND METHODS

All patients hospitalized at National Hospital and Medical Center, Lahore, Pakistan over 90 days period (October 1, 2016 till December 31, 2016) with serum sodium (Na^+) level of less than 135 mmol/L (Normal 135-145 mmol/L) were included in this study. Patients who have had prior history of chronic hyponatremia or hyponatremia during previous hospitalization were also included. The first admission serum electrolyte report was used as inclusion criteria. Patients who developed hyponatremia during hospitalization were also included. All patients with pseudo hyponatremia (secondary to Hyperlipidemia & hyperproteinemia) or hyponatremia secondary to mannitol or hyperglycemia were excluded thus including true hyponatraemic patients only. Standard diagnostic criteria were used to diagnose different etiologies of hyponatremia. Patients' volume status was assessed clinically as hypervolemic, euvolemic & hypovolemic.

Patients suspected of having pseudohyponatremia were excluded from study group. Only patients with 'true' hyponatremia were included. Following laboratory tests were obtained in all of the patients with hyponatremia. Serum electrolytes, complete blood count, renal function tests including blood urea nitrogen, serum creatinine, thyroid function tests, serum cortisol, serum uric acid, serum osmolality, random urine sodium, random urine osmolality, urine complete and chest x-rays. Ultrasound KUB, 2D Echocardiogram and serum BNP were done in selected cases as indicated. Normal serum sodium range in our hospital lab (Chughtai's Lab) is 135–145 meq/l, serum osmolality is 275–293 mosm/kg of water, and urine osmolality is 500–850 mosm/kg water. Hyponatremia is defined as $\text{Na}^+ < 135$ meq/l and severe hyponatremia defined as $\text{Na}^+ < 120$ meq/l. Endocrinology, cardiology and nephrology consultations were requested as needed. SIADH is diagnosis of exclusion and was defined by the classic Bartter-Schwartz criteria, which can be summarized as follows:

- Hyponatremia with corresponding hypo-osmolality
- Continued renal excretion of sodium
- Urine less than maximally dilute
- Absence of clinical evidence of volume depletion
- Absence of other causes of hyponatremia
- Correction of hyponatremia by fluid restriction

Patients were managed based on standard guidelines. If patient had hyponatremia of unknown duration or for more than 48 hours than that was considered chronic hyponatremia. For chronic hyponatremia sodium was not increased more than 10-12 meq in first 24 hours to avoid central pontine myelinolysis. Acute hyponatremia was defined as low serum sodium level developed within last 48 hours. Hypertonic saline, demeclocycline and tolvaptan were not available. Hyponatremia was managed by treating underlying cause, water restriction, oral salt tablets, normal saline with or without sodium bicarbonate and furosemide in various combinations. Hypertonic saline was given to only four patients who had very severe symptomatic hyponatremia, three with serum sodium of 105, 109, 110 mmol/L and fourth with sodium of less than 100 mmol/L. It was not easy to arrange hypertonic saline and in most cases family made this arrangements.

RESULTS

Total of 2560 patients were hospitalized during this 90 day time period and 108/2560 (4.2%) had hyponatremia with serum sodium of less than 135 mmol/L. Twenty two (20.3%) patients out of 108 had serum sodium less than 120. There were 60 (55.5%) males, 48 (44.4%) females. Mean age was 56 years. In most patients with mild hyponatremia stopping the causative drug or treating the underlying cause along with water restriction corrected sodium. In patients with

hypovolemia hyponatremia correcting the fluid deficit with normal saline helped correct serum sodium.

Following were the causes of hyponatremia:

Table No.1: Etiology of Hyponatremia. CLD = chronic liver disease, CHF = congestive heart failure.

Total with hyponatremia	108	(100%)
Euvoemia	46	
SIADH	30	(27.7%)
Hypothyroidism	2	(1.85%)
Adrenal insufficiency	2	(1.85%)
Drugs	10	(9.25%)
Primary polydipsia	2	(1.85%)
Hypervolemia	34	
CHF	12	(11.11%)
CLD	18	(16.6%)
Nephrotic syndrome	2	(1.85%)
ESKD on dialysis	2	(1.85%)
Hypovolemia	28	(25.9%)

Two patients each with hypothyroidism and adrenal insufficiency received thyroxine and steroids to correct sodium. A patient with primary polydipsia was counseled to restrict fluid and it corrected her sodium in hospital. But she was hospitalized again after 2 weeks with hyponatremia secondary to poor compliance with fluids and she was referred to psychiatry. Hyponatremia secondary to idiopathic SIADH, chronic liver disease (CLD), congestive heart failure (CHF) were most difficult to manage. Serum sodium stayed around 128-136 in most of these patients despite the use of furosemide. Four patients with very severe hyponatremia (serum sodium less than 100, 105, 109, 110 mmol/L) needed almost a liter of 3% saline to correct sodium initially and this helped to bring sodium to safe range of above 115-120 mmol/L. Many patients also responded to normal saline with sodium bicarbonate to create relatively hypertonic IV fluid (tonicity 1.5-2.5%). This bicarbonate solution was especially used in patients who had some degree of metabolic acidosis. Depending on the degree of serum bicarbonate, sodium and need to correct sodium, this fluid was prepared based on the recommendations of nephrologist. One patient had low sodium of unclear etiology but responded to holding pregabalin. Pregabalin was restarted by her physician and she came back in OPD with low sodium of 121 which responded again to just stopping pregabalin.

None of the patients developed any complications as a result of hyponatremia or treatments of hyponatremia. Most of these patients were managed in general ward except few with acute and severe hyponatremia who were managed in ICU. Almost 50% of patients lost for follow up but most of others had their serum sodium well in range except few with CLD, advanced CHF and idiopathic SIADH.

DISCUSSION

The prevalence of hyponatremia in our cohort of patients was 4.2%. Epidemiological studies have shown prevalence between 5-30% in various clinical settings depending on different etiological risk factors¹⁻³. The prevalence of hyponatremia in our study is somewhat lower than values mostly reported in western literature. Our slightly low prevalence could have been secondary to the fact we included all patients including obstetrics & gynecology, surgical, medical and short stay hospitalization. Many of these patients were otherwise healthy and had been hospitalized for short stay for elective surgery or delivery of newborn or for procedures like angiogram to rule out acute coronary syndrome etc. Recently, Sandar Win, Komal Patel, Maria V DeVita et al. reported a prevalence of 4.7% in their hospitalized patients. Our data showing prevalence of 4.2 % corresponds to the prevalence reported by them.

In terms of etiology of hyponatremia, we found, like others, SIADH as being the most common cause of hyponatremia in hospitalized patients¹⁻². CLD was also very common cause of hyponatremia. This was probably secondary to the fact that hepatitis B & C and hence cirrhosis and CLD are prevalent in south East Asia and Pakistan. In terms of etiological factors our study findings are consistent with other studies⁴.

Management of hyponatremia remains challenging and needs vast knowledge, multidisciplinary approach, non-pharmacological, pharmacological measures and availability of hypertonic saline, vasopressin receptor antagonist etc. Hyponatremia among hospitalized patients has been associated with increased morbidity and mortality, but whether the mortality is associated with hyponatremia itself or the underlying illness remains unclear⁵⁻⁸. Evaluation of the patients' volume status is important in assessing the type of hyponatremia, which will guide the type of management required. If the patient has serious symptoms of hyponatremia (e.g., seizures), then more rapid correction through the use of hypertonic saline may be necessary to prevent cerebral edema and complications⁸. Since hypertonic saline is not freely available and tolvaptan is not available at all, treatment of patients with severe hyponatremia could be difficult and challenging. We were able to manage all patients except few who required 3% saline. Based on our experience and after review of literature following could be the possible recommendations in our set up.

Treat underlying Cause: stop diuretics like hydrochlorothiazide, selective serotonin uptake inhibitors and other possible drugs. Treating underlying correctable cause of hyponatremia.

Water restriction: will work in all cases and should be the first recommendation irrespective of etiology. It will work wonders in patients with primary polydipsia. How

much water should be restricted can be estimated based upon patients sodium level, urine osmolality and current water intake. Fluid restriction is usually 1 to 1.5 L per day.

Salt Intake: can be increased to raise serum sodium. Salt restriction should be removed and salt can be liberalized in diet. Salt can be given in the form of salt (NaCl) tablets or capsules. Each capsule or tablet usually has around 500 mg of NaCl. Blood pressure and volume status should be monitored closely. Oral rehydrating solutions should be avoided given higher content of potassium unless potassium is low also.

Normal saline: The most common treatment option proposed for patients with hypovolemic hyponatremia is replacement of both salt and water through the intravenous infusion of sodium chloride solutions (6-8). Normal or hypotonic fluids should be avoided unless there is clear evidence of hypovolemia and dehydration. It can also make hypervolemic hyponatremia worse. In cases of SIADH the utilization of normal saline depends on urine osmolality which is usually fixed. If urine osmolality is less than 308 mmol/L, it might help to correct hyponatremia. If urine osmolality is more than 308 (usually more than 450 mOsm/kg H₂O in SIADH), hypotonic or normal saline will make hyponatremia worse since urine osmolality is fixed and free water will be retained after urine is excreted at higher osmolality. Addition of sodium bicarbonate can help increase the tonicity of solution and it will help correct hyponatremia. Furosemide can also help normal saline improve hyponatremia quicker by dumping more free water in urine since furosemide impairs renal tubular responsiveness to ADH.

Demeclocycline: it has been recommended in case of SIADH but not very useful secondary to side effects and poor efficacy. The effect of demeclocycline was non-significant in all analyses¹⁰ and its role is declining with the invent of newer V2 receptor antagonists like tolvaptans. Moreover it is not available in Pakistan.

Hypertonic saline: very useful when acute symptomatic and severe hyponatremia must be corrected promptly. Some center like SIUT, Shifa and shoukat khanum prepare their own 3% saline but it is not commonly available in pharmacies. In terms of replacement, desired sodium deficit can be calculated using the following formula.

$$\text{Na}^+ (\text{mEq given as 3\%}) = (\text{Na}^+ \text{ desired}) - (\text{Na}^+ \text{ measured}) \times \text{estimated TBW}$$

This gives the amount of sodium in mEq to be given as 3% saline over time t

There are 513 mEq of sodium in one liter of 3% saline. To determine the volume of hypertonic saline to be given over time t, divide the number of mEq of sodium to be given by 513 mEq/L

Then give this volume over time t. Addition of lasix can increase the efficacy of 3% saline.

The patient who had serum sodium of 105 and marked neurological symptoms of altered mental status, we decided hypertonic saline (3% saline, OSM =1026) should be given initially in view of the marked hyponatremia and neurologic symptoms. This is how we calculated the desired sodium rise of 15 mmol/L over first 30 hours.

Na^+ deficit = $0.6 \times 70 \times (120-105)$, = 630 meq =1200mL of 3% saline

At 40 ml/h over 30 h to raise the plasma Na^+ concentration by 0.5 meq/L/h.

Usually 50-100 ml/hr for 4-6 hours will increase sodium by 6-8 meq/L which is usually enough to reduce symptoms acutely

V2 Receptor Antagonist: Oral Tolvaptan is easily available in USA and has been recommended and approved to manage hyponatremia secondary to idiopathic SIADH, CHF and CLD. Tolvaptan is the only V2R antagonist available in Canada and is a selective oral antagonist of the V2 receptor, causing a dose-dependent increase of dilute urine (13-16). A four-year open-label extension study of the SALT trials, known as SALTWATER, found that the increases in serum sodium levels were maintained over longer periods of time.¹²⁻¹⁵

Unfortunately tolvaptan is not available in Pakistan. But if and when available the dose must be started at 15 mg daily and incrementally increased to maximum dose of 60 mg daily as needed. During tolvaptan use, water or fluids are not restricted to avoid rapid correction of sodium. It causes aquaresis or free water loss by inhibiting ADH receptor. It is indicated and FDA approved for hyponatremia due to SIADH, cirrhosis or CLD and CHF when aquaresis rather diuresis is needed because of hyponatremia. By causing free water loss and retaining sodium, it corrects sodium and treat fluid overload especially in CHF & CLD.

CONCLUSION

Hyponatremia is common in hospitalized patients of Pakistan. Euvolemic hyponatremia was the most common type, a significant number of which was secondary to SIADH. Management of hyponatremia is challenging but we were able to manage hyponatremia in most of our patients despite non-availability of 3% saline or V2 receptor antagonists.

Author's Contribution:

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

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Comparison of Negative Appendectomy Rate between Alvorado Score and Adult Appendicitis Score at Allama Iqbal Memorial Teaching Hospital Sialkot

Adnan Butt¹, Nimra Ikram¹ and Kamran Hamid²

ABSTRACT

Objective: To study Comparison of Negative Appendectomy rate between Alvorado score and Adult Appendicitis score at Idrees Teaching Hospital, Sialkot & Allama Iqbal Memorial Teaching Hospital, Sialkot.

Design of Study: Prospective study

Place and Duration of Study: This study was conducted at the Emergency department of Idrees Teaching Hospital, Sialkot & Allama Iqbal Memorial Teaching Hospital, Sialkot during April 2015 to April 2017.

Materials and Methods: We analyzed data of 1139 appendectomies prospectively over period of 2 years for negative appendectomies at emergency department of Allama Iqbal Memorial teaching Hospital Sialkot. Patients were divided in two groups (Group A 579 cases according to Alvorado score and Group B 560 cases according to Adult Appendicitis Score). Negative appendectomy rate for both groups was calculated after histopathology report. The Performa was designed to record age, gender, positive appendectomies and negative appendectomies. The data was analyzed for results on SPSS version 10.

Results: The incidence of appendectomy was highest (42.66%) cases 486 at the age group 15-25 years and this incidence went on decreasing with advancement of age. There was higher incidence (54.52%) 621 cases of appendectomy in male population and (45.47%) 518 cases in female population coming to the emergency department. According to histopathology the incidence of negative appendectomy was (19.22%) 219 cases in group A and (3.59%) 41 cases in group B but the incidence of positive appendectomy was (29.32%) 334 cases in group A and (42.58%) 485 cases in group B. According to Alvarado (MANTRELS) score the incidence of negative appendectomy was (19.22%) 219 cases but according to adult appendicitis score the incidence of negative appendectomy was (3.59%) 41 cases.

Conclusion: It showed that adult appendicitis score is much better than Alvarado score for diagnoses of appendicitis.

Keywords: Negative Appendectomy, Alvorado score, Adult Appendicitis score.

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INTRODUCTION

Intense an infected appendix is the most widely recognized sign for emergency surgery around the world, with rate of 1.17 for each 1000 and lifetime danger of 8.6% in men and 6.7% in ladies. The frequency is most elevated in youths and youthful grown-ups, however the rate of confounded an infected appendix indicates little change between various age groups^{1,2}.

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In spite of the fact that an exceptionally normal and long-known marvel, a ruptured appendix remains an analytic test for specialists and emergency doctors. Clinical conclusion alone prompts a negative appendectomy rate of 15 to 30%. The analysis is exceptionally trying for ladies of rich age^{3,4,5}. Early surgical mediation is the customary highest quality level for avoiding affixed puncturing. High rate of superfluous negative appendectomies, be that as it may, prompts pointless grimness and even mortality^{6,7}. The incessant utilization of figured tomography (CT) with its high affectability and specificity in finding of an infected appendix has diminished the quantity of negative appendectomies^{4,8,9}. Preoperative CT appears to profit most ladies 45 years of age and more youthful^{10,11}. The utilization of CT may, be that as it may, postpone appendectomy in clinically run of the mill instances of intense a ruptured appendix, and in this manner even raise the hazard for puncturing^{12,13}. Expanded utilization of CT is related with hoisted danger of disease particularly in youthful patients,

whose occurrence of intense a ruptured appendix is most prominent¹⁴. A few scoring frameworks for diagnosing an infected appendix as of now exist¹⁵⁻²¹. The best known is the Adult Appendicitis Score.

MATERIALS AND METHODS

We analyzed data of 1139 appendectomies prospectively over period of 2 years for negative appendectomies at emergency department of Idrees Teaching Hospital, Sialkot & Allama Iqbal Memorial teaching Hospital Sialkot. Patients were divided in two groups (Group A 579 cases according to Alvarado score and Group B 560 cases according to Adult Appendicitis Score). Negative appendectomy rate for both groups was calculated after histopathology report. The performa was designed to record age, gender, positive appendectomies and negative appendectomies. The data was analyzed for results on SPSS version 10.

RESULTS

There were two diagnostic scores for appendicitis as shown in following table.

Table No.1: Alvarado (Mantrels) score.

The Alvarado (Mantrels) Score .	Score
Symptoms	
Migratory RIF pain	1
Anorexia	1
Nausea and vomiting	1
Signs	
Tenderness (RIF)	2
Rebound tenderness	1
Elevated temperature	1
Labs	
Leukocytosis	2
Shift to left	1
Total	10

RIF, right iliac fossa

The incidence of appendectomy was highest (42.66%) cases 486 at the age group 15-25 years and this incidence went on decreasing with advancement of age (table 3). There was higher incidence (54.52%) 621 cases of appendectomy in male population and

(45.47%) 518 cases in female population coming to the emergency department (table 4).

Table No.2: Adult Appendicitis Score

Symptoms		Score
Pain in RLQ		2
Pain Relocation		2
RLQ Tenderness		3/1*
Guarding	Mild	2
	Moderate/Severe	4
Laboratory Tests		
Blood Leukocyte Count ($\times 10^9$)	>7.2 and <10.9	1
	>10.9 and <14	2
	>14	3
Neutrophil %	>62 and <75	2
	>75 and <83	3
	>83	4
CRP(mg/L) <24hr	4 and < 11	2
	11 and <25	3
	25 and <83	5
	>83	1
CRP(mg/L) >24hr	12 and <53	2
	53 and <152	2
	>152	1

RLQ right lower quadrant, CRP C reactive protein

*Men and women age 50+/women, age 16-49

Table No .3: Age distribution in appendectomies

Sr No	Age (Years)	Cases	Percentage
1	15-25	486	42.66%
2	26-36	248	21.77%
3	37-47	171	15.01%
4	48-58	132	11.58%
5	59- 69	81	7.11%
6	79-89	19	1.66%
7	90 & above	2	0.17%
	Total	1139	100 %

Table No.4:Gender Distributions in appendectomies

Sr No.	Gender	Cases	Percentage
1	Male	621	54.52%
2	Female	518	45.47%
	Total	1139	100 %

Table No. 5: Distribution of Positive and Negative Appendectomy according to histopathology

Sr. No.	Positive/Negative Appendectomy	Group A			Group B		
		Male (%)	Female (%)	Total (%)	Male (%)	Female(%)	Total(%)
1	Positive Appendectomy	175 (15.36%)	159 (13.95%)	334 (29.32%)	278 (24.40%)	207 (18.17%)	485 (42.58%)
2	Negative Appendectomy	113 (9.92%)	106 (9.30%)	219 (19.22)	20 (1.75%)	21 (1.84%)	41 (3.59%)
3	Other Pathology	16 (1.40%)	10 (0.87%)	26 (2.28%)	19 (1.66%)	15 (1.31%)	34 (2.98)
	Total			579 (50.83%)			560 (49.16%)

According to histopathology the incidence of negative appendectomy was (19.22%) 219 cases in group A and (3.59%) 41 cases in group B but the incidence of positive appendectomy was (29.32%) 334 cases in group A and (42.58%) 485 cases in group B (table 5). According to Alvarado (MANTRELS) score the

incidence of negative appendectomy was (19.22%) 219 cases but according to adult appendicitis score the incidence of negative appendectomy was (3.59%) 41 cases (table 6). It showed that adult appendicitis score is much better than Alvarado score for diagnoses of appendicitis.

Table No.6: Distribution of Positive and Negative Appendectomy according to Score

Sr. No.	Score	Positive Appendectomy		Negative Appendectomy		Other Pathology	
		Group A (%)	Group B (%)	Group A (%)	Group B (%)	Group A (%)	Group B (%)
1	Alvarado Score >7	246 (21.59%)	0 (0%)	36 (3.16%)	0 (0%)	10 (0.87%)	0 (0%)
2	Alvarado Score <5	35 (3.07%)	0 (0%)	111 (9.74%)	0 (0%)	7 (0.61%)	0 (0%)
3	Alvarado score 5-6	54 (4.74%)	0 (0%)	72 (6.32%)	0 (0%)	9 (0.79%)	0 (0%)
	Total	335 (29.41%)	0 (0%)	219 (19.22%)	0 (0%)	26 (2.28%)	0 (0%)
4	Adult Appendicitis score >16	0 (0%)	283 (24.84%)	0 (0%)	6 (0.52%)	0 (0%)	7 (0.61%)
5	Adult Appendicitis Score 11-15	0 (0%)	180 (15.80%)	0 (0%)	12 (1.05%)	0 (0%)	12 (1.05%)
6	Adult Appendicitis Score <10	0 (0%)	21 (1.84%)	0 (0%)	23 (2.01%)	0 (0%)	15 (1.31%)
	Total	0 (0%)	484 (42.49%)	0 (0%)	41 (3.59%)	0 (0%)	34 (2.98%)

DISCUSSION

Intense an infected appendix is the most widely recognized sign for emergency surgery around the world, with rate of 1.17 for each 1000 and lifetime danger of 8.6% in men and 6.7% in ladies. The frequency is most elevated in youths and youthful grown-ups, however the rate of confounded an infected appendix indicates little change between various age groups^{1,2}.

In spite of the fact that an exceptionally normal and long-known marvel, a ruptured appendix remains an analytic test for specialists and emergency doctors. Clinical conclusion alone prompts a negative appendectomy rate of 15 to 30%. The analysis is exceptionally trying for ladies of rich age^{3,4,5}. Early surgical mediation is the customary highest quality level for avoiding affixed puncturing. High rate of superfluous negative appendectomies, be that as it may, prompts pointless grimness and even mortality^{6,7}. The incessant utilization of figured tomography (CT) with its high affectability and specificity in finding of an infected appendix has diminished the quantity of negative appendectomies^{4,8,9}. Preoperative CT appears to profit most ladies 45 years of age and more youthful^{10,11}. The utilization of CT may, be that as it may, postpone appendectomy in clinically run of the mill instances of intense a ruptured appendix, and in this manner even raise the hazard for puncturing^{12,13}.

Expanded utilization of CT is related with hoisted danger of disease particularly in youthful patients, whose occurrence of intense a ruptured appendix is most prominent¹⁴. A few scoring frameworks for diagnosing an infected appendix as of now exist¹⁵⁻²¹. The best known is the adult appendicitis score^{20,21}.

CONCLUSION

It showed that adult appendicitis score is much better than Alvarado score for diagnoses of appendicitis.

Author's Contribution:

Concept & Design of Study: Adnan Butt
 Drafting: Nimra Ikram
 Data Analysis: Nimra Ikram, Kamran Hamid
 Revisiting Critically: Kamran Hamid, Adnan Butt
 Final Approval of version: Adnan Butt

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

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Comparison of Efficacy of Fosfomycin and Ceftriaxone in the Treatment of Urinary Tract Infections in Children

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ABSTRACT

Objective: To compare the efficacy of oral Fosfomycin and Intravenous ceftriaxone in the treatment of urinary tract infections (UTIs) in children upto 16 years of age.

Study Design: Randomized Clinical Trial (RCT)

Place and Duration of Study: This study was conducted at the Department Pediatrics, MTI HMC Peshawar from November 2016 to April 2017.

Materials and Methods: 390 children with UTI were randomly allocated in two groups A (195) to receive fosfomycin and B (195) to receive ceftriaxone. Urine culture was done at the 5th day of the start of therapy to determine the effect of drug.

Results: We found the mean age group of our whole sample was 9.4 ± 2.3 years. The mean age of children in group A was 9.4 ± 2.4 years while in group B it was 9.3 ± 2.2 years ($p = 0.949$). There were 61.5% males in group A compared to 67.7% in group B ($p = 0.204$). On follow up, repeat urine culture was performed in all children and it was observed that 72.3% children in fosfomycin group and 60% children in ceftriaxone group were having negative urine culture (efficacy) $p = 0.01$.

Conclusion: Fosfomycin is effective compared to ceftriaxone in the treatment of UTIs (urinary tract infections) in children.

Key Words: Urinary Tract Infection, Urine Culture, Pyrexia, Fosfomycin, Ceftriaxone, Abbreviations: HMC: Hayatabad Medical Complex, C & S: culture and sensitivity, UTI: Urinary tract infection.

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INTRODUCTION

Infants and young children are prone to multiple problems. UTIs are quite common in these age groups leading to acute, recurrent and chronic illnesses. UTIs occur approximately in 8% of girls and 1.7 % of in their first seven years of life, with a recurrence rate of 10% to 30%¹.

In pediatric age group the sample collection varies depending upon the age of the child from infants to adolescent². The clinical manifestations of urinary tract infection (UTI) in young patients are most of the time not specific and taking a urine sample in critical patients is extremely difficult³. In most of the cases UTI is missed and not diagnosed in time at primary care center⁴. Therefore it is recommended that clinicians at all level should obtain urine sample for routine examination and culture in acutely ill young children⁵.

Several pathogens cause urinary tract infections and the most frequent occurring is *Escherichia coli*. Other pathogens causing UTIs in children are *Klebsiella*, *Proteus*, *Enterobacter*, *Citrobacter* and *Enterococcus*⁶. Amoxicillin has been used as first line antibiotic for UTI and as an empirical therapy for a long time but due to increasing *E. coli* resistance this is no more favorable choice⁷. The growing resistance has been documented for cephalosporins for *Enterobacter* species in children⁸. Fosfomycin has not been used frequently for the treatment of urinary tract infections in the recent years. But its use has increased very recently because of increasing resistance to the routine used antibiotics in the treatment of the UTIs⁹. Though an old antibiotics, Fosfomycin has been used only for the treatment of uncomplicated urinary tract infections in routine¹⁰. Now a day, studies have defined the role of this medicine in several clinical condition and not merely uncomplicated UTIs^{11,12}. Fosfomycin has been used orally in treating young children with clinical diagnosis of cystitis¹³. One of the reasons of the high efficacy of the oral formulation of fosfomycin for the treatment of UTIs is its rapid absorption and achievement of high urinary concentrations and presence for several days in the blood¹⁴.

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The present study is designed to compare the efficacy of fosfomycin with ceftriaxone in the treatment of UTI in our local pediatric population. UTI among children is not an uncommon in our population and if not treated and managed well in time, it can lead to chronic complication like cystitis. This study is designed keeping in view the importance of treatment for UTI in children. The results of this study will be shared with other local pediatricians and if the efficacy of fosfomycin is found to be significantly more than ceftriaxone, we will recommend fosfomycin for the routine treatment of children with UTI.

MATERIALS AND METHODS

This RCT (randomized controlled trial) was carried out in the Pediatrics Unit Medical Teaching Institute Hayatabad Medical Complex, Peshawar from November 2016 to April 2017. Consecutive (non probability) sampling technique was used for all those pediatric patient who visited the tertiary level hospital. A total of 195 in each group keeping 77.5% efficacy of fosfomycin¹² and 66.2% efficacy of ceftriaxone¹⁴, 95% confidence interval and 80% power of the test, using WHO sample size calculations.

All children with urinary tract infection on urine culture with age group 5 to 16 years and either gender were included in the study. Patients with history of intake of any type of antibiotic in the last one week were excluded from the study.

RESULTS

The study was conducted on 390 children presenting with UTI. The mean age of the whole sample was 9.4 ± 2.3 years. The mean age of children in group A was 9.4 ± 2.4 years while in group B it was 9.3 ± 2.2 years. The difference was statistically not significant after applying independent sample T test with a p value of 0.949. While distributing the patients with regards to gender, we observed that the difference between both the groups was statistically not significant after applying chi square test. (P value 0.204).

Table No. 1: Age in Categories Between Both Groups (n= 195 each)

Age Group	Treatment Groups		Total
	Fosfomycin Group	Ceftriaxone Group	
5 to 8 years	63	51	114
	32.3%	26.2%	29.2%
> 8 to 12 years	120	117	237
	61.5%	60.0%	60.8%
> 12 to 16 years	12	27	39
	6.2%	13.8%	10.0%
Total	195	195	390
	100.0%	100.0%	100.0%

Table No. 2: Gender Distribution in Both Treatment Groups (n=195 each)

Gender of the Patient	Treatment Groups		P Value
	Fosfomycin Group	Ceftriaxone Group	
Male	120	132	0.204
	61.5%	67.7%	
Female	75	63	
	38.5%	32.3%	
Total	195	195	
	100.0%	100.0%	

Table No. 3: Comparison of Efficacy Between Treatment Groups (N=195 Each)

Efficacy of Drug	Treatment Groups		P Value
	Fosfomycin Group	Ceftriaxone Group	
No	54	78	0.01
	27.7%	40.0%	
Yes	141	117	
	72.3%	60.0%	
Total	195	195	
	100.0%	100.0%	

Table No. 4: Age Groups up to 8.00 Years Wise Stratification of Efficacy

Efficacy of the drugs	Treatment Groups		P Value
	Fosfomycin Group	Ceftriaxone Group	
No	0	24	< 0.001
	0.0%	47.1%	
Yes	63	27	
	100.0%	52.9%	
Total	63	51	
	100.0%	100.0%	

Table No. 5: Age Groups 8:01 to 12:00 Years Wise Stratification of Efficacy

Efficacy of the Drugs	Treatment Groups		P Value
	Fosfomycin Group	Ceftriaxone Group	
No	42	54	< 0.001
	35.0%	46.2%	
Yes	78	63	
	65.0%	53.8%	
Total	120	117	
	100.0%	100.0%	

All the patients in either group were subjected to standard dose of the drug according to international protocols. After 5th day of start of regime, repeat urine culture was performed in all children and it was observed that 72.3% children in fosfomycin group and 60% children in ceftriaxone group were having negative urine culture (efficacy). The difference was statistically significant after applying chi square test with a p value of 0.01.

Table 1 shows age categories, table 2 shows gender wise distribution of the patients while rest of the four tables show efficacy comparison in toto and in separate group respectively.

Table No. 6: Age Groups 12.01 to 16.00 Years Wise Stratification of Efficacy

Efficacy of the Drugs		Treatment Groups		P Value
		Fosfomycin Group	Ceftriaxone Group	
No		12	0	< 0.001
		100.0%	0.0%	
Yes		0	27	
		0.0%	100.0%	
Total		12	27	
		100.0%	100.0%	

DISCUSSION

Acute urinary tract infections (UTIs) are the most frequently occurring pathologies of pediatric age group and causing at least one episode of acute urinary tract infection in 8.4% of the girls and 1.7% of the boys in the first seven years of life. UTIs lead to frequent hospitalization if pediatric age group especially in the first year of life (40%)¹⁵. UTI is responsible for a majority of transient renal damage (app 40%) of children affected and permanent damage to some extent (about 5%)^{16, 17}. The commonest presenting features of UTI in pediatric age group are fever, lethargy, anorexia, and vomiting. The most notorious bug in causing of UTI is *Escherichia coli* in over 80% of cases¹⁸. Recurrence of UTI is a major issue (app 30%) and the risk factors include vesicoureteric reflux (VUR), bladder instability and previous infections. Recurrence of UTI occurs more commonly in girls than boys¹⁹. Febrile urinary tract infections have the highest incidence during the first year of life in both sexes, whereas non-febrile urinary tract infections occur predominantly in girls older than 3 years. No doubt UTI management is a real challenging task and involves multidisciplinary approach including pediatricians, and urologists. The important thing is that recurrence of the UTI should be tackled very effectively. The reason is that multiple courses of antibiotic can lead to multi-drug resistance in these kids^{20,21}.

Fosfomycin is an old antibiotic agent that has been used for the treatment of uncomplicated urinary tract infections in many clinical settings. In our study we found that Fosfomycin is highly effective in treating the routine urinary tract infections and is introduced orally with easy as compared to most of the antibiotics which needs parenteral administration which is more invasive and needs prolonged hospital stay or close supervision by health professionals. The overall response of UTIs in our study to Fosfomycin was quite encouraging as compared to intravenous administration of ceftriaxone. The infection clearance and course of the antibiotic

therapy was shorter and more effective in Fosfomycin group as compared to cephalosporin group. The duration of Fosfomycin was less than half and the response was 72.3 % as compared to 60% in ceftriaxone group. Efficacy of Fosfomycin has been studied isolated or compared with other antibiotics. The efficacy of this medicine has been found as high as 99 % in urinary tract infections²². A study conducted in Turkey by Hosbul T et al found only 2 % resistance to Fosfomycin in uncomplicated urinary tract infections²³. Florea C found that *E. Coli* urinary tract infections responded very well to Fosfomycin but the response was equally well to third generation cephalosporin as compared to first and second generation cephalosporin which was not encouraging²⁴.

CONCLUSION

Fosfomycin is highly effective compared to ceftriaxone in the treatment of UTI in children. However, the clinical significance of fosfomycin is on a rise not only for UTIs but also for other infections particularly gastrointestinal infections.

Recommendation: We recommend more randomized controlled trials with larger sample sizes and involving multiple centers to draw solid conclusions about the best therapy for pediatric UTI.

Author's Contribution:

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 Revisiting Critically: Muhammad Bilal Khattak, Arshia Munir
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Socioeconomic Status of Patients with End Stage Renal Disease and the Microeconomic Impact of Hemodialysis

Impact of
Socioeconomic
Status of
Hemodialysis
Patients

Amer Azhar, Mufti Baleegh-ur-Raheem Mahmood, Ahmad Zeb Khan and Tariq Ikram

ABSTRACT

Objective: The aim of this study is to exactly know the socioeconomic status and the microeconomic impact of End Stage Renal Disease in our Hemodialysis dependent patients.

Study Design: Descriptive / cross-sectional study.

Place and Duration of Study: This study was conducted at the Department of Nephrology, Khyber Teaching Hospital Peshawar, Pakistan from July 2015 to January 2016.

Materials and Methods: Data concerning the study questions pertaining to the socioeconomic status of hemodialysis patients and the microeconomic impact of hemodialysis dependency was collected on a proforma asking questions about the impact of hemodialysis dependency. Socioeconomic status of patients was assessed using the modified Kuppuswami socioeconomic scale.

Results: A total of 177 ESRD patients on maintenance Hemodialysis were studied, of which 111 (62.7%) patients were male (mean age 43.1 years, SD ± 14.8 , Range 18-70 years), while the remaining 66 were females (mean age 42.3 years, SD ± 15.2 , Range 18-80 years)(M:F=1.4:1). Despite Hemodialysis being free of cost, 47.4% patients were spending more than PKR 5000 per month as additional health related cost. Around 93.2% patients were currently unemployed as opposed to 43.5% before hemodialysis. Renal transplantation was not performed in majority (84.7%) patients due to the lack of affordability. Majority of our patients (84.8% males and 74.7% females) belonged to lower middle and upper lower socioeconomic classes.

Conclusion: Thus we conclude that hemodialysis dependency incurs a significant economic cost on our patients. The rate of unemployment is very high in our patients. Most of our patients belong to the lower socioeconomic groups. Other modalities of renal replacement therapy that keep the patients socioeconomically viable such as CAPD and transplantation should be utilized and subsidized instead of hemodialysis alone.

Key Words: End Stage Renal Disease (ESRD), Chronic Kidney Disease (CKD), Hemodialysis, Economic impact, Socioeconomic status.

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INTRODUCTION

Symptoms and complications related to End Stage Renal Disease (ESRD) severely compromise the physical and mental functionality of the patients.¹ This loss of functional capacity severely affects the ability of the patient to perform his living and occupational activities.

Renal Replacement Therapy (RRT) is offered to such patients to maintain their quality of life and functional status as near to normal as possible, so as to preserve their productivity.

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Hemodialysis (HD), the commonest modality of renal replacement therapy,² binds the patients to remain attached to hemodialysis machine for about 12 hours in a week, more commonly during the working hours of the day. This affects employability of the patients in addition to the already compromised functional status.³ The unemployment rate among hemodialysis patients is reported to be around 75%.⁴ Multiple studies have reported the adverse effects of unemployment, lower income and lower socioeconomic status of patients on their Quality of life (QOL), death rate, loss to follow up, malnutrition, hemoglobin levels and rate of renal transplantation.^{5,6}

The average age of newly diagnosed ESRD patients in the developing world is reported to be around 40 years, as opposed to the average age of around 60 years in the developed world.⁷ Thus the disease affects people at the prime of their age. A commentary on the burden of ESRD in India and Pakistan reported that, around 70% patients stopped RRT within the first 3 months due to lack of affordability. Of the patients who underwent Hemodialysis only 40% received regular Hemodialysis⁸

MATERIALS AND METHODS

This was a descriptive cross-sectional study, conducted at Department of Nephrology, Khyber Teaching Hospital Peshawar. Data was collected over a period of 06 months (July 2015 to January 2016) after the approval of synopsis. The Sample size was taken to be a minimum of 177, keeping 50% proportion of frequency of Hemodialysis dependent patients (empirical value), with 95% confidence interval and 5% margin of error. The population size was taken as 325, which is approximately the total number of hemodialysis patients in this hemodialysis center. Consecutive, non-probability sampling technique was utilized. All patients above the age of 18 years and both genders, being managed on maintenance Hemodialysis at this center were included in this study. Maintenance hemodialysis was defined as hemodialysis dependency for at least three months.

Approval was obtained from the hospital research and ethical committee. Informed consent was obtained from all patients after counseling. All patients were asked to fill a proforma and were assisted by a research assistant in this regard. The study proforma asked questions to assess the microeconomic impact of hemodialysis dependency on the individual patient and their families. The study proforma also contained the Kuppaswamy socioeconomic status assessment tool^{9,10} modified to the most recent all-India consumer price index for industrial workers (CPI-IW=266, September 2015),¹¹ with currency conversion to Pakistani rupee at the exchange rate of 1.58 (December 6th, 2015).¹² The Socioeconomic status of patients was categorized according to the Kuppaswamy Socioeconomic status scale as:-

Total score	Socioeconomic Class
26-29	Upper
16-25	Upper middle
11-15	Lower middle
5-10	Upper lower
< 5	Lower

RESULTS

A total of 177 ESRD patients on maintenance Hemodialysis were studied, of which 111 (62.7%) patients were male (M:F=1.4:1). The mean age for male patients was 43.1 years (SD $\pm$ 14.8, Range 18-70 years), while the mean age for females was 42.3 years (SD $\pm$ 15.2, Range 18-80 years). The impact of transportation for dialysis was assessed as "cost of travelling" and "transportation time" for a single dialysis session. Figure 1.

The health related cost of hemodialysis dependency was assessed as monthly medical expenditure. Figure 2. This data pertains to the two largest government facilities where hemodialysis, Erythropoietin and Iron supplements are provided free of cost to the patients.

Therefore at the time of acquisition of this data, patients were not exposed to these costs. However patients were still paying for medications and laboratory workup for other co-morbidities.

The employment status of our patients before and after hemodialysis dependency is depicted in figure 3.

None of the patients were receiving any financial assistance from any source apart from the free Hemodialysis facility. None of the patients had any health insurance policy which could assist them in bearing the financial cost of their disease.

All the patients were well informed of renal transplantation as a superior alternative to hemodialysis. The major reason for the patients not doing renal transplantation was reported by the patients as lack of affordability (84.7%), followed by non-availability of a kidney donor (8.5%), transplantation not offered by the physician (5.6%) and lack of medical fitness for transplantation (1.10%). None of the patients knew about CAPD as an alternate strategy of renal replacement therapy.

The socioeconomic status of the patients was assessed as described in methodology and is shown in figure 4.

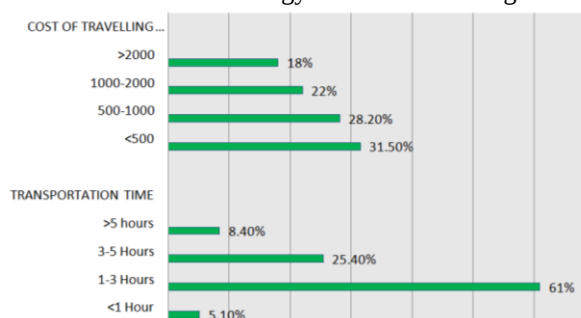


Figure No.1: Transportation

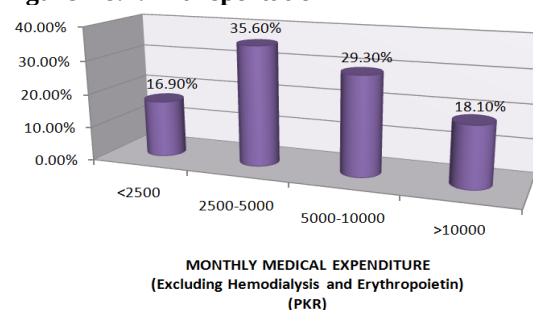


Figure No.2: Medical cost

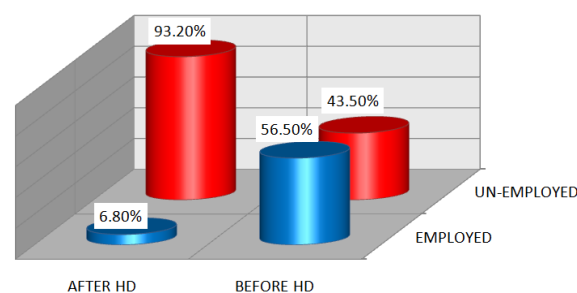


Figure No.3: Relationship of employment status of dialysis dependency.

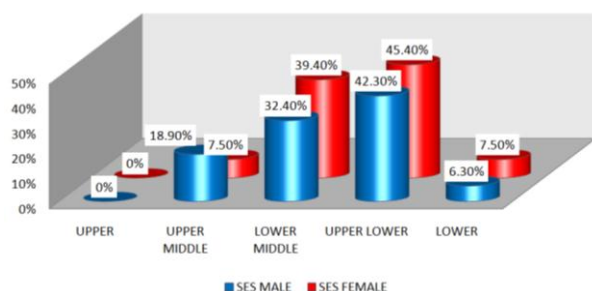


Figure No.4: Socioeconomic status.

DISCUSSION

In our study the mean age for male and female patients was 43.1 years and 42.3 years respectively. Other regional studies have reported similar mean age.^{13,14} This age is significantly younger than that reported for western populations' i.e. 60.2 years for Europe and 60.5 years for USA.¹⁵ Thus our patients are landing into Dialysis dependency at a much younger age as compared to the patients from more developed countries.

Our patients had a longer travel time and higher cost of travel for dialysis. Around 61% patients required a travel time of 1-3 hours while 25.4% patients required 3-5 hours of travelling time on the day of hemodialysis. Longer travelling time has been associated with greater mortality and lower quality of life in dialysis dependent patients.¹⁶ The UK Renal association guidelines recommend that the travel time to dialysis facility should be under 30 minutes.¹⁷ Around half of the patients (50.2%) were spending from PKR 500-2000 per session and 18% were spending even more than that in order to travel to and from dialysis center. Jeloka estimated the average monthly travel cost of ESRD patients in India to be 1654 ± 1085 INR (Indian rupees) per month.¹⁸ By today's exchange rate it converts to PKR 2577±1691 per month. Thus in our patients, transportation incurs a major financial burden on the patients.

Average cost of a single hemodialysis session was reported to be 4500 Indian rupees in 2012. This included direct cost (medical and non-medical) which was around 75% of the total cost and Indirect cost due to missed working hours and loss of job and income. If hemodialysis was done at the recommended frequency of three sessions a week, a minimum total sum of 13500 Indian Rupees per week (about 54000 Indian Rupees per month) was required.¹⁹ By today's exchange rate¹² this makes up to 7110 Pakistani rupees per session, 21330 per week, and 85320 rupees per month. Our data pertains to the two largest government facilities where hemodialysis and erythropoietin is provided free of cost to the patients. However patients were still paying for medications for other comorbidities. Around half (47.4%) patients were spending more than PKR 5000 per month as additional

health related cost. For our patients this cost is significant and our patients mostly, are unable to afford proper medical care even when hemodialysis is subsidized by the government.

Around 87% of patients were unemployed at the time of the study and additional 6.2% were retired from their service. Thus a total of 93.2% patients were unemployed. Only the remaining 6.8% of the total were currently employed after starting hemodialysis. Other studies from Pakistan have yielded similar unemployment rates.^{20,21} The unemployment rates in hemodialysis dependent patients reported from different regions of the world range from 71.1% to 88.5%.^{22,23} This loss of employment adversely affects Quality of life of ESRD patients,²⁴ and is also associated with psychiatric diseases.²² Only Around 43.5% of the patients were un-employed before the initiation of hemodialysis. Thus there was a significant increase in the unemployment rate after starting HD.

There is no insurance policy for our patients and for our patients the loss of earnings is not being compensated by any source. Mere subsidization of dialysis does not solve this problem and other therapies which allow a greater functional independence can help solve these issues. Patients with renal transplant have the highest employment percentages, followed by CAPD and lastly Hemodialysis.²⁵ In a study from Japan, 36% of Hemodialysis patients lost their employment as compared to only 10% CAPD patients.²⁶ Thus short of renal transplantation, CAPD could prove to be a viable option for our patients.

Renal transplantation and CAPD have the potential to allow the patient to continue his life activities as normally as possible. All of our patients recognized renal transplantation as an alternative to hemodialysis. Around 84.7% patients stated lack of affordability as a reason for not having kidney transplant. For 8.5% patients a kidney donor was not available. Thus only 6.7% of our patients are truly not suitable for transplantation and if efforts are made around 90% patients could possibly become renal transplant recipients successfully. When asked about CAPD, None of the patients knew about this modality suggesting that CAPD was not discussed with the patients. This confirms the general practice in our society, of nephrologists not offering CAPD to the patients. The institution of CAPD and further strengthening of renal transplantation can significantly contribute towards the socio-economic independence of our patients.

A great majority of patients, (84.8% males and 74.7% females) were in Lower Middle and Upper Lower Classes. This reflects the fact that government hospitals are primarily serving the poor masses. The socioeconomic class of ESRD patients significantly affects the disease and its outcome. Lower SES classes are more prone to progress to ESRD secondary to any cause while this trend progressively decreases for

higher SES classes.²⁷ Lower SES patients are also found to have more advanced disease at initial encounter.²⁸ Patients from higher SES classes have a better survival as compared to the lower groups.²⁹ Thus lower socioeconomic status could be an important factor affecting the already poor morbidity and mortality figures of our patients.

CONCLUSION

Thus we conclude that hemodialysis dependency incurs a significant economic cost on our patients and their families. Patients have to bear considerable cost even if hemodialysis itself is subsidized. The rate of unemployment is very high in our patients. Most of our patients belong to the lower socioeconomic group, which further aggravates the brunt of a resource draining disease. Measures to improve socioeconomic state and viability of hemodialysis patients need to be inculcated in any program directed towards management of these patients. Other modalities of RRT that keep the patients socioeconomically viable such as CAPD and transplantation should be utilized and subsidized instead of hemodialysis alone.

Author's Contribution:

Concept & Design of Study: Amer Azhar
 Drafting: Amer Azhar
 Data Analysis: Mufti Baleegh-ur-Raheem Mahmood, Ahmad Zeb Khan
 Revisiting Critically: Ahmad Zeb Khan, Tariq Ikram
 Final Approval of version: Amer Azhar

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

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Hematological Abnormalities with Low Dose Methotrexate in Rheumatoid Arthritis Patients

Hematological
Abnormalities of
Methotrexate in
Rheumatoid
Arthritis

Muhammad Abbas¹, Amir Khan¹, Muhammad Khalid², Sajjad Ali Shah¹ and Shah Zaib¹

ABSTRACT

Objective: Methotrexate is the most commonly used DMARD by the physicians in Pakistan. It is very effective in arresting the disease process and preventing joint damage. Prolong use of methotrexate may cause some unwanted effects including hematological abnormalities which may be a cause of extra concern for the physicians and patients as well.

Study Design: Descriptive/cross sectional study.

Place and Duration of Study: This study was conducted at the Medical Units of Mardan Medical Complex (M.M.C) from January 2015 to December 2016.

Materials and Methods: Adult 112 male and female patients with rheumatoid arthritis were enrolled in the study. American college of rheumatology (ACR) / European league against rheumatism (EULAR) diagnostic criteria was used for rheumatoid arthritis. They were given 7.5 mg of methotrexate once weekly and were followed for six months with regular monthly full blood count.

Results: Out of 112 patients 23 were males and 89 were females. They age of patients ranged from 21 to 60 years. Mean age of the study population was 36.66 years. Anemia was found in six patients (5.4%), leucopenia was found in four patients (3.6%), thrombocytopenia was found in three patients (2.7%) and pancytopenia was found in only one patient (0.9%).

Conclusion: Hematological abnormalities is a common side effect of low dose methotrexate and these patients require regular monitoring of blood count for detecting and treatment of these abnormalities.

Key Words: Methotrexate, Hematological abnormalities, rheumatoid arthritis (RA).

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INTRODUCTION

RA is an autoimmune systemic disorder characterized by chronic polyarticular synovitis due to release of different cytokines leading to irreversible joint damage¹. Since MTX in low doses is less toxic, cost low and is highly effective so it is mostly preferred DMARD by the clinicians for rheumatoid arthritis^{2,3}. Half life of MTX is 7-10 hrs, it is mainly metabolized in the liver and excreted by the kidneys^{4,5}. The rate of discontinuation of MTX in RA due to toxicity has been found from 10-37%^{1,6}. Few retrospective studies have shown the rate of thrombocytopenia around 4.1% and pancytopenia around 0.96-1.4%¹.

Since rheumatoid arthritis is an autoimmune disorder and methotrexate is an immunosuppressive agent so it is preferred in rheumatoid arthritis⁷. Methotrexate is usually given in low doses to patients with rheumatoid arthritis.

G,I,T complications are more commonly encountered side effects while stomatitis, hepatotoxicity, skin rashes, pulmonary and hematological toxicity are less common side effects with low dose methotrexate in rheumatoid arthritis patients⁸. 3% of the methotrexate treated rheumatoid arthritis patients develop hematologic toxicity⁹. Pancytopenia is rare but its occurrence is increased with co-administration of other drugs, low folate levels, hypoalbuminaemia, old age, renal dysfunction, dehydration, and concomitant infection^{9,10}. Pancytopenia observed with methotrexate may be acute or chronic. Acute pancytopenia due to methotrexate is secondary to allergic type of reaction and is rapid in onset while chronic pancytopenia is more insidious in onset^{11,12}. Dehydration increases the hematologic toxicity of methotrexate particularly in elderly patients with compromised renal function^{13,14}. NSAIDs reduces the renal excretion of methotrexate and contributes to its hematological toxicity^{15,16}.

Methotrexate is most commonly used DMARDs by the physicians for rheumatoid arthritis in Pakistan. Though it is a very effective drug but it may cause some undesirable effects which may be distressing for the patients. Hematological abnormalities are one of the such effects which may occur with low dose methotrexate in rheumatoid arthritis. This study is aimed to know the exact prevalence of hematological

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abnormalities in these patients so that it can be identified and managed accordingly.

MATERIALS AND METHODS

This was a descriptive cross sectional study conducted at Medical units of Mardan medical complex (M.M.C) from January 2015 to December 2016. Study included 112 diagnosed adult cases of rheumatoid arthritis. American college of rheumatology (ACR)/European league against rheumatism (EULAR) diagnostic criteria was used for diagnosing rheumatoid arthritis¹⁷. Pancytopenia was defined as W.B.C count $< 4 \times 10^9/l$, Hb $< 11\text{gm/dl}$, and platelet count $< 130 \times 10^9/l$. To find out the frequency of low dose methotrexate induced hematological abnormalities in rheumatoid arthritis patients was the main objective of study. Ethical and research committee of the hospital was approached for the approval of study. Patients were selected by non-probability convenient sampling method after an informed verbal consent. Adult male and female patients were selected for study. At the start of study patients were thoroughly examined and routine baseline investigation were done. Only those patients were enrolled for study in whom there was no evidence of anemia, leucopenia and thrombocytopenia. Anemia was defined as Hb $< 11\text{gm/dl}$, leucopenia was taken as W.B.C count $< 4 \times 10^9/l$ and thrombocytopenia was considered to be of platelet count less than $130 \times 10^9/l$. Patients with renal insufficiency or hepatic abnormalities were also excluded from study. Similarly patients with major illnesses like Diabetes Mellitus, Hypertension and ischemic heart diseases were excluded. Patients already taking other disease modifying anti rheumatic drugs were included only with a normal blood count. Then these patients were given 7.5 mg of methotrexate weekly and were followed for six months with a regular monthly full blood count. All information was recorded on Performa for analysis using Statistical Software for Social Sciences (SPSS) version 15. Frequency and percentages were calculated for categorical variables, while mean $\pm$ SD was calculated for numerical variables. Also hematological abnormalities were stratified among age and gender to see the effect modifications. All results were presented in the form of tables and graphs.

RESULTS

Out of 112 diagnosed cases of RA, 23 (20.5%) were males and 89 (79.5%) were females. Age range was from 21 to 60 years with mean age of 36.66 years. Mean hemoglobin was 13.11, mean total leukocyte count (T.L.C) was 6733.8750 and mean platelet count was 296053.5714. Age and smoking were two other parameters included in the study but they bear no significant association with the hematological abnormalities (p-value > 0.05). Similarly gender and

body weight has no significant association with hematological abnormalities, (p-value > 0.05). Percentages and means of the study population and different hematological parameters are given in tables, and most of these changes were observed mainly in the last two months of follow up except pancytopenia which was observed early in the first month of the study.

Table No. 1: Age and Gender of Patients.

Gender of patient	No of patients	% of total n	Min	Max	Mean	Std. Deviation of age
Male	23	20.5%	30	58	43.7826	9.94511
Female	89	79.5%	21	60	34.8315	8.96488
Total	112	100.0%	21	60	36.6696	9.82403

Table No. 2: Hematological Parameters

Para-meters	No of patients	Mean	Std. Deviation	Mini	Max
Heamo-globin	112	13.1161	1.86357	9	17
Total white cell count	112	6733.8750	1904.99553	3000	10000
Platelets count	112	296053.5714	86442.61199	90000	450000

Table No. 3: Hematological Abnormalities

Abnormality	No. of patients	% of patients
Anemia	6	5.4%
Leucopenia	4	3.6%
Thrombocytopenia	3	2.7%
Pancytopenia	1	0.9%

DISCUSSION

Adverse drug reactions during the treatment of rheumatoid arthritis with DMARDs can lead to significant morbidity and mortality. It is estimated that between 3% and 11% of hospital admissions can be attributed to these drug side effects. Any drug can conceivably have a toxic or undesired effect. However, a substantial portion of undesirable drug reactions may be preventable and treatable if detected early.

Pancytopenia a rare but potentially fatal complication of methotrexate therapy, may occur acutely within one to two months of starting methotrexate and is not dependent on dose and route of administration. Acute pancytopenia is due to an allergic type of reaction and is rarely avoidable, more commonly it occurs late as a cumulative effect^{11, 12}. In our study we were encounter with a single patient who developed pancytopenia acutely.

Methotrexate is inhibitor of enzyme dihydrofolate reductase leading to decrease production of thymidylate and DNA. Tissues undergoing rapid cellular turnover

with a high fraction of cells in S phase cycle (oral mucosa, G.I tract , bone marrow cells and testicular tissue) are more susceptible to its cytotoxic effect. Low levels of intracellular folates have been found in hepatocytes and peripheral blood lymphocytes of RA patients treated with MTX^{18,19}. Folate supplementation have been found to be beneficial in reducing hepatotoxicity , mucosal and G .I side effects²⁰, but up till now no studies have shown beneficial role of folic acid supplementation on MTX induced hematological abnormalities . This also occurs in our study as all our patients were receiving folic acid supplementation. Stomatitis precede or accompany pancytopenia and may be taken as a warning sign²¹. Patients with mucositis and neutropenia have four times higher risk of septicemia than individuals without mucositis²². These ulcers not only provide route of entry for endogenous oral flora but are also favorable site for secondary infections. Our single patient with pancytopenia did not develop oral lesions it may be due to fact that he developed pancytopenia acutely.

Hematological toxicity with low dose MTX occurs in 2-4% of cases²³. Our study correlates with these findings. Renal impairment or reduced renal blood flow as it occurs with NSAIDs increases the frequency of hematological toxicity²⁴. Therefore MTX is contraindicated in any patients with a GFR less than 30 ml/min²⁵. Though we did not included patients with renal impairment in our study but NSAIDs may interfere with the study results as almost all of the patients were on NSAIDs for symptomatic control of pain which need further studies on large scale to confirm this relation.

Edelman et al in his study reported age as a major contributor for MTX induced hematological toxicity through an unknown mechanism²⁶. In our study age was found to be insignificant risk factor (p value > 0.05). We follow our patients for only six months, it may be due to prolong duration of treatment with MTX in elderly patients that may cause hematological abnormalities which needs further workup. The main limitation in our study was simultaneous use of other DMARDs by our patients as well and that may have an effect on hematopoietic system along with methotrexate in rheumatoid arthritis patients.

According to pharmacokinetics of methotrexate, the drug and its metabolite is highly plasma proteins bound, hypoalbuminemia will lead to high level of free methotrexate and consequently high risk of myelosuppression. This may be a contributing factor to myelosuppression in our study as rheumatoid arthritis patients consumes high level of albumin at site of inflammation leading to hypoalbuminemia, once hematological abnormalities occur discontinuation of the drug is the only option but the use of G-CSF and methylprednisolone are also beneficial.²⁷

CONCLUSION

Methotrexate induced hematological abnormalities are relatively common and it may be a cause of increasing concern for the physicians and patients as well. Fortunately life threatening pancytopenia is rare. Certain factors such as advance age, renal dysfunction and interaction of methotrexate with certain drugs increases the chances of pancytopenia. So it is advisable to exercise extreme care in the use of methotrexate specially in the presence of associated risk factors causing pancytopenia, by regular monitoring of blood count. Prompt discontinuation of methotrexate with development of hematologic toxicity is the only solution.

Author's Contribution:

Concept & Design of Study:	Muhammad Abbas
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Data Analysis:	Sajjad Ali
Revisiting Critically:	Amir Khan
Final Approval of version:	Amir Khan

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

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Immunoexpression of Cytokeratin 20 and Cytokeratin 7 in Colorectal Adenocarcinoma in Association to Histological Grade

Muhammad Tariq¹, Pervez Mohammad¹ and Muhammad Ashraf Salam²

ABSTRACT

Objective: To observe the immunoexpression of CK20/CK7 as a tumor marker and its association with histological grade of colorectal adenocarcinoma.

Study Design: Observational / cross sectional study.

Place and Duration of Study: This study was conducted at the Department of Pathology and Surgery, Post Graduate Medical Institute Lahore and Jinnah Medical College Peshawar from July, 2013 to February, 2015

Materials and Methods: Surgical specimens / paraffin blocks of 60 histopathologically diagnosed cases of colorectal adenocarcinoma were included in this study. Three sections, 4µm- thick from each blocks were cut and were stained with H&E and for CK20 and CK7 immunostain respectively. All the slides were evaluated for colorectal adenocarcinoma along with expression of CK20 and CK7.

Results: CK2-/CK7 – immune-phenotype was seen in 38 out of 60 (63.33%) cases of colorectal adenocarcinomas. While the CK20+/CK7+ immunophenotype was detected in 9 out of 60 (15%) cases of colorectal adenocarcinomas. Similarly the CK20-/CK7- immunophenotype expression pattern was observed in 11/60 (18.33%) cases of colorectal adenocarcinomas. We also observed the CK20 expression in 47 out of 60 (78.33%) and CK7 expression in 11 out of 60 (18.33%) in colorectal adenocarcinomas.

Conclusion: There is an association of histological grade and pattern of expression of CK20/CK7.

Key Words: Cytokeratin 20 (CK20), cytokeratin 7 (CK7), colorectal adenocarcinoma, immunohistochemistry (IHC).

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INTRODUCTION

The use of tumor biomarkers is two thousand year old which has been published in old Egyptian papyrus, in which inflammation of breast was differentiated from breast carcinoma (Waxman, 1985)¹. According to the history the 1st cancer indicator in modern medication was recognized by Bence-Jones in 1846 (Waxman, 1985)¹. The glycoprotein molecule was collected from specimens of carcinoma colon, exposed the initial cancer antigen far ahead labeled as carcinoembryonic antigen (Gold and Freeman, 1965)².

Tumor markers consists of different types of materials like the cell surface antigens, hormones, enzymes, proteins, oncofetal antigens, oncogenes and receptors (Diamandis, 2002)³. The major role of these markers is screening and early detection, to confirm the diagnosis and prognosis of treatment (Lindblom and Liljegren, 2000; Sokoll and Chan, 2004; Goedegebuure et al., 2004, Cooper, 2004).^{4,5,6,7}

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The main use of biomarkers in medical treatment is to confirm the diagnosis. It can also be used for the follow up of patient who is taking treatment of cancer (Cooper, 2004).⁷

The Cytokeratins (CKs) are the major complex collection of intermediate filaments proteins. Their role is very important in the growth and differentiation of the epithelial cells and are crucial for the normal tissue morphology and physiology. These intermediate filaments proteins show specificity in both normal tissue and in their tumors. Due to this unique property immunohistochemistry of intermediate filaments is extensively used in histopathology (Moll et al., 1982)⁸. Cytokeratins up to some extent are resistant to degradation and are thus providing resistance to surrounding stress. Barrier defects, inflammation, hyperproliferation and dedifferentiation are keratin related diseases, showing their essential contribution to epithelial functions (Schwarz et al., 2015)⁹.

So far, twenty distinct cytokeratins have been discovered. On the basis of molecular weight and isoelectric facts cytokeratins were categorized and classified into 2 groups:

Type one (1) and type two (2) cytokeratins.

The type 1 “cytokeratins comprising of acidic, low molecular weights (40-56.6 kDa) proteins contains e.g. CK10, CK11, CK12, CK13, CK14, CK15, CK16, CK17, CK18, CK19, and CK20.

The type 2 “cytokeratins include basic, high molecular weight (52-67 kDa) proteins including CK1, CK2, CK3, CK4, CK5, CK6, CK7, CK8, and CK9 Bragulla & Homberger, 2009, (Iwatsuki & Suda, 2010).

As defined by Bayrak et al. (2011)¹⁰ cytokeratin 7 (CK7) is basic (type II) and cytokeratin 20 (CK20) is acidic (type I) cytokeratins. Their expression was deliberated in different primary and metastatic malignancies and this appearance pattern was found to be altered in colorectal carcinomas regarding the histological grade. CK7 was identified in 17.3% and CK20 in 81.1% cases of colorectal adenocarcinomas. CK7-/CK20+ had the highest proportion (65.8%) in colorectal carcinomas. The CK7-/CK20+ immunophenotype was detected in 15.3%, CK7-/CK20- in 16.9% and CK7-/CK20- in 2% colon adenocarcinomas. CK20 positively was more common in low grade carcinomas than in high grade carcinomas (85.1% versus 47.6%) (Bayrak et al; 2011)⁸. The CK7-/CK20+ phenotype is highly sensitive and specific markers founded in colorectal carcinoma (Bayrak et al; 2012). The objective of this study was to observe the immunoexpression of CK20 & CK7 in colorectal adenocarcinoma as a Tumor markers and see the association.

MATERIALS AND METHODS

This study was performed at the Department of Pathology and Surgery. Post Graduate medical Institute Lahore & Jinnah Medical College Peshawar. Sample collection was done from July 2013 to February 2015, keeping in view the inclusion and exclusion criteria. Written informed consent was taken and recorded. The study was approved by the ethical committee. The patients having colorectal adenocarcinoma were selected according to the following recruitment criteria:-

Both male and female patients of all ages diagnosed histopathologically as primary colorectal adenocarcinoma were included in this study.

The patients already on chemotherapy and radiotherapy were excluded.

60 colorectal Adenocarcinoma Biopsy were included in this study. After recording history and findings of physical examination each biopsy was placed in a plastic jar and immersed in tenfold volume of 10% buffered formaline solution. The jar was labeled with the patient name, age, sex and registration number. A proforma was attached to each case. All relevant clinical information like presenting complaints, duration, report of investigations etc were recorded. Detailed gross examination of the specimen 1.Color 2.Weight 3.Size 4. Cut surface was carried out and findings were recorded.

Tissue processing was done according to Spencer and Bancroft, 2008. All the specimens were fixed in 10% buffered formaline solution. After twenty four hours of

fixation, representative tissue sections were administered in automated processor in ascending alcohol concentrations and numerous change of xylene. Afterward dispensation, paraffin blocks were prepared in L-shaped metallic moulds. A rotatory microtome was used to obtain 3 to 4 micron thick sections. These sections were taken on the albumenized slides and were processed for staining with Haematoxylin and Eosin staining was done as per standard protocol. (Kiernan, 2008; Gamble.M, 2008)¹¹.

Microscopy was performed by using Binocular Microscope (Olympus) for the histopathological diagnosis and categorization of colorectal adenocarcinomas (2000; Fleming, 2012.)¹².

Staining Cytokeratin 20 and Cytokeratin 7 Immunohistochemical (IHC) was performed by using commercially available (Dako, Denmark) and reagents according to manufacturer's instructions. Press et al., 2005).¹³

Data Analysis: Data was analyzed by the method of Levesque, 2007 using SPSS version 20. Qualitative data, like expression of CK20 and CK7 was presented in the form of frequency and percentages. The association among the qualitative variables was calculated and analyzed statistically using chi square test. Quantitative data like age was given in the form of mean $\pm$ S.D. A P-value ≤ 0.05 was measured as statistically significant.

RESULTS

The study was consisted of sixty histopathologically diagnosed cases of colorectal adenocarcinomas. A detailed history of each case was recorded age, sex, complaints and site of colorectal biopsy was recorded. The immunostaining was carried out on all cases for CK20 and CK7 and expression was observed.

The descriptive statistics of age (in years) of 60 cases of colorectal adenocarcinomas, the minimum age was 16 years and maximum 85 years, the mean age of the patients was 54.40 ± 19.66 years. There were 6 out of 60 (10%) patients 16-29 years, 9 out of 60 (15%) 30-49 years, 34 out of 60 (5.67%) patients were 50-69 years and 11 out of 60 (18.33%) were above 70 years of age. In this study there were 33 out of 60 (55%) males and 27 out of 60 (45%) females patients.

The histological grades of tumors was also assessed as shown in Figure 1, Grade-` was seen in 26/60 (43.33%) Grade 2 15/60 (25%) and Grade 3 was seen in 19/60 (31.67%).

The CK20/CK7 immunophenotype stain results and frequencies of different immunophenotype positively is given in Table 1.

The CK20 and CK 7 expression were imposed with tumors grade Table 2 showing the different vesicles showing P value and its significances.

The CK20-/CK7- immunophenotype was detected in 10/19 cases (52.63%) in high grade carcinoma and in

1/41 cases (2.44%) in low grade carcinoma ($X^2 = 23.201$; p-value = 0.001) highly significant

Similarly CK20+/Ck7+ immunophenotype was observed in 8/19 cases (42.1%) in high grade carcinoma and in 1/41 cases (2.44%) in low grade carcinoma ($X^2 = 19.986$; p-value = 0.031) significant.

While CK20+/Ck7+ immunophenotype was expressed in 2/19 cases (10.52%) in high grade carcinoma and in 0/41 cases (0%) in low grade carcinoma ($X^2 = 0.599$; p-value = 0.435) insignificant.

The results of this study indicate that the association exists among Ck20/Ck7 expression and the grade of colorectal adenocarcinoma.

Table No. 1: Ck20/Ck7 Stain Results

Results	Frequency	Percentage (%)
CK20 ⁺ /CK7 ⁻	38	63.33%
CK20 ⁻ /CK7 ⁻	11	18.33%
CK20 ⁺ /CK7 ⁺	9	15.00%
CK20 ⁻ /CK7 ⁺	2	3.33%
Total	60	100%

Table No. 2: Different Variables Showing P-Value and its Significance

Variables	P-value	Significance*
CK20 Positivity (low grade vs high grade)**	0.035	Significant*
CK7 Positivity (high grade vs low grade)	0.039	Significant*
CK20+/CK7- Immunophenotype (low grade vs high grade)	0.000	Highly Significant*
CK20-/CK7- Immunophenotype (high grade vs low grade)	0.001	Highly Significant*
CK20+/CK7+ Immunophenotype (high grade vs low grade)	0.031	Significant*
CK2-/CK7- Immunophenotype (high grade vs low grade)	0.435	Insignificant

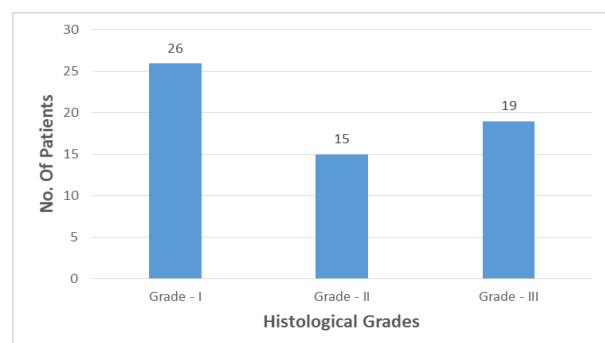


Fig- 1: Histological Grades **Grade I (well differentiated), Grade II (moderately differentiated) and Grade III (Poorly differentiated). Grade I and Grade II is low grade and Grade III is high grade.

Note: - Grade I (well differentiated), Grade II (moderately differentiated) and Grade III (poorly differentiated) Grade I and Grade II is low grade and Grade III is high grade. Grade II (moderately differentiate adenocarcinoma immunostain CK20 shown in Fig 3 and immunostain CK7 (Fig 4).

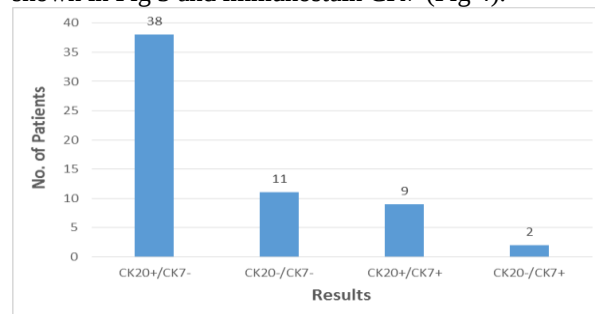


Figure No.2: Frequencies of different immunophenotype positivity *Association is significant at p-value ≥ 0.05 **Grade I (well differentiated), Grade II (moderately differentiated) and Grade III (poorly differentiated). Grade I and Grade II is low grade and Grade III is high grade.

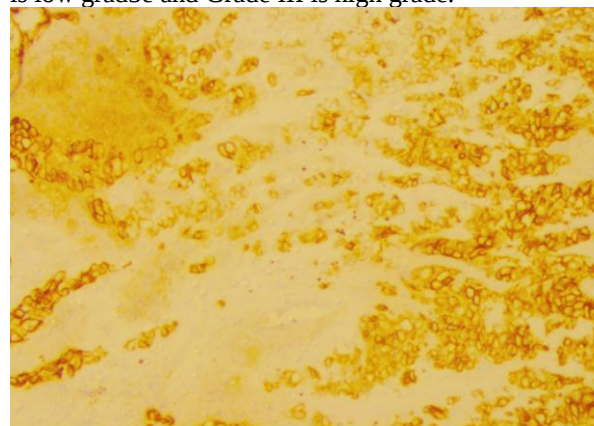


Fig-3: Moderately differentiated (Grade II) adenocarcinoma (Immunostain CK20+ X40)

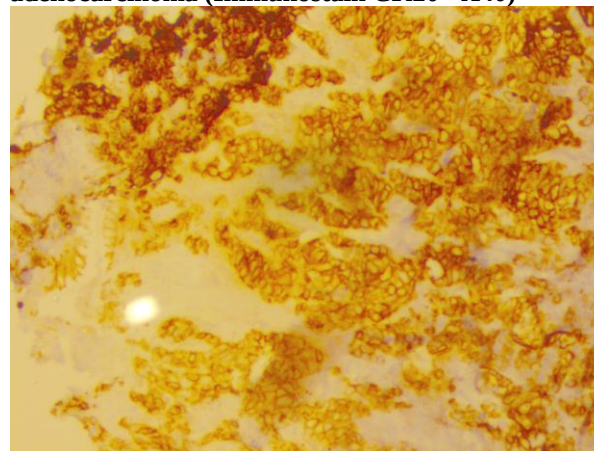


Fig-4: Moderately differentiated (Grade II) adenocarcinoma (Immunostain CK7+ X40)

DISCUSSION

Cytokeratin (CKs) are the major complex collection of intermediate filaments proteins. Their role is very important in the growth and differentiation of the epithelial cells and are crucial for the normal tissue morphology and physiology. These intermediate filaments protein show specificity in both normal tissue and their tumors. Due to this unique property immunohistochemistry of intermediate filaments is extensively used in histopathology 2010.

A study conducted by Bayrak et al; (2012)¹⁴ claimed that CK20 was detected in 99/118 (83.89%) and CK7 was expressed by 26/118 (2%) of colorectal adenocarcinomas. These observations are in accordance with the present study.

The studies are required to find the role of CK20 and CK7 in high grade colorectal adenocarcinomas, a study was conducted by (Hernandez et al; 2005)¹⁵ in their findings claimed that CK7 expression and CK20 loss are highly associated to high grade colorectal adenocarcinomas. These observations are also seen our study.

A study also observed that in colorectal adenocarcinoma loss of CK20 was associated with high tumor grade, $P \leq 0.001$ (significant) as has also been seen in the present study.

According to our observations the CK20 and CK7 patterns of expression varied according to histological grade in colorectal adenocarcinomas. CK20 was expressed in 81.1% and CK7 in 17.3% cases of colorectal adenocarcinoma. CK20+/CK7- had the highest proportion (65.8%) in colorectal adenocarcinomas. The CK20+/CK7- immunophenotype was identified in 15.3%, CK20-/CK7- in 16.9% and CK20-/CK7+ in 2% colorectal adenocarcinomas. CK20 positivity was more common in low grade adenocarcinomas than in high grade adenocarcinomas (85.1% versus 47.6%), more or less similar results were recorded in this study.

A significance difference in the relative expression of CK20 and CK7 between malignant and normal colorectal tissues and by the tumor differentiation was detected in this study. Specifically, it was demonstrated that compared with normal tissues, colorectal adenocarcinomas were likely to be highly positive for CK20 (both in CK20+/CK7- and CK20/CK7+ immunoprofiles). Furthermore, compared with low grade colorectal adenocarcinomas, high grade colorectal adenocarcinomas showed a higher proportional of CK20+/CK7+, CK20-/CK7- and CK20-/CK7+ immunoprofile.

CONCLUSION

This study concludes that there is an association of histological grade and pattern of expression of CK20/CK7.

Author's Contribution:

Concept & Design of Study:	Muhammad Tariq
Drafting:	Pervez Mohammad
Data Analysis:	Muhammad Ashraf Salam
Revisiting Critically:	Pervez Mohammad, Muhammad Ashraf Salam
Final Approval of version:	Muhammad Tariq

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Effect of Covering of Head on Phototherapy Induced Hypocalcemia in Full Term Neonates with Jaundice

Phototherapy
Induced
Hypocalcaemia
in Neonates with
Jaundice

Rahida Karim, Jahanzeb Khan Afridi and Mariam Farooq

ABSTRACT

Objective: To see the effect of head covering on frequency of phototherapy induced hypocalcaemia in full term neonates with jaundice.

Study Design: Case control study.

Place and Duration of Study: This study was conducted at the Department of Pediatrics, Hayatabad Medical Complex, Peshawar from 01.07.2016 to 31.12.2016.

Materials and Methods: In this study the total sample size was 128 patients using 13.88% preparation of hypocalcemia among neonates with lead covered during phototherapy 95% confidence interval and 6% margin of error. More over consecutive (Non probability) sampling technique was used for sample collection.

Results: Our study show that in cases group mean age was 11 days with SD $\pm$ 3.27. Where as in control group mean age was 10 days with SD $\pm$ 2.93. In cases group 62% neonates were male, 38% neonates were female. Where as in control group 65% neonates were male, 35% neonates were female. In cases group 15% neonates had hypocalcaemia. Where as in control group 42% neonates had hypocalcaemia.

Conclusion: Our study concludes that head covering on frequency of phototherapy induced hypocalcaemia is 15% in full term neonates with jaundice.

Key Words: Head Covering, Phototherapy, Hypocalcaemia, Neonates, Jaundice

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INTRODUCTION

Jaundice is one of the common presentations in neonates during first week of life. Worldwide 60% full term neonates are estimated to be affected by jaundice¹. In Pakistan a study showed that 27.6% new-borns from an area of Karachi were referred to neonatal centre with jaundice.² In North America and Europe 0.4 to 2.7 per 100,000 live births develop kernicterus while in developing countries it is reported as 3% of total neonatal hospital admissions.³

In some neonates it may result in acute bilirubin encephalopathy which can progress to kernicterus.¹ Early and aggressive treatment of hyperbilirubinemia can prevent this serious complication. Mainstay of treatment is phototherapy and exchange transfusion¹. These therapies decrease unconjugated bilirubin to non-toxic levels. Improved phototherapy equipment and techniques have reduced the need of exchange transfusions.^{4, 5}

Phototherapy is associated with some complications including skin rash, diarrhoea, hyperthermia, dehydration, DNA damage, degeneration of retina, bronze baby syndrome, patent ductus arteriosus in preterm neonates and hypocalcaemia. Hypocalcaemia in new-borns causes apnoea, convulsion and tetany. It can also cause long-term complications such as mental retardation, physical disability, and educational failure.^{6, 7}

To prevent hypocalcaemia during phototherapy intravenous calcium is used in some studies but it may result in cardiac arrest or hypotension. So some means are required to prevent hypocalcaemia during phototherapy.

A latest study was done in Iran in which heads of neonates were covered during phototherapy and it was observed that frequency of hypocalcaemia is less in study group (13.88%) than control group (38.88%).⁸ To my knowledge no such study has been done in our province and being working in busy tertiary care hospital like ours it is of great benefit for both neonate and hospital to treat such common condition with such an easy way (by covering the heads of neonates). The results of this study will be shared with local paediatricians to increase awareness and to design future strategies for the treatment of phototherapy induced hypocalcemia.

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MATERIALS AND METHODS

This was case control study conducted in department of Pediatrics, Hayatabad Medical Complex, Peshawar from 01.07.2016 to 31.12.2016.

The sample size was 128, using 95% confidence interval, and 90% power of the test and 6% margin of error. Sampling technique was consecutive (Non-probability).

Neonates of both sexes, with gestational age ≥ 37 week, birth weight than 2500 grams with normal calcium level and hyperbilirubinemia were included in the study.

Babies with history of asphyxia, hypothyroidism, hemolytic anemia and sepsis were excluded, all these condition may lead to disturbed serum calcium level.

Data Collection Procedure: Approval was taken from hospital ethical committee. After evaluating neonates for inclusion and exclusion criteria, written informed consent was taken from parents. Full term healthy infants were divided into two groups randomly with the help of computer generated codes and placed in envelopes. In one group head was not covered (control group) and in other head was covered with stockinet cap (case group) during phototherapy. Sex, birth weight, serum total bilirubin levels and serum calcium levels, was checked before start of phototherapy. Complete blood picture with reticulocyte count, C-reactive protein, blood culture and sensitivity and thyroid function test was done before phototherapy to rule out haemolytic anaemia, sepsis and hypothyroidism. Routine phototherapy was instituted with 4 lamps, 40 watts, blue light with a wave length of 420-470 nanometres and at a distance of 40 cm from the body surface. Serum Calcium levels and serum total bilirubin was repeated 48 hours after starting phototherapy.

Data Analysis: All data was entered and analysed by using SPSS version 16.0. Frequencies and percentages for qualitative variables like gender and hypocalcaemia. Mean and standard deviation was calculated for quantitative variables like age, birth weight, calcium level and bilirubin levels. Hypocalcaemia was stratified with age, gender, birth weight to see the effect modification. Post stratification chi-square tests were used in which $P \leq 0.05$ was considered as significant. All the results were presented in the form of tables and charts and odds ratio were also be calculated.

RESULTS

A total of 128 patients were observed to determine the effect of head covering on frequency of phototherapy induced hypocalcaemia in full term neonates with jaundice and the results were analyzed as:

Age distribution among two groups was analyzed as in cases group 68(53%) neonates were in age 1-10 days, 38(30%) neonates were in age 11-20 days and 22(17%) neonates were in age 21-28 days. Mean age was 11

days with SD ± 3.27 . Where as in control group 64(50%) neonates were in age 1-10 days, 45(35%) neonates were in age 11-20 days and 19(15%) neonates were in age 21-28 days. Mean age was 10 days with SD ± 2.93 . (table 1)

Gender distribution among two groups was analyzed as in cases group 79(62%) neonates were male, 49(38%) neonates were female. Where as in control group 83(65%) neonates were male, 45(35%) neonates were female. (table 2)

Body weight among two groups was analyzed as in cases group 87(68%) neonates had weight < 3 kg, 41(32%) neonates had weight ≥ 3 kg. Mean weight was 2 kg with SD ± 1.83 . Where as in control group 83(65%) neonates had weight < 3 kg, 45(35%) neonates had weight ≥ 3 kg. Mean weight was 2.5kg with SD ± 1.27 .

Calcium level among two groups was analyzed as in cases group 67(52%) neonates had calcium level 1.5 - 1.9 mmol/L, 61(48%) neonates had calcium level 1.9 - 2.25 mmol/L. Mean calcium level was 1.9 mmol/L with SD ± 1.51 . Where as in control group 64(50%) neonates had calcium level 1.5 - 1.9 mmol/L, 64(50%) neonates had calcium level 1.9 - 2.25 mmol/L. Mean calcium level was 2 mmol/L with SD ± 1.96 . (table 3)

Bilirubin level among two groups was analyzed as in cases group 67(52%) neonates had bilirubin level ≤ 257 $\mu\text{mol/L}$, 61(48%) neonates had bilirubin level > 257 $\mu\text{mol/L}$. Mean bilirubin level was 260 $\mu\text{mol/L}$ with SD ± 11.83 . Where as in control group 64(50%) neonates had bilirubin level ≤ 257 $\mu\text{mol/L}$, 64(50%) neonates had bilirubin level > 257 $\mu\text{mol/L}$. Mean bilirubin level was 259 $\mu\text{mol/L}$ with SD ± 10.91 . (table 4)

Hypocalcaemia among two groups was analyzed as in cases group 19(15%) neonates had hypocalcaemia, 109(85%) neonates didn't had hypocalcaemia. Where as in control group 54(42%) neonates had hypocalcaemia, 74(58%) neonates didn't had hypocalcaemia. P value was 0.0001 and the odds ratio was 0.2389. (table 5).

P value and odds ratios of hypocalcaemia with respect to age groups were (0.0004; 0.2363) in age group 1-10 years, (0.0089; 0.2566) in age group 11-20 years, (0.0402; 0.2171) in age group 21-28 years. (table 6)

P value and odds ratios of hypocalcaemia with respect to gender were (0.0002; 0.2456) in male, (0.0025; 0.2281) in female.

P value and odds ratios of hypocalcaemia with respect to weight were (0.0001; 0.2409) with weight < 2 kg, (0.0049; 0.2346) weight > 2 kg.

Table No.1: Age Distribution (n=256)

Age	Case	Control
1-10 days	68(53%)	64(50%)
11-20 days	38(30%)	45(35%)
21-28 days	22(17%)	19(15%)
Total	128(100%)	128(100%)
Mean and SD	11 days ± 3.27	10 days ± 2.93

T test was applied in which P value was 0.0105

Table No.2: Gender Distribution (n=256)

Gender	Case	Control
Male	79(62%)	83(65%)
Female	49(38%)	45(35%)
Total	128(100%)	128(100%)

Chi square test was applied in which P value was 0.6040

Table No.3: Calcium Level (n=256)

Calcium level	Case	Control
1.5 - 1.9 mmol/L	67(52%)	64(50%)
1.9 - 2.25 mmol/L	61(48%)	64(50%)
Total	128(100%)	128(100%)
Mean and SD	1.9 mmol/L ± 1.51	2 mmol/L ± 1.96

T test was applied in which P value was 0.6479

Table No.4: Bilirubin Levels (n=256)

Bilirubin level	Case	Control
≤ 257µmol/L	67(52%)	64(50%)
> 257µmol/L	61(48%)	64(50%)
Total	128(100%)	128(100%)
Mean and SD	260 µmol/L ± 11.83	259 µmol/L ± 10.91

T test was applied in which P value was 0.4827

Table No.5: Association of Hypocalcemia with Covered and un Covered Head (n=256)

Hypocalcemia	Case	Control
Yes	19(15%)	54(42%)
No	109(85%)	74(58%)
Total	128(100%)	128(100%)

Chi square test was applied in which P value was 0.0001
Odds ratio: 0.2389

Table No.6: Stratification of hypocalcemia w.r.t age distribution (n=256)

Age	Hypocalcemia	Case	Control	P value	Odd ratios
1-10 days	Yes	10	27	0.0004	0.2363
	No	58	37		
Total		68	64		
11-20 days	Yes	6	19	0.0089	0.2566
	No	32	26		
Total		38	45		
21-28 days	Yes	3	8	0.0402	0.2171
	No	19	11		
Total		22	19		

DISCUSSION

Jaundice is one of the common presentations in neonates during first week of life. Worldwide 60% full term neonates are estimated to be affected by jaundice¹. In Pakistan a study showed that 27.6% new-borns from an area of Karachi were referred to neonatal centre with jaundice.² In North America and Europe 0.4 to 2.7 per 100,000 live births develop kernicterus while in developing countries it is reported as 3% of total neonatal hospital admissions.³

Our study show that in cases group mean age was 11 days with SD ± 3.27. Where as in control group mean age was 10 days with SD ± 2.93. In cases group 62% neonates were male, 38% neonates were female. Where as in control group 65% neonates were male, 35% neonates were female. In cases group mean weight was 2 kg with SD ± 1.83. Where as in control group mean weight was 2.5kg with SD ± 1.27. In cases group mean calcium level was 1.9 mmol/L with SD ± 1.51. Where as in control group mean calcium level was 2 mmol/L with SD ± 1.96. In cases group mean bilirubin level was 260 µmol/L with SD ± 11.83. Where as in control group mean bilirubin level was 259 µmol/L with SD ± 10.91. In cases group 15% neonates had hypocalcaemia, 85% neonates didn't had hypocalcaemia. Where as in control group 42% neonates had hypocalcaemia, 58% neonates didn't had hypocalcaemia.

A latest study was done in Iran in which heads of neonates were covered during phototherapy and it was observed that The mean±SD weight and age of the neonates were 3080±389.3 grams and 4.52±1.3 days, respectively. 32 (44.4%) neonates were boys and 40 (55.6%) were girls. The average time of phototherapy was three days (range: 3-5 days). The mean±SD serum bilirubin level was 14.3±1.2 mg/dl. Hypocalcaemia was found in 14 (38.88%) out of 36 newborns in the control group⁸

As far as adverse events of exchange Transfusion in both groups were concerned, based on our observations we found out that more neonates suffered from Hypocalcemia in comorbid group as compared to control group (29.03% vs 9.67%) which were statistically significant (p<0.00637). This conforms to many studies in literature which have consistently found higher proportions of neonates suffering from hypocalcemia. This is readily explained by different pathophysiological mechanisms which lead to deranged metabolic functions in neonates suffering from comorbid conditions like Sepsis, severe anemia, Pneumonia, and as a consequence blood calcium level drops more readily in such babies. However sex stratification in both comorbid and control group lead to the observation that male neonates suffering from hypocalcemia were relatively higher than female neonates (34.21% vs 20.83%) and (10% vs 9.37%). This is in contrast to what we found from some other studies in the literature where it has been reported that more female neonates suffered from Hypocalcemia as compared to male neonates.^{9, 10}

Romagnoli and colleagues were the first to suggest an association between hypocalcaemia and phototherapy in neonates.¹² Other researchers also observed a significant decrease in serum calcium levels in newborn rats after exposure to fluorescent day light.¹¹ In another study on 20 term and 20 preterm neonates with hyperbilirubinemia, 75% of term and 90% of preterm

neonates developed hypocalcaemia after phototherapy.¹³ The results of the above mentioned studies are consistent with ours. In one study hypocalcaemia was observed in 30% of the term neonates receiving phototherapy¹⁴ which is lower than the above mentioned studies. We found that three infants in the control group with calcium level below 7 mg/dl and were controlled by a physician.

The role of calcium in the body includes blood coagulation, neuromuscular excitability, cell membrane integrity and function, and cellular enzymatic and secretory activity. Cellular permeability to sodium ions and increased cell membrane excitability are the signs of hypocalcaemia and other non-specific signs are apnea, seizure, jitteriness, increased extensor tone, clonus, hyper-reflexia, and stridor.¹⁵

Studies on 63 full-term newborns weighting more than 2500 grams, confirmed the emergence of hypocalcaemia after phototherapy, and researchers recommended prophylactic calcium for one of the infants who developed apnea.¹⁶ In one study, 27.3% of the premature infants who were irritable had hypocalcaemia during phototherapy. Moreover, vitamin D had no role in the pathogenesis of phototherapy induced-hypocalcaemia¹⁷ and administration of calcium was thus recommended during phototherapy.^{12, 15}

Hypocalcaemia in infants may be symptomatic or asymptomatic.¹⁸ Some studies have reported asymptomatic hypocalcaemia in neonates.¹² None of the newborns in our study had symptomatic hypocalcaemia and had phototherapy-induced hypocalcaemia.

In addition, sometimes hypomagnesaemia and hypocalcemia can occur concomitantly. One study reported that 16 out of 29 neonates developed concomitant hypomagnesaemia and hypocalcaemia.⁹ In case of decreased calcium levels, infants might also need magnesium. But in our study, no significant difference in magnesium levels was found between the two groups 48 hr after starting phototherapy ($P=0.24$), which indicated that none of the infants had magnesium amount below 1.2 mg/dl. It was not necessary to give magnesium to the infants with hypocalcaemia.

It is suggested that covering the pineal gland only helps prevent hypocalcaemia. The level of calcium in the control group reached the normal range after phototherapy. In fact, light affected melatonin concentration followed by a decrease in serum calcium level. This study showed that neonates requiring phototherapy were at a higher risk of developing hypocalcaemia.

CONCLUSION

Our study concludes that head covering on frequency of phototherapy induced hypocalcaemia is 15% in full term neonates with jaundice.

Author's Contribution:

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Data Analysis:	Rahida Karim, Marium Farooq
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Comparison of Fibrinogen Level and Factor VIII in Single and Multiple Vessels Ischemic Heart Disease

Ayesha Samad Dogar

Fibrinogen Level
and Factor VIII
in Single
Ischemic Heart
Disease

ABSTRACT

Objective: To determine the levels of fibrinogen and FVIII in single and multiple vessels ischemic heart disease patient's.

Study Design: Cross sectional / comparative study.

Place and Duration of Study: This study was conducted at the Department of Pathology, Post Graduate Medical Institute and Punjab Institute of Cardiology, Lahore from 24th October 2014 to 20th April 2015.

Materials and Methods: The study included 80 diagnosed ischemic heart disease patients who were divided into three groups, group 1 comprised of 40 patients with single vessel disease followed by group 2a with double vessel and group 2b were with multiple vessel disease. The parameters studied in these groups were risk factors like age, gender, hypertension, smoking, positive family history; number of vessels and the level of FVIII and fibrinogen and the subsequent data was recorded. Mean $\pm$ standard deviation, frequency distribution and percentages were calculated. SPSS version 20 was utilized to obtain statistical significance. Pearson's chi-square and Fisher's exact test were applied.

Results: In the present study, there were 80 diagnosed IHD patients out of which 40 (50%) had single vessel disease and 40(50%) had double and multiple vessels disease. Mean $\pm$ SD of fibrinogen was 305.1 ± 56.7 with a p- value of 0.85. Mean $\pm$ SD of FVIII was 191.2 ± 48.2 with a p- value of 0.80.

Conclusion: In the present study the levels of fibrinogen was raised in single vessel disease and FVIII were increased in multiple vessel disease patients. Hence it was concluded that these patients can be screened out on the basis of these two haemostatic parameters as they play a significant role in ischemic heart disease patients.

Key Words: Ischemic heart disease (IHD), Factor VIII (FVIII), Fibrinogen.

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INTRODUCTION

Ischemic heart disease (IHD) is a leading cause of global morbidity and mortality which accounts for 17.3 million deaths worldwide and is expected to raise by 2030 to 23.3 million¹. It is a growing global public health problem which is contributing to 30% mortality and 10% of disease burden². Worldwide it is affecting the quality and expectancy of life while placing a huge burden on the community as a whole³⁻⁴. IHD is growing in South Asians parallel to the industrial world; Pakistan with a population of 140 million has shown a high prevalence of over 30% of the population in over 45 years. Currently in Pakistan one in four of the middle aged adult are suffering from IHD⁵. In Pakistan the prevalence of IHD is 2.3% in male population.

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Statistics reveal that the chance of suffering from myocardial infarction in an average healthy adult before 60 years of age is one in five and the chance of dying is one in fifteen⁶. Pakistan is highly ranked in the world regarding IHD risk with 30% to 40 % mortality claiming 200,000 lives/year⁷.

In IHD there is restriction to the blood flow and failure of the oxygen delivery due to accumulation of atherosclerotic plaque in the coronary arteries resulting in platelet aggregation and thrombus formation which deprives myocardial cells of oxygen⁸.

Fibrinogen factor (1) is a water soluble glycoprotein with a molecular weight of 340 KDa. It is synthesized by the hepatocytes acts as an acute phase reactant and it is a key component of blood coagulation system⁹⁻¹⁰. Among all the coagulation factors of plasma the highest concentration is of fibrinogen¹¹. Fibrinogen is the main protein of coagulation process which is converted to fibrin by the action of thrombin and forms a clot that helps to reduces blood loss and initiates repair¹². It contributes in the formation of plaque in atherosclerosis and participates in the coagulation cascade as a precursor of fibrin, stimulates platelet aggregation, increases blood viscosity, promotes smooth muscle proliferation, migration and regulates cell adhesion⁹.

Multiple Metaanalysis based on the growing number of prospective epidemiological studies reported fibrinogen having a direct, independent statistically significant association with IHD. Elevated fibrinogen level also contributes to the premature development of IHD in 25-37 years and in < 45 years of age group. Caerphilly study conducted in South Wales concluded that fibrinogen has the potential to increase the prediction of IHD in middle aged men. Angloscandinavian Cardiac Outcome Trails (ASCOT) concluded that fibrinogen is a strong independent predictor of IHD⁹.

Meadle has reported the association between hemostatic parameters like elevated fibrinogen with increased mortality rate in IHD individuals. Lowe has emphasized on the fact that high fibrinogen levels have been seen in cardiac patients with multiple stenosed vessels as compare to single stenosis or absent stenosis¹³.

FVIII a β_2 - globulin is produced in the liver, spleen and lymph nodes. In plasma 95% of FVIII circulates in a FVIII-vWf complex. FVIII plays a role in activating FX which directly generates thrombin, to produces stable fibrin and also it participates in clot formation. FVIII-vWf complex provide help in adhesion of platelet to the arterial subendothelial while resulting in its increased concentration in damaged vessel regions¹⁴.

In the coagulation cascade FVIII acts as a cofactor with FIX to activate FX. It plays an active role in the formation of thrombin activation and generation of a fibrin-rich thrombus¹⁵. Multicenter Progetto Lombardo Athero-Thrombos (PLAT) study suggested that elevated clotting factors like FVIII, fibrinogen, vWf and/or leucocytosis leads to ischemic event¹⁴.

Result of Northwick Park Heart Study indicated that in one third of the population with highest FVIII levels, the risk of IHD will be 44 % compared to one third with the lowest FVIII level. Infarction caused increase in FVIII level and the extent of elevation might be a reflection of infarction size, thus offering an alternative explanation than hypercoagulability for the prognostic values of FVIII level after heart injury¹⁶.

MATERIALS AND METHODS

The study was conducted at the Department of Pathology, Post Graduate Medical Institute (PGMI) Lahore from 24.10.2014 to 20.4.2015. Diagnosed cases of IHD who underwent coronary angiography were selected from Punjab Institute of Cardiology. Forty single vessels and forty multiple vessels IHD patients were taken in which obstructive lesions was >70% in any one coronary artery.

The patients were informed and consent was taken before blood sampling. A questionnaire was filled for each patient, samples were collected and tests were performed to collect the required data.

Blood was drawn from the ante-cubital veins. 9 parts of blood and 1 part of 3.8% trisodium -citrate was centrifuged for ten minutes at room temperature at

2500xg. The supernatant plasma was placed in 1.5ml tubes and the sample was frozen at -20°C. Test were performed on the sample after thawing at 37°C. Test was performed on an Automated Blood Coagulation Analyzer Sysmex CA- 550. According to the standard procedure laid down in the literature of the FVIII Kit and fibrinogen kit (Clauss quantitative assay).

Inclusion criteria:

1. Age >25 years
2. All diagnosed cases of ischemic heart disease undergoing angiography.

Exclusion criteria: Patients suffering from any of the following were excluded from the study

1. Peripheral arteriopathy
2. Acute pulmonary, liver and renal diseases
3. Pregnancy
4. Coagulation disorders
5. Venous thromboembolism
6. Disseminated malignancy
7. Patients who are on drugs like anticoagulant and oral contraceptive pills (OCP's)
8. Diabetes Mellitus

RESULTS

Age Distribution in the Study Groups: The minimum age in the study group was 30 years and maximum age was 80 years with a Mean $\pm$ SD 54.5 $\pm$ 9.49. Age distribution showed that (42.5%) of the patients were between 51-60 yrs and (22.5%) were above 60 yrs. (Table 1)

Table No. 1: Age Distribution in the Study Groups

Age group	1 (1VD)	2a (2VD)	2b (3VD)	%age	Total
<40years	5	0	1	7.5	6
41-50 years	11	5	6	27.5	22
51-60 years	17	5	12	42.5	34
>60 years	7	1	10	22.5	18
Total	40	11	29	100	80

Key: 1 (1VD) = group 1 with one vessel disease 2a (2VD) = group 2a with two vessel disease, 2b (3VD) = group 2b with multiple vessel disease. n=frequency and %=Percentage Using Fischer exact test, p value = 0.25 (Non significant)

Table No. 2: Gender Distributions in the Study Groups

Sex	1 (1VD)	2a (2VD)	2b (3VD)	%age	Total Freq. (n)
Male	35	10	26	88.8	71
Female	5	1	3	11.3	9
Total	40	11	29	100	80

Key: 1=group1 with one vessel disease (1VD), 2a group2 with 2vessel disease, 2b group with 3vessel disease. Using Fischer exact test, p value = 0.93 (Non significant)

Gender Distributions in the Study Groups: The study population is divided into three groups those in group1 with single vessel were 35 male followed by 5 females. In group 2a are IHD patients with double vessel involvement while group 2b represents multiple vessel involvement 26 male patients (Table 2)

Hypertension in the Study Groups According to the Number of Vessels Involved IHD patients on antihypertensive were 28/80 out of which 13 patients had single vessel disease (Table 3)

Table No. 3: Hypertension in the Study Groups According to the Number of Vessels Involved

Hypertension	1(1VD)	2a(2VD)	2b (3VD)	Total
No	27	8	17	52
Yes	13	3	12	28
Total	40	11	29	80

Key: 1=group1 with one vessel disease (1VD), 2a group2 with 2vessel disease, 2b group with 3vessel disease. Using Fischer exact test, p value = 0.68 (Non significant)

Assessment of Smokers According to the Number of Vessels Involved IHD 19 had single vessel disease whereas 15 had multiple vessel disease (Table 4)

Table No. 4: Assessment of Smokers According to the Number of Vessels Involved

History of smoking	1 (1VD)	2a(2VD)	2b(3VD)	Total
No	21	5	14	40
Yes	19	6	15	40
Total	40	11	29	80

Key: 1=group1 with one vessel disease (1VD), 2a group2 with 2vessel disease, 2b group with 3vessel disease. Using Pearson Chi-Square, p value = 0.90 (Non significant)

Fibrinogen Level in the Study Groups: The Fibrinogen level in 80% of the ischemic heart disease patients was within normal range as none of them had any acute episode during the chronic phase of the disease. Hyperfibrinogenemia was reported in only 20% of study group (Table 5)

Table No. 5: Fibrinogen Level in the Study Groups

Fibrinogen (mg/dl)	1(1VD)	2a(2VD)	2b(3VD)	Freq. & %age n
Normal (181-350mg/dl)	31	9	24	64 (80)
High (>350 mg/dl)	9	2	5	16 (20)
Total	40	11	29	80 (100)

Key: 1=group1 with one vessel disease (1VD), 2a group2 with 2vessel disease, 2b group with 3vessel disease. n=frequency and %= percentage. Using Fischer exact test, p value = 0.85

FVIII Level in the Study Groups: FVIII level was elevated in 11 patients of group 1, 3 patients of group 2a and in 10 patients of group 2b with had multiple vessel disease. Elevated FVIII level was observed only in 30% of the study population whereas 70% had FVIII level within the normal range (Table 6)

Table No. 6: FVIII Level in the Study Groups

FVIII (%)	1 (1VD)	2a (2VD)	2b (3VD)	Freq. & %age
<200%	29	8	19	56 (70)
>200%	11	3	10	24 (30)
Total	40	11	29	80 (100)

Key: 1(1VD) = group1 with one vessel disease, 2a (2VD) = group 2a with two vessel disease, 2b (3VD) = group 2b with three vessel disease. Using Fischer exact test, p value=0.80 (Non significant)

DISCUSSION

The aim of the present study was to find out the levels of fibrinogen and FVIII in angiographically diagnosed IHD patients and to compare these levels in single and multiple coronary vessels. As stated in the literature review many haemostatic abnormalities have been reported to be associated with IHD. The abnormal activation leads to increase in the blood procoagulant which causes the clotting dysfunction. Due to the activation of platelet and the coagulation system there is marked shift of the haemostatic balance towards hypercoagulability. It has been observed in previous studies that FVIII and fibrinogen level increase with the formation of atherosclerosis.

In the present study, age distribution in group1, 2a and 2b did not show any significant difference. Regarding age the study was in accordance with the study conducted by Bhalli et al., 2011¹⁷. The IHD patients were divided in the following age groups in the present study (≤ 40 years 7.5%, 41-50 years 27.5%, 51-60 years 42.5% & >61 years 22.5%) which resembles the age groups studied by Bhalli et al., 2011. The mean $\pm$ SD in the present study was 54.5 ± 9.49 which was in accordance to Bhalli et al., 2011 was observed to be 54.26 ± 11.60 . The p-value regarding age was found to be non significant $P=0.25$ and this finding was consistent with the study conducted by Saruc et al., 1999 $p>0.05$.

In the present study fibrinogen levels was studied in 80 diagnosed IHD patients. Hyperfibrinogenemia was observed in 16 patients out of which 9 patients were of group1 as compared to 7 group 2a & 2b it was similar to the study conducted by Shi et al., 1999¹⁸ in both the studies it is emphasized that those cardiac patients with stenosed vessels display elevated fibrinogen levels as compared to those with absent stenosis. Hence it is proved that elevated fibrinogen level can be taken as an independent risk factor of IHD and stroke.

The present study was in accordance to the study done by Shi et al., 2010.¹⁹ The Mean $\pm$ SD 305 ± 56.7 compared to 302 ± 90 mg/dl.

Evidence suggests that fibrinogen is an acute phases reactant being a very effective predictor of clinical events, it plays a role in early stage of plaque formation and late complications of IHD but in the present study the cases selected were all stable chronic IHD patients who came for angiography after a couple of months so it was not an emergency or any acute episode of angina where fibrinogen is markedly raised. Its elevated levels can be taken as a complication of the disease but not as a cause of disease.

In the present study high level of FVIII with Mean $\pm$ SD 191.24 ± 48.2 was observed in 24 patients with 11/40 group 1 and 13/40 group 2a & 2b. It was in accordance with Martinelli et al., 2010²⁰ Mean $\pm$ SD 172 ± 55 . It was found in both the studies that the baseline elevation of FVIII is due to recurrent venous thrombotic events as compared to single events. So the severity of disease can be assessed by the raised FVIII level and number of vessel involvement.

FVIII assessment is not helpful in chronic stable IHD patients. It is only raised in acute atherosclerotic episodes where it forms a complex with vWF and carries it to the site of vessel injury where it results in the formation of occlusive thrombi. As it is an acute phase reactant it has a significant role in acute coronary artery disease.

CONCLUSION

1. IHD was seen to be more common in middle age group i.e. between 51 to 60 years.
2. Hyperfibrinogenemia was commonly found in IHD patients with single vessel disease.
3. Elevated FVIII levels were found in double and multiple vessel disease. So it can guide in assessing the disease severity.
4. It was observed that Fibrinogen and FVIII levels cannot be taken as parameters to assess the severity of disease in chronic ischemic heart disease patients; they are only helpful in acute episodes of the ischemic heart disease.

Recommendations: Research should be undertaken on a larger scale with a larger sample size, so that population based results may be derived.

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Hypoglycemic Episodes among Cirrhotic Patients Presenting with Hepatic Encephalopathy to Tertiary Care Hospital

Hypoglycemic
Episodes among
Cirrhotic
Patients

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ABSTRACT

Objective: To determine the frequency of hypoglycemic episodes among cirrhotic patients presenting to tertiary care hospital.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Medicine, Khyber Teaching Hospital from May, 2017 to October, 2017.

Materials and Methods: 150 male and female cirrhotic patients aged between 18 and 65 years, and fulfilling the inclusion criteria were recruited in the study. Patients were stratified into different grades of hepatic encephalopathy according to West Haven criteria. A random blood sugar level of 72mg/dl was taken as cut off level. Those presenting with levels less than 72mg/dl were labeled as having hypoglycemia. Data collected were entered in SPSS 23. Mean $\pm$ SD were calculated for continuous variables and categorical variables were expressed as frequencies and percentages. Effect modifiers were controlled through stratification. Chi square test was used by taking p-value less than or equal to 0.05 as significant for post stratification. Results were presented as tables.

Results: A total of 150 patients with hepatic encephalopathy due to liver cirrhosis were included in the study. Male to female ratio was 1.42:1. Average age of the patients was 52.24 years $\pm$ 10 SD. Average blood glucose level in patients with hepatic encephalopathy due to liver cirrhosis was 88 mg/dl $\pm$ 6.32 SD. Majority (102 (68%)) of patients had more than or equal to 72mg/dl blood glucose level while 48 (32%) patients had less than 72mg/dl blood glucose level. Majority (48.66%) of the patients presented in Grade II hepatic encephalopathy. Among cirrhotic patients with hepatic encephalopathy that presented with hypoglycemia, 4 were aged <30 years, 10 were aged between 31 and 45 years, 26 were aged between 46 and 60 years and 8 were aged >60 years. 34.17% male and 29.57% female patients developed hypoglycemia. Slightly more hypoglycemic episodes were seen among patients with higher grades of encephalopathy

Conclusion: Hypoglycemia is seen among patients with hepatic encephalopathy due to liver cirrhosis. It is not yet clear whether hypoglycemia is jointly responsible for the increased short-term mortality of patients with hepatic encephalopathy due to liver cirrhosis or is only a consequence of the severity of the disease or the complications. Further multi-centered trials are recommended to prove this relationship.

Key Words: Hypoglycemic episodes; cirrhotic; hepatic encephalopathy; West Haven Criteria

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INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome which is manifested by altered and deteriorated mental status, psychomotor dysfunction, memory impairment, increased reaction time, inability to concentrate, stupor and in its most severe form - coma^{1, 2}.

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It may develop at an annual rate of 8% in cirrhotic patients according to a study conducted in Far East³. A past history of hepatic encephalopathy is associated with problems at work place, and also causes financial burden on the care givers of such patients. Financial burden can also lead to poor drug compliance, thereby reducing the chances of improvement. A multidisciplinary approach is needed to address this issue and to devise treatment modalities not only in accordance with patients' clinical situation, but also after taking into consideration the collateral issues especially of finances⁴.

The clinical diagnosis of overt hepatic encephalopathy is based on two concurrent types of symptoms: impaired mental status, as defined by Conn's score (also called West Haven criteria) (on scale from 0 to 4,

with greater score indicating more severe impairment),⁵ and impaired neuromotor function².

A very narrow line exists between decompensated chronic liver disease with and without hepatic encephalopathy, and insults like constipation, hypovolemia, infection, hypoglycemia, hypokalemia, gastrointestinal bleeding and tranquilizers can precipitate encephalopathy in predisposed patients⁶. Hypoglycemia is associated with increased mortality in patients with acutely decompensated liver cirrhosis. It is not yet clear whether hypoglycemia is jointly responsible for the increased short-term mortality of patients with acute decompensated liver cirrhosis or is only a consequence of the severity of the disease or the complications⁷. Severe persistent hypoglycemic states, however, may cause long-lasting coma, seizures, and a myriad of other global and focal neurologic deficits⁸, some of which may be mistaken for cerebrovascular accidents or other acute neurological disorders⁹. In analogy to hypoxic encephalopathy, this syndrome has been named hypoglycemic encephalopathy. However, the underlying pathophysiology in both entities are markedly distinct¹⁰.

The pathophysiology of clinical deterioration in hepatic encephalopathy patients with hypoglycemia is not clear. Diabetic patients with chronic liver disease usually develop accelerated liver fibrosis. They are also more prone to bacterial infections¹¹. In one

study, about 80% of patients presenting with compensated liver cirrhosis had some type of glucose metabolism disorders¹¹. In another study, 28.5% of patients had acute glucose disturbances out of which 15.7% were hypoglycemic and 12.8% were hyperglycemic⁷. In another study, out of 100 cases of HE due to liver cirrhosis, 39% were found to have hypoglycemia¹².

From the current study, we aim to determine the frequency of hypoglycemia in cirrhotic patients with hepatic encephalopathy. Blood glucose disturbances are a predisposing factor for hepatic encephalopathy, but at the same time, patients with HE and no prior glucose abnormalities can also develop hypoglycemia. Therefore, hypoglycemia seems to be having a cause and effect relationship with HE. Once local data is collected regarding this finding, we can then compare the results with other studies, and can come up with recommendations regarding routine monitoring of blood glucose in cirrhotic patients with HE.

MATERIALS AND METHODS

This Cross sectional study was conducted in the Department of Medicine, Khyber Teaching Hospital, Peshawar from May, 2017 to October, 2017. 150 male and female patients aged 18-65 years and above, with hepatic encephalopathy were recruited in the study. Patients with concomitant chronic renal failure and who were on haemodialysis, patients with acute fulminant

hepatitis, and patients having history of diabetes and taking anti diabetic drugs were excluded from the study. This study was conducted after approval from hospital ethical and research committee. All admitted patients meeting the inclusion criteria were included in the study. The diagnosis and severity of HE was based on West Haven Criteria⁷. The purpose and benefits of study were explained to the patients and a written informed consent was obtained.

All patients were subjected to detailed history and examination. 5 ml of blood was taken from all patients under strict aseptic technique and was sent to hospital laboratory on the same day. Blood glucose level for all patients was measured from the hospital clinical laboratory. Patient information including name, age, gender and address were recorded in the study Pro forma. Strict exclusion criteria were followed to control confounders and bias in study results. Patients with random blood sugar levels less than 72 mg/dl were labeled as having hypoglycemia¹³. Data collected were entered in SPSS 23. Mean $\pm$ SD were calculated for continuous variables like age and blood glucose levels and categorical variables like gender and hypoglycemia were expressed as frequencies and percentages. Effect modifiers like age, gender and level of severity of encephalopathy were controlled through stratification. Chi square test was used by taking p-value less than or equal to 0.05 as significant for post stratification. Results were presented as tables.

RESULTS

A total of 150 patients with hepatic encephalopathy due to liver cirrhosis were included in the study. There were 88 (58.66%) males and 62 (41.33%) females. Male to female ratio was 1.42:1. Average age of the patients was 52.24 years $\pm$ 10 SD with range 18-65 years. Patients' age was divided into four categories, out of which most common age group for liver cirrhosis was between 46 and 60 years. 15 (10%) patients were under 30 years of age; 41 (27.33%) patients were in the age group 31-45 years; 60 (40%) patients were in the age group 46-60 years, and the remaining 34 (22.66%) patients were older than 60 years (Table 1).

Table No.1: Age-Wise Distribution of Patients

Age Group (Years)	Frequency (n)	Percentage (%)	Mean $\pm$ SD
< 30	15	10	52.24 $\pm$ 10
31 – 45	41	27.33	
46 – 60	60	40	
>60	34	22.66	

Average blood glucose level in patients with hepatic encephalopathy due to liver cirrhosis was 88 mg/dl $\pm$ 6.32SD. Majority (102 (68%)) of patients had more than or equal to 72mg/dl blood glucose level while 48 (32%) patients had less than 72mg/dl blood glucose

level (Table 02). Of these 48 patients, 41(27.33%) patients were symptomatic of hypoglycaemia.

Table No.2: Hypoglycemia Among Cirrhotic Patients with Hepatic Encephalopathy

Hypoglycemia	Number of Patients (n)	Percentage (%)
Yes	102	68
No	48	32

Majority (73 (48.66%) of the patients presented in Grade II HE (Table 03).

Table No.3: Hepatic Encephalopathy Grades Among Patients

Grade of Hepatic Encephalopathy	Number of Patients (n)	Percentage (%)
I	7	4.66
II	73	48.66
III	48	32
IV	22	14.66

Among cirrhotic patients with hepatic encephalopathy that presented with hypoglycemia, 4 were aged <30 years, 10 were aged between 31 and 45 years, 26 were aged between 46 and 60 years and 8 were aged >60 years (Table 04).

Table No.4: Age Wise Distribution of Hypoglycemia Among Cirrhotic Patients with Hepatic Encephalopathy

Age (Years)	Hypoglycemia		Total	p-value
	Yes	No		
<30	4	47	51	0.184
	7.84%	92.15%	100%	
31-45	10	42	52	
	19.23%	80.76%	100%	
46-60	26	36	62	
	41.93%	58.06%	100%	
>60	8	25	33	
	24.24%	75.75%	100%	
Total	48	102	150	
	32%	68%	100%	

Table No.5: Gender-wise distribution of hypoglycemia among cirrhotic patients with hepatic encephalopathy

Hypoglycemia	Gender		Total	p-value
	Male	Female		
Yes	27 (34.17%)	21 (29.57%)	48 (32%)	0.265
No	52 (65.82%)	50 (70.42%)	102 (68%)	
Total	79 (100%)	71 (100%)	150 (100%)	

No difference was noted in incidence of hypoglycemia among male and female patients with encephalopathy. 34.17% male and 29.57% female patients developed hypoglycemia (Table 5).

Similarly, not much difference was noted in the occurrence of hypoglycemia among different strata of hepatic encephalopathy; however, slightly more hypoglycemic episodes were seen among patients with higher grades of encephalopathy (Table 06).

Table No.6: Distribution of Hypoglycemia over grades of hepatic encephalopathy

Grade of Encephalopathy	Hypoglycemia		Total	p-value
	Yes	No		
I	12	25	37	0.876
	32.43%	67.6%	100%	
II	9	36	45	
	20%	80%	100%	
III	15	18	33	
	45.45%	54.54%	100%	
IV	12	23	35	
	34.28%	65.71%	100%	
Total	48	102	150	
	32%	68%	100%	

DISCUSSION

Liver diseases affect millions of people worldwide. However, in the developing countries where cost of health care has always been an issue, chronic diseases such as liver cirrhosis and its complications are a major health problem and pose a big challenge to the health economy. Because of poverty, poor hygienic conditions, inadequate education and lack of counselling, the number of cirrhotic patients is increasing and most of them land up in medical wards with different complications. Most of these patients do not receive treatment at early stage; as a result of which they progress to decompensated cirrhosis with reduced chances of complete recovery.

Chronic liver disease is becoming an epidemic in Pakistan due to a very high prevalence of hepatitis B and C in our community. As a result increasing number of patients come with one or another complication of cirrhosis liver^{13,14}. It is a major cause of mortality and morbidity worldwide¹⁵. It is also a common cause of mortality amongst Pakistani population and frequent cause of admission in our hospitals¹⁶. Cirrhosis develops in about 10-20% of the patients within 5-30 years. The most common cause of cirrhosis in our setup is viral hepatitis as compared to West where alcoholic liver disease is more common¹⁷. Majority of patients (90%) with chronic liver disease had evidence of HBV, HCV or coinfection. Severe disease is reported in patients with co-infection and cirrhosis is recorded in 74% of patients^{18,19}. HCV is now more common as compared to HBV in our country, and there is high frequency of HCV seropositive individuals of both sexes among patients referred for management of chronic liver disease²⁰.

In a local study, results showed that out of 240 patients enrolled in the study, 148 were male (61.7%) and 92 were female (38.3 %) ²¹. Another local study of 100 patients showed 67 (67%) males and 33 (33%) females ²². In a local case series study conducted at Department of Medicine, Liaquat University of Medical & Health Sciences Jamshoro, Pakistan, which included 222 patients, 144 (65%) were male and 78 (35%) were female ²³. Male preponderance has also been reported in various international studies. In a study on seven patients, five were males admitted to the Unit of Gastroenterology and Hepatology of the “Hospital Português” of Salvador, BA, Brazil ²⁴.

In our study, overall mean age was 52.24 years $\pm$ SD. Similar results have also been reported in a local study in which patients mean age was 53.09 with SD= 8.85 years ²⁵. The association between liver cirrhosis and alterations of glucose tolerance has been extensively documented ²⁶. They range from postprandial hyperglycemia to clinically overt, non-ketotic, non-insulin dependent diabetes mellitus (i.e., type 2 diabetes mellitus) ²⁷⁻²⁸. The risk of hypoglycemia has been well demonstrated in clinical studies and in animal models. Unfortunately, the ideal method of preventing hypoglycemia and glucopenic brain injury has not been established. Certainly, following the onset of hypoglycemia, blood glucose levels require frequent monitoring and continuous infusions of 10–20% dextrose.

CONCLUSION

It can be concluded that hypoglycemia is a common finding among patients with hepatic encephalopathy due to liver cirrhosis. It is not yet clear whether hypoglycemia is jointly responsible for the increased short-term mortality of patients with hepatic encephalopathy due to liver cirrhosis or is only a consequence of the severity of the disease or the complications. Further trials are recommended to prove this relationship.

Author's Contribution:

Concept & Design of Study:	Aliena Badshah
Drafting:	Iqbal Haider
Data Analysis:	Main idea, Wazir Mohammad
Revisiting Critically:	Zahid Marwat
Final Approval of version:	Aliena Badshah

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Pulmonary Recruitment Maneuver: An Effective Way to Reduce Postoperative Pain after Laparoscopic Cholecystectomy

Laparoscopic
Cholecystectomy
Induced Shoulder
Pain

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ABSTRACT

Objective: To compare mean laparoscopy induced shoulder pain score with and without pulmonary recruitment maneuver in patients undergoing laparoscopic cholecystectomy.

The aim of this study is to evaluate the efficacy of pulmonary recruitment maneuver in reducing post operative pain after laparoscopic cholecystectomy.

Study Design: Randomized control trial study

Place and Duration of Study: This study was conducted at the conducted at Department of Surgery, Unit-III, Jinnah Hospital Lahore from May 2016 to June 2017.

Materials and Methods: Both males and females of age between 16-60 years were included in the study. Group 1 consists of 30 patients who underwent intervention and Group II placebo group who are healthy participants. Clinically and sonographically diagnosed case of cholelithiasis and chronic cholecystitis underwent laparoscopic cholecystectomy by two senior consultant surgeons.

Results: The mean age of 60 patients was (37.33±9.837) years. More females 43 (71.7%) were in study as compared to males 17 (28.3%). On comparison, age, operative time, body mass index, VAS at 12th hour, VAS at 24th hour, there was statistically significant difference in pain score at 12 hours between intervention and placebo group, however, the difference was not significant at 24 hours.

Conclusion: Pulmonary recruitment manure is helpful in reducing early postoperative pain at 12hours however there was no difference in pain score after 24 hours.

Key Words: Laparoscopy induced shoulder pain, Laparoscopic cholecystectomy, Pulmonary recruitment maneuver, Visual analogue scale.

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INTRODUCTION

Laparoscopic procedures like cholecystectomy, hernia repair have become the standard of care all over the world because of less postoperative pain, small incisions, short hospitalizations, and earlier return to normal activity.^{1,2} Thirty five to 80% Patients complain of shoulder and upper abdominal pain after laparoscopic procedures.³ The trapped carbon dioxide between liver and diaphragm causes upper abdominal discomfort and irritation of phrenic nerve resulting in referred shoulder tip pain in the C4 dermatome.^{4,5} Abdominal and shoulder tip pain results in delayed recovery after laparoscopic cholecystectomy.⁶

Pulmonary recruitment maneuver (PRM) has been proposed to reduce shoulder and upperabdominal pain as it helps in evacuation of residual carbon dioxide by increasing intraabdominal pressure to facilitate the expulsion of residual carbon dioxide.⁷

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MATERIALS AND METHODS

This randomized control trial was conducted from May 2016 to June 2017 in the department of surgical unit-III, Jinnah Hospital Lahore. Sixty patients of symptomatic cholelithiasis age 16-60 years of both gender were included in the study. Non-probability purposive sampling technique was used for the induction of patients into the study. Patients with empyema gallbladder, gangrene, rupture and bile leakage and conversion to open surgery were excluded. Other exclusion criteria were diabetes, patients on antidepressants or antipsychotics, and BMI>40 kg/m² were excluded. Patients were randomly divided into two groups, manual pulmonary inflations group (intervention group) and control group. Both the patient and investigator responsible for recording of postoperative pain score were not aware of patient's group allocation. Treatment allocation envelop was opened by the anesthetist just before the procedure. Only the anesthetist was aware of the treatment allocation. Visual analogue scale (VAS) from 0 (no pain) to 10 (worst possible pain) was explained to the patients before surgery and was recorded at 12 and 24 hours post operatively. Laparoscopic cholecystectomy was performed with standard four port technique by

two senior consultants and pneumoperitoneum pressure was kept at 14 mm Hg in all the procedures.

On completion of the procedure, in the no intervention group (control group); the deflation of pneumoperitoneum was achieved by gentle compression of the abdomen. In the intervention group, after deflation of pneumoperitoneum pulmonary inflation was performed with a positive pressure for five times to expel residual gas. For postoperative analgesia, all patients were given 50 mg diclofenac sodium twice daily and tramadol HCL 20 mg 6hourly. Data was collected on a structured questionnaire containing age, sex, body mass index (BMI), VAS for recording of pain score. BMI more than 30kg/m² and duration of procedure operative time were treated as effect modifier and dealt by stratification. Data was analyzed using SPSS version 17.0, mean±standard deviation was used in qualitative variables like age, pain score on visual analogue scale, operative time and BMI. Frequencies and percentages are used for both qualitative and quantitative variables. An independent sample t-test applied to determine statistical difference in pain score at 12 and 24 hours in both groups (intervention and placebo groups). Data was stratified for duration of procedure and BMI. A p-value ($p \leq 0.05$) was considered as significant.

RESULTS

The mean age of 60 patients was (37.33±9.837) years ranging from 24 to 59 years were included in the study. Body mass index ranged from 26 to 38 with mean of (32.73±3.058) kg/m². While duration of operation ranging from 24 to 51 minutes with mean (37.62 ± 9.031) minutes (Table 1). Out of 60 patients participated in the study, 43(71.7%) were females and 17(28.3%) were males participants. Table 2 shows the 30 (50%) patients were randomly selected in intervention group and 30(50%) were randomly selected in placebo group. Table 3 presents the groups comparison by age, body mass index, operative time, and visual analogue scale (VAS) at 12th hour and 24th hours. On age comparison, mean age in intervention group was (37.17±9.833) and mean age of placebo group was (37.5 ± 10.006), however this difference was not statistically significant ($p=0.61$). On duration of operation time comparison, the mean intervention duration time was (35.93 ± 8.678) and mean placebo group duration time was (39.3±9.207), this difference was also not significant ($p=0.15$). In intervention group, the mean body mass index was (32.83±2.995) and in placebo group mean body mass index slightly differ (32.63±3.168), which also shows no difference. Comparison of groups VAS at 12 hours depicts that mean VAS scores at 12 hours in intervention group was (4.15±1.459) and in placebo group was (5.83±2.995), this difference is perfectly statistically significant ($p=0.000$). On group's comparison at VAS at 24 hours,

the intervention group VAS mean scores was (3.32±1.214) and placebo group VAS mean scores was (4.63±2.85), the probability value shows no difference. Table 4 shows cross tabulation of both groups by gender. Moreover, of 43(100%) females, 19 (44%) were experienced intervention and 24 (56%) were in placebo group. 11 (64%) were selected in intervention group remaining 6 (36%) were in placebo group. Chi-square test shows no association between males and females in terms of intervention and placebo groups ($p=0.836$).

Table No.1: Distribution of sampled population (n=60)

Variable	No.	Mini	Max	Mean±SD
Age (years)	60	24	59	37.33±9.83
Body mass index	60	26	38	32.73±3.05
Operative time	60	24	51	37.62±9.03

Table No.2: Demographic profile

Variable	No.	%age
Gender		
Male	17	28.3
Female	43	71.7
Groups		
Intervention	30	50.0
Placebo	30	50.0

Table No.3: Comparison of different Variables in groups

Variables	Intervention group (n=30)	Placebo group (n=30)	P value
Age (years)	37.17±9.833	37.5±10.006	0.61
Duration of operation	35.93±8.678	39.3±9.207	0.15
Body mass index	32.83±2.995	32.63±3.168	0.802
VAS at 12 hours	4.15±1.459	5.83±2.995	0.000*
VAS at 24 hours	3.32±1.214	4.63±2.85	0.461

*Statistically Significant $p<0.05$.

Table No.4: Cross tabulation between Group & Gender

Group	Gender		Total	P value
	Female	Male		
Intervention	19 (44%)	11 (64%)	30 (50%)	0.836
Placebo	24 (56%)	6 (36%)	30 (50%)	
Total	43 (100%)	17 (100%)	60 (100%)	

*Statistically significant $p<0.05$

DISCUSSION

Despite all the advances in minimal access surgery, postoperative pain after laparoscopic cholecystectomy is still a serious problem, and about 80% patients have significant pain and require analgesia after laparoscopic cholecystectomy.⁸ Radiologic studies demonstrate the presence of pneumoperitoneum for as long as 24 h after laparoscopic cholecystectomy.⁹⁻¹⁰ Many patients (35–80%) have so far reported shoulder and upper abdominal pain after laparoscopic procedures.³ Although the exact pathogenesis of postoperative pain is still not fully understood but the most plausible explanation of pain is carbon dioxide retention and irritation of diaphragm causes referred pain in C4 dermatome.⁴ Likewise, residual carbon dioxide in subphrenic space also causes upper abdominal pain. It has been shown that gas insufflation with increased intra-abdominal pressure has a linear relationship between abdominal compliance during the procedure and the resultant severity of postoperative pain.¹¹

To offer effective analgesia, along with NSAIDs and opioids pain modifying agents such as pregabalin and ketamine have also been investigated. All parenteral analgesics may be associated with adverse effects, so search for non pharmacological ways of managing pain have been investigated.¹²⁻¹³

In a similar study, active aspiration of CO₂ resulted in less postoperative pain in the early postoperative hours than those patients where active evacuation of pneumoperitoneum was not done.¹⁴ This shows that the active expulsion of the residual carbon dioxide after laparoscopic procedures results in less postoperative pain.

Pulmonary recruitment manoeuvre (PRM) has been proposed to reduce postoperative pain after laparoscopic cholecystectomy as it achieves the evacuation of residual carbon dioxide by increasing intraabdominal pressure. The study determines the mean difference in pain scores at 12 and 24 hours, results showed that there is a significant difference at 12 hours but the difference was non-significant at 24 hours. These results depict early reduction of pain in patients undergoing pulmonary recruitment manoeuvre secondary to increased washing of carbon dioxide. However, at 24 hours when there is equal rate of loss of abdominal distension the mean pain score was equally distributed in either groups. There is evidence that residual gas gets absorb after 24 hours of laparoscopy.⁹⁻¹⁰ In another trial, patients in the active aspiration group of residual gas received less opioids compared to non aspiration group.¹⁴ This difference of analgesia was most noticeable after one hour of surgery: (control group 3.9 to 1.9 mg, intervention group 2.7 to 1.3mg; $P = 0.056$). We suggest that at present sample size pulmonary recruitment manoeuvre

is a cost effective simple technique to reduce early post-operative pain.

CONCLUSION

Pulmonary recruitment manure is helpful in reducing early postoperative pain at 12 hours however there was no difference in pain score after 24 hours.

Author's Contribution:

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Screening of Diabetes and HIV Infection in Newly Diagnosed Pulmonary Tuberculosis Patients

Rizwan Hafeez, Sajjad Ahmed Khan, Azzan Mujahid and Abdullah Irshad

ABSTRACT

Objective: Aim of the study was to investigate the prevalence of diabetes and HIV infection by screening in newly diagnosed pulmonary tuberculosis patients.

Study Design: Cross sectional study.

Place and Duration of Study: This study was conducted at the Pulmonology Department of Shahida Islam Medical College, Lodhran from 10 June 2016 to 10 June 2017.

Materials and Methods: This study was conducted after taking approval from the institutional ethical committee. Total 159 newly diagnosed pulmonary tuberculosis patients were recruited by non-probability consecutive sampling. Mean and SD was calculated for numerical variables like age, BMI, fasting blood glucose (FBG), Hemoglobin and monthly income. Frequency and percentages were calculated for categorical variables like gender, smoking status, educational status, alcohol consumption, prevalence of HIV and diabetes, Chi square test was used to check significant difference in PTB and Non PTB patients. P value of <0.05 was taken as significant.

Results: Significant difference was found between age ($p=0.000$), BMI ($p=0.000$), FBG ($p=0.000$), hemoglobin ($p=0.000$), gender ($p=0.002$) and alcohol consumption ($p=0.034$), in groups, except education status ($p=0.090$) and monthly income ($p=0.068$). The main outcome variables of this study were HIV infection and diabetes. HIV infection was noted in 3.1% ($n=5$) and 1.9% ($n=3$) patients for PTB and non-PTB group respectively. While, 8.2% ($n=13$) and 4.4% ($n=4$) patients suffered from diabetes, for both the groups respectively.

Conclusion: The results of our study revealed that on screening of newly diagnosed pulmonary tuberculosis patients with HIV infection and diabetes, their prevalence was high as compared to non-pulmonary tuberculosis group. But this difference was statistically non significant (P value 0.474 and 0.166).

Key Words: Pulmonary tuberculosis, Diabetes, HIV infection.

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INTRODUCTION

Diabetes is metabolic disorder. Insulin resistance is the main pathogenesis in development of type 2 diabetes mellitus. Type 2 diabetes usually affects elderly patients. Type 2 diabetes mellitus is accelerating pandemic throughout the world¹. 230 million population of the world suffer from diabetes. It has been estimated that this population will reach up to 552 million until 2030². It is recorded that 471 billion USD were spent to treat diabetes in 2012³. For the developing countries, it is a great socio economic burden. It is alarming that prevalence of diabetes has significantly risen in past two decades. In 2011 diabetes prevalence was ranging from 7.6% (5.2 million people) to 11% in Pakistan and it is expected to reach up to 15% (14 million) until 2030⁴.

Pakistan is on number 7 place in list of countries having diabetes mellitus. It is estimated that if this trend continues then it will become number 4. Overall ratio of diabetes is that its prevalence in urban population is 22.04% and in rural area is 17.15% in Pakistan⁵. Pakistan health care system is overburdened and under resource in dealing with this situation. Considering the present situation, it demands a national effort in not only treating but more on preventing the diabetes mellitus. Many complications are associated with diabetes mellitus. Cardiovascular diseases due to diabetes is main cause of premature illness and deaths⁶. It is main cause of renal failure and blindness. It is associated with amputations due to diabetic foot development.

Tuberculosis is one of the main public health problem worldwide⁷. It has been investigated that one third population of world is suffering from mycobacterium infection⁸. Patients of pulmonary tuberculosis clinically present mainly with cough, fever, hemoptysis and weight loss. Diabetes is well known risk factor for tuberculosis⁹. World health organization has classified that eight of ten countries which have highest burden of diabetes also have high burden of tuberculosis¹⁰. In developing countries such as Pakistan, India,

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Bangladesh and Brazil where tuberculosis is endemic, the burden of these two diseases and interaction between them will be more dangerous. World health organization has declared global epidemic both diabetes and tuberculosis¹¹.

Relationship and association of HIV with tuberculosis is great socio economic threat and public health problem in developing countries. World health organization had estimated in 1992 that about four million population of the world had been infected by both HIV and mycobacterium tuberculosis¹². Association between HIV and tuberculosis is evident by high incidence of tuberculosis in HIV infected patients. In developing countries where health care systems are already overburdened these two epidemics impose grave social and medical implications.

To best of our knowledge in south Punjab of Pakistan no study had been conducted to investigate the prevalence of diabetes and HIV infection in newly diagnosed pulmonary tuberculosis patients. So this study was conducted to investigate the prevalence of these diseases in newly diagnosed pulmonary tuberculosis patients. It will provide a base for further research on this issue and will create awareness. Study done by Qiuzhen Wang et al. was taken as reference study¹³.

MATERIALS AND METHODS

This cross sectional study was conducted in the Pulmonology department of Shahida Islam Medical College, Lodhran. From 10 June 2016 to 10 June 2017 after taking approval from the institutional ethical committee. Total 159 newly diagnosed pulmonary tuberculosis patients were recruited by non-probability consecutive sampling. To study the prevalence of diabetes and HIV infection in non-tuberculosis group, by cluster random sampling 159 subjects were recruited from same communities as that of tuberculosis patients. Written permission of study was signed by each individual recruited in study. Exclusion criteria of study were: 1) patients with age < 18 years of age, 2) patients who had already taken anti tuberculosis drugs, 3) patients who were known to have diabetes and HIV infection 4) patients who had any history of oncological disorder and 5) patients who had other immunosuppressive conditions. Sample size of study was calculated by using a reference study done by Qiuzhen Wang et al. for which confidence interval was taken as 95%, study strength and odd ratio of diabetes in newly diagnosed pulmonary tuberculosis patients was 3.17%¹³.

All patients were recruited from outpatient department. Detailed medical history of individual was taken and through clinical examination was conducted to record any complication of the disease and to assess any sign of other immunosuppressive disorder. Blood pressure and vitals were recorded at time of pulmonary

tuberculosis patients. Blood samples were also taken to check glucose levels and hemoglobin level. Personal information like age, gender, living area, income, body mass index duration of symptoms was taken by filling the Performa.

Pulmonary tuberculosis was diagnosed according to the guidelines of National Tuberculosis Program. Patients were investigated with smear examination who were suspected to have pulmonary tuberculosis. Patients who were smear negative but having clinical and radiological suspicion were also labelled as pulmonary tuberculosis after discussing it with radiologist and chest consultants.

Diabetes was diagnosed by using standard method of checking fasting plasma glucose levels as recommended by World Health Organization. Venous blood was used after overnight fasting to check plasma glucose level. Patients having plasma glucose level greater than 126mg/dl were diagnosed as diabetics. Screening of HIV infection was done in each individual recruited in study by using ELISA method.

Data was analyzed by using SPSS volume 23. Quantitative variables like age, body mass index, plasma glucose levels and age were statistically analyzed by their mean and standard deviation and t-test was applied to check the significance. Qualitative variables like gender, living area, HIV infection, diabetes and income were statistically analyzed by frequency and percentage and chi-square test was used to check the significance. P value < 0.05 was considered as statistically significant.

RESULTS

In this study, a total number of 100% (n=318) patients were included, divided into two equal groups, 50% (n=159) in each i.e. PTB and non-PTB group. The Mean±S.D of age, BMI, FBG and hemoglobin of the patients of PTB group was 46.14±2.92 years, 21.16±2.46 kg/m², 6.02±1.15 and 10.82±1.74 g/dl respectively. While, the Mean±S.D of age, BMI, FBG and hemoglobin of the patients of non-PTB group was 48.48±3.20 years, 23.31±2.24 kg/m², 5.13±1.72 and 12.53±1.64 g/dl respectively. Gender distribution, in PTB group, was observed as 74.8% (n=119) males and 25.2% (n=40) females. While, in non-PTB group, there were 58.5% (n=93) males and 41.5% (n=66) females. There were 28.3% (n=45) and 13.2% (n=21) smokers in PTB and non-PTB group respectively. Education status of PTB group was observed as 35.2% (n=56) illiterate, 39% (n=62) matric and 25.8% (n=41) graduate or above. However, in non-PTB group, 37.1% (n=59) illiterate, 28.3% (n=45) matric and 34.6% (n=55) graduate or above. Income level of the patients of PTB group observed as 35.2% (n=56) patients had <200000 rupees/year and 64.8% (n=103) had >200000 rupees/year. While, 25.8% (n=41) patients of non-PTB group had <200000 rupee/year income and 74.2%

(n=118) had >200000 rupee/year income. There were 10.7% (n=17) and 4.4% (n=7) patients used alcohol of PTB and non-PTB group respectively. Significant difference was found between age ($p=0.000$), BMI ($p=0.000$), FBG ($p=0.000$), hemoglobin ($p=0.000$), gender ($p=0.002$) and alcohol consumption ($p=0.034$), in groups, except education status ($p=0.090$) and monthly income ($p=0.068$). (Table. 1& 3).

The main outcome variables of this study were HIV infection and diabetes. HIV infection was noted in 3.1% (n=5) and 1.9% (n=3) patients for PTB and non-PTB group respectively. While, 8.2% (n=13) and 4.4% (n=4) patients suffered from diabetes, for both the groups respectively. No significant difference was found between HIV ($p=0.474$) and diabetes ($p=0.166$), in groups. (Table. 2). (Figure. 1).

Table No. 1: Characteristics of PTB and Non-PTB patients

Variable	PTB (n=159)	Non-PTB (n=159)	Test of Sig.
Age	46.14± 2.92 years	48.48± 3.20 years	$t=-6.81$, $p=0.000$
BMI	21.16± 2.46 kg/m ²	23.31± 2.24 kg/m ²	$t=-8.13$, $p=0.000$
Fasting blood glucose	6.02± 1.15	5.13± 1.72	$t=-8.94$, $p=0.000$
Hemoglobin	10.82± 1.74 g/dl	12.53± 1.64 g/dl	$t=5.39$, $p=0.000$
Gender	M=74.8%, F=25.2%	M=58.5%, F=41.5%	$\chi^2=9.56$, $p=0.002$
Smoking Status	Smokers=2 8.3%	Smokers=13 13.2%	$\chi^2=11.01$, $p=0.001$
Education Status	Illiterate=3 5.2% Matric=39% graduate or above=25.8%	Illiterate=37 37.1% Matric=28.3% graduate or above=34.6%	$\chi^2=4.82$, $p=0.090$
Monthly Income	<200000=3 5.2% >200000=6 4.8%	<200000=25 8% >200000=74 74.2%	$\chi^2=3.33$, $p=0.068$
Alcohol Consumption	10.7%	4.4%	$\chi^2=4.51$, $p=0.034$

Table No. 2: Distribution of HIV and Diabetic in groups

Variable	PTB (n=159)	Non-PTB (n=159)	Test of Sig.
HIV	3.1%	1.9%	$\chi^2=0.513$, $p=0.474$
Diabetic	8.2%	4.4%	$\chi^2=1.92$, $p=0.166$

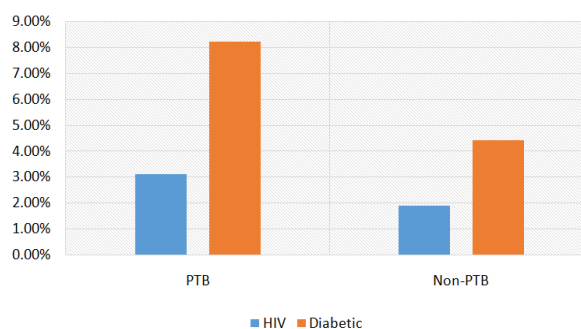


Figure No.1: Distribution of HIV and Diabetic in groups

Table No. 3: Association of groups between effect modifiers

Variable	Groups		Total	Chi-Square P-value
	PTB	Non-PTB		
Gender	Male	93	212	0.002
	Female	66	106	
Smoking	Yes	21	66	0.001
	No	138	252	
Educational Status	Illiterate	59	115	0.000
	Matric	45	107	
	Graduate or above	55	96	
Income	<200000	41	97	0.068
	>200000	118	221	
Alcohol	Yes	7	24	0.034
	No	152	294	
Diabetic	Yes	7	20	0.166
	No	152	298	
HIV	Yes	3	8	0.474
	No	156	310	

DISCUSSION

Results of study showed that prevalence of diabetes mellitus on screening in newly diagnosed pulmonary tuberculosis patients was higher (8.2%) than in non-pulmonary tuberculosis (4.4%) group. Similarly study also showed that HIV infection on screening was higher (3.1%) in newly diagnosed pulmonary tuberculosis patients than in non-pulmonary tuberculosis (1.9%) group. But this difference was statistically non-significant with P value 0.474 and 0.166.

To best of our knowledge there was no data available about prevalence of diabetes and HIV infection among newly diagnosed pulmonary tuberculosis patients as well as comparative data from non-pulmonary tuberculosis controls from the same community collected at same time. The study was designed to discover the hidden prevalence of HIV infection and diabetes mellitus in newly diagnosed pulmonary tuberculosis patients in Pakistan generally and in our local geographical area specially. Strength of this study is that, to define diabetes mellitus accurately, primary data obtained from newly diagnosed

pulmonary tuberculosis patients and non-pulmonary tuberculosis group was used. While in other studies, either the prevalence of diabetes mellitus in non-pulmonary tuberculosis patients was not reported or it was estimated from secondary data with inherent biases¹⁴⁻¹⁵. Study done by Tahir et al. showed that prevalence of diabetes mellitus among pulmonary tuberculosis patients is 14.8%¹⁶. Study done by Jabbaret al. in Karachi and found that tuberculosis was ten times more prevalent in diabetic patients than in non-diabetic patients and prevalence was also increased with increase in duration of diabetes mellitus¹⁷. Another study carried out by Zheng et al. found that prevalence of diabetes mellitus in tuberculosis was ranging from 5% to more than 50%¹⁸. Results of study done by Mukhtar et al. showed that diabetes is associated with unfavorable outcomes in pulmonary tuberculosis patients¹⁹. Study of Alavi et al. concluded that pulmonary tuberculosis should be considered at top of the list in every diabetic patients who presented with cough, sputum and dyspnea with cavitation and miliary mottling on chest x ray²⁰. Many studies had been done to evaluate the prevalence and association of tuberculosis in already known HIV infected patients. But data is very limited about screening of HIV infection in newly diagnosed pulmonary tuberculosis patients. It has been noted that incidence of HIV infection is growing in our region. Study done by Giri et al. showed that 17% HIV infected patients had tuberculosis co-infection²¹. Study carried out by Chisti et al. found that pulmonary tuberculosis can be a common cause of acute pneumonia in severely malnourished or HIV infected children under five years old²².

CONCLUSION

The results of our study revealed that on screening of newly diagnosed pulmonary tuberculosis patients with HIV infection and diabetes, their prevalence was high as compared to non-pulmonary tuberculosis group. But this difference was statistically non significant (P value 0.474 and 0.166).

Author's Contribution:

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Association Between Periconceptional Folic Acid Deficiency and Occurrence of Skeletal Anomalies in Newborns

Riasat Ali Nehra¹, Noor ul Mobeen¹, Akmal Bhatti² and Hafsa³

ABSTRACT

Objective: This study was planned to detect the connection among environs component (folic acid inadequacy) and development of Skeletal anomalies during intrauterine life.

Study Design: Case control study.

Place and Duration of Study: This study was conducted at the CLAP Hospital Johar Town and Arif Hospital Kasur from 1st January 2014 to 31st Dec. 2014.

Materials and Methods: It was a suitable sampling, two existing groups differing in outcome were identified and compared among, 100 sufferers of CLP and allied skeletal anomalies in neonates age not more than 6 months, in various Hospitals of Lahore. Mothers were asked whether they took folic acid or not during their early pregnancy.

Results: The skeletal anomalies number was quite high between mothers having deficiency of folic acid and other vitamins (11% as compared to 2.4% of controls).

Conclusion: Pregnant mothers who have not taken folic acid and other vitamins throughout their early pregnancy developed cleft lip with associated skeletal anomalies in their offspring.

Key Words: Skeletal anomalies, Environmental factors (folic acid and vitamins deficiency).

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INTRODUCTION

There are many skeletal disorders more than 350.¹ Skeletal dysplasia is defined as generalized abnormality of the skeleton. Skeletal anomalies are usually associated with other facial (cleft lip) or organ system anomalies.⁴ These abnormalities are congenital or environmental teratogen exposure.⁵⁻⁸ Old persons had no knowledge regarding formation of baby during pregnancy.⁹

Teratogen effect skull and facial tissue development and with limb defects have also been caused by teratogens. A considerable number of cases of cleft lip and palate have associated skeletal anomalies. These anomalies in newborns varies as low as 4.3% to as high as 63.4% in which 13% are skeletal and 47% are cleft palate.¹⁰

Classification of Skeletal anomalies are commonly;

Syndactyly, It is fusion of one or more fingers and toes.

Polydactyly, This is presence of extra fingers or toes

Clubfoot, In this anomaly front part of the foot turns toward the inside of heel

Congenital hip dislocation¹¹. In this hip and thigh bones are underdeveloped and leads to dislocation of hip

Some rare limb anomalies are absence of finger, toes, or partial or complete absence of an arm or leg

Folic acid is a water soluble vitamin B and co-factor enzyme which is important for formation of purine and thymidine nucleotides and from homocysteine, methionine is synthesized. Deficiency of vitamin B result impaired folate and its deficiency leads to developmental anomalies like neural tube defects and associated skeletal anomalies. Disease can be limited by elevated folic acid intake in first trimester of pregnancy.¹²

The critical organogenesis period is, between six to nine week and deficiency of folate or low dose causes developmental anomalies¹³

One third of cleft lip cases with skeletal anomalies can be protected if folic acid is taken in first trimester of pregnancy, better nutrition and other vitamins intake have additional benefits.¹⁴ Multiple associated anomalies can occur due to environmental teratogens like folate deficiency. In a study at Jordan out of 44 associated anomalies 15.9% were skeletal anomalies¹⁵ In a study by Tolarova in 1982 high dose of folic acid (10mg) per day reduce the risk of congenital anomalies including skeletal anomalies¹⁶ Genes are also involved in congenital abnormalities but an interaction of genes

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with nutritional deficiency enhances the pathogenesis of congenital anomalies¹⁷

Children with CLP and associated skeletal anomalies feel more anxiety. They respond differently as compared to normal children¹⁸

MATERIALS AND METHODS

Neonates having Cleft Lip or Cleft palate and allied skeletal anomalies who were brought by their mother for treatment in mentioned hospitals. Help was taken by concerned consultant. Neonate was entered according to inclusive criteria after taking permission from mother or close relative. This study was approved by Advanced board of King Edward Medical University Lahore.

Interview: A questioners, was framed and proforma was designed and different answers told by mother were entered on the questioners paper with special emphasis about intake of folic acid and supplementary vitamins.

Data analysis: Ninety-five percent confidence-interval, SPSS, 20.00 and Odds Ratio was estimated. Interval of introduction was outlined by Mean $\pm$ SD.

RESULTS

Folic acid and nutritional deficiency have been associated with cleft lip and palate and associated skeletal anomalies.



Figure No.1:Club foot

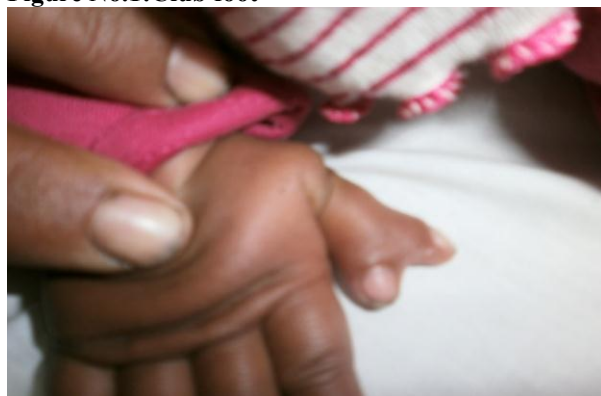


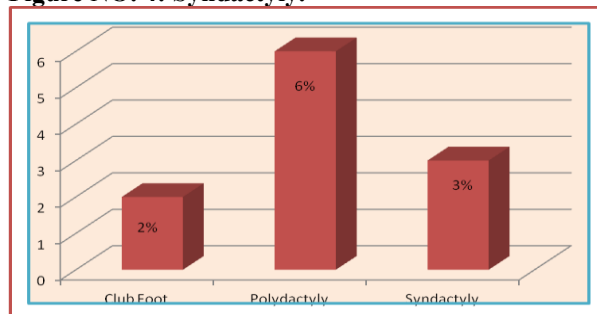
Figure No.2: Polydactyly



Figure No.3:Polydactyly with cleft lip



Figure NO. 4: Syndactyly.



Graph 1: Associated Skeletal Anomalies.

Table No. 1: Frequency of Associated Skeletal Anomalies Among Cases.

	Skeletal Anomalies	
	Yes	No
Club Foot	2%	98
Polydactyly	6%	94
Spina bifida	0	100
Club Hand	0	100
Syndactyly	3%	97
Total anomalies	11%	

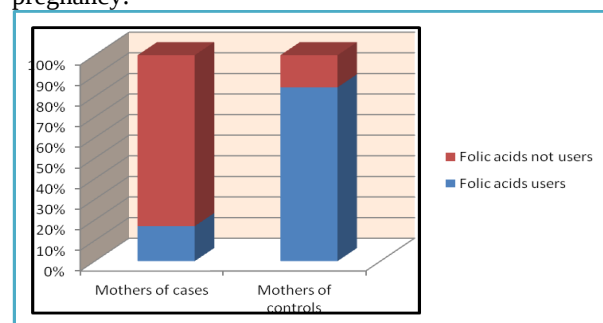
Table No. 2: Association Between of use of Folic Acid Tablets in Cases & Controls.

	Group	
	Cases	Controls
Yes	17	422
No	83	78
	100	500

Chi-Square Test= 24.34 p-value= 0.000
Odds Ratio= 26.41

Associated skeletal anomalies were seen in 11% of cases. The most common anomaly seen in 6% of cases was polydactyly, followed by syndactyly in 3% patients and 2% of patients had Club.

There were 17% patients whose mother told that during their pregnancy they used folic acid tablets, While 84.4% mothers of controls used folic acid tablets. Odds ratio was significant showing 26.41 times more risk if the mother does not use folic acid tablets during their pregnancy.



Graph 2: History of Folic Acid Intake

DISCUSSION

Results are variable between separate countries of studies. In connection to this research, so many components are responsible in the development of CLP with associated skeletal anomalies.¹⁹

In this study associated anomalies of the skeletal system with cleft lip and palate were studied which were present in 11% of the patients, polydactyly was the commonest 6% followed by syndactyly 3% and club foot 2% (table 1, Graph 1). The incidence of these anomalies may vary from as low as 4.3% to as high as 63%. Most common are the skeletal anomalies which account for 13% of the total.⁰ A retrospective study in Boy Town Hospital (USA) has reported orofacial anomalies followed by cardiovascular, central nervous system and skeletal anomalies.²⁰ In a study data from Sweden skeletal malformations were the commonest accounting for 33% of total malformation.²¹

The risk of orofacial with associated skeletal anomalies increases 26.41 times if the mother does not take any folic acid supplements during early pregnancy (Table 2, Graph 2). The protective effect of folic acid depends with dose and period of intake.¹⁴ A research conducted by Stoll and Wehby G, in Norway National and Iowa university respectively have reported a one third decrease in congenital anomalies including skeletal if 400 micrograms or more folic acid per day is taken by pregnant mothers.²² Our study is comparable with other studies as protective role of folic acid supplement against orofacial and skeletal anomalies.

CONCLUSION

At completion, the role of environmental component is revealed in this area for orofacial cleft development

with associated skeletal anomalies like club foot syndactyly and polydactyly etc. Taking into account of these outcomes, various issues can be addressed. Future planning for health of pregnant mother and baby can be made. Antenatal care is important for health of mother and taking additional nutrition and folates congenital anomalies can be avoided.

Author's Contribution:

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Data Analysis:	Akmal Bhatti, Hafsa
Revisiting Critically:	Riasat Ali Nehra, Noor ul Mobeen
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Morphometric Analysis of Lower Pole Calyceal Anatomical Factors in Normal Healthy Kidneys and Their Clinical Significance

Atika Khurshid¹, Waqar Azim Niaz² and Kamil Shuaat³

ABSTRACT

Objective: To measure anatomical factors particularly in relation to the lower pole calyceal anatomy of normal healthy kidneys in our population in order to find their clinical significance.

Study Design: Observational / Cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Anatomy, Watim Dental College, Rawat, Department of Urology, Shaafi International Hospital, Islamabad and Department of Radiology, Al-Nafees Medical College & Hospital, Islamabad from July 2015 to April 2017.

Materials and Methods: 25 healthy kidney donors between 18 – 60 years aged, who were referred to the kidney transplant service at Shaafi International Hospital, Islamabad having normal renal function, coming through ethical and official processes of kidney donation, and submitting a written consent were included. A total of 50 kidneys (from 25 IVU films) were available for the purpose of this study. The source of IVU films was from Radiology department. The data was collected using predesigned, pretested Pro-forma. The parameters measured were Lower Calyceal Infundibular Length (LCIL), Lower Calyceal Infundibular Width (LCIW) and Lower calyceal infundibulo – ureteropelvic angle (LCIUPA). Obtained data was presented as range, mean $\pm$ standard deviation, and percentage (%) distribution. Microsoft Excel program version 2016 was used for statistical analysis.

Results: The mean age was 26.9 ± 6.8 years (minimum age was 20 years and maximum age was 41 years). The mean LCIL was $26.9 \pm$ SD of 6.8 and mean LCIW was $8.6 \pm$ SD of 2.4. The mean LIUPA was $53.6 \pm$ SD of 23.3.

Conclusion: Measurement of lower calyceal anatomical factors is essential in order to identify favourable and unfavourable factors in management of lower calyceal renal stones. Knowledge of these factors is of immense value in deciding best method of treatment of lower calyceal stones in a patient for a successful outcome. Further studies are needed in a 3 dimensional views of renal pelvicalyceal anatomy in order to reflect the data more accurately.

Key Words: Lower calyx, Infundibular Length, Infundibular Width, Infundibulo ureteropelvic Angle, Anatomy.

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INTRODUCTION

Renal collecting system comprises three major calyceal systems namely upper, middle and lower calyces that arise from the renal pelvis each of which then are subdivided into three to five minor calyces. Morphology of renal collecting system has many variations. Although, the arrangement of renal collecting system are similar on both sides in an individual, at times there are variations on each side of a particular individual.

Kidney stones are a common problem and can form in any part of the renal collecting system but they are most frequent in lower pole calyx.

Although gravity was initially thought to be the main factor in lower calyceal stone formation, but it does not explain, why a single stone forms on one side and not in the other kidney in a same person, thus suggesting the possible role of lower calyceal special anatomical factors also as a cause ¹. In view of this, it is very logical to consider different pelvicalyceal properties as the key factor in lateralization of the stone and also as a risk factor for their formation ².

Kidney stone treatment modalities have been revolutionized recently with plethora of minimally invasive techniques which require detailed knowledge of pelvicalyceal anatomy. In addition such knowledge play an essential role in the selection of best method of kidney stone treatment for a particular patient. In this modern era of urological procedures for management of renal stones such as Extracorporeal Shock Wave Lithotripsy (ESWL), Flexible Ureterorenoscopy, Retrograde Intra Renal Surgery (RIRS) and Percutaneous Nephrolithotomy (PCNL), the selection

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of best possible procedure that results in complete clearance of a kidney stone, requires detailed analysis of pelvicalyceal anatomy of the involved kidney³.

Intravenous Urography (IVU) is considered to be the procedure of choice when anatomical details of the pelvicalyceal anatomy is required⁴, although other studies have suggested the use of Computed Tomographic Urography (CTU) with comparable results⁵.

Review of the available literature revealed that studies usually measured several anatomical factors such as infundibular length, infundibular width, infundibulo - ureteropelvic angle and lower pole ratio mostly for lower pole calyx. These anatomical parameters are now considered to have a significant impact on stone formation and recurrence^{1, 5-6}. In addition, an analysis of these parameters would indicate the likely effectiveness of a chosen method of treatment. Lower calyceal infundibulo-pelvic angle is the most important factor that can predict the stone clearance status after extracorporeal shockwave lithotripsy in adults⁷ and children⁸, although some studies are non-suggestive of this factor⁹.

Although, some data for our population for ultrasonographic assessment of renal size and cortical thickness is available¹⁰, but few studies have been done in the knowledge of detailed anatomy of pelvicalyceal system in local settings^{3, 21}.

MATERIALS AND METHODS

In this cross-sectional study, 25 healthy kidney donors who were referred to the kidney transplant service at Shaafi International Hospital, Islamabad (July 2015 through April 2017) were included. Inclusion criteria included were: Age 18–60 years, having normal renal function, coming through ethical and official processes of kidney donation, and submitting a written consent. Exclusion criteria included poor image quality on IVU, kidneys with duplicated renal artery and vein, kidneys with renal stones, kidneys having large cysts and pelvic kidney. A total of 50 kidneys (from 25 IVU films) were included in this study.

The source of IVU films was from Radiology department. The data was collected using predesigned, pretested Pro-forma. The parameters measured were as follows:

1. Lower Calyceal Infundibular Length (LCIL)
This length is the distance measured from the most distal point at the bottom of the lower calyx to a midpoint of the lower lip of the renal pelvis¹¹.
2. Lower Calyceal Infundibular Width (LCIW)
This width was measured at the narrowest point along the respective infundibular axis.
3. Lower calyceal infundibulo – ureteropelvic angle (LCIUPA)

The infundibulo-ureteropelvic angle (IUPA) was measured between infundibular and ureteropelvic axes.

The 3 major radiographic features of the lower pole calyx were easily measured on standard IVU using a ruler and protractor.

All the measurements were done according to the method described by Elbahnasy et al.¹² (Fig. 1).

Obtained data is being presented as range, mean $\pm$ standard deviation, and percentage (%) distribution. Microsoft Excel program version 2016 was used for statistical analysis.

RESULTS

A total of 50 normal kidneys of healthy kidney donors (from 25 IVU films) were studied. The mean age was 26.9 ± 6.8 years (minimum age was 20 years and maximum age was 41 years).

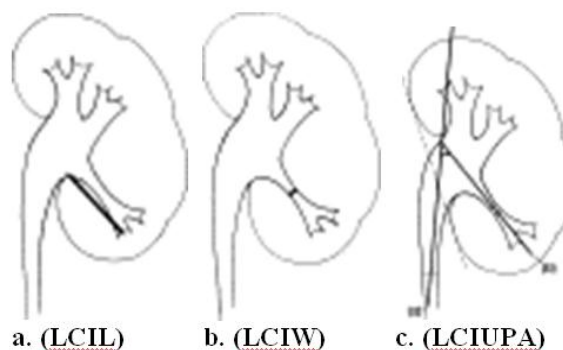


Figure No.1: a. (LCIL) b. (LCIW) c. (LCIUPA)

The result of all lower calyceal parameters observed are shown in table.

The mean LCIL was $26.9 \pm$ SD of 6.8 and mean LCIW was $8.6 \pm$ SD of 2.4. The mean LCIUPA (as measured according to Elbahnasy method) was $53.6 \pm$ SD of 23.3.

Table No.1: Analysis of variables of lower calyceal anatomical factors

Variables	No of kidneys	Range	Mean	SD
LCIL (mm)	50	10.4 – 45.8	26.9	6.8
LCIW (mm)	50	4.1 – 16.6	8.6	2.4
LCIUPA (degree)	50	17 – 129	53.6	23.3

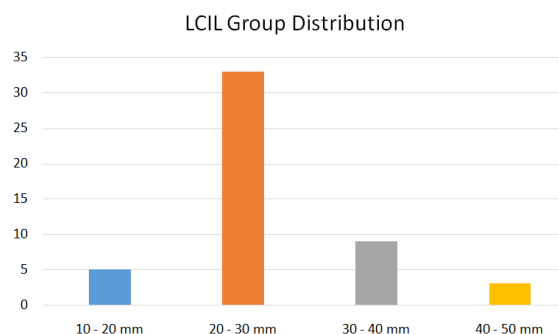
LCIL: Lower Calyceal Infundibular Length, **LCIW:** Lower Calyceal Infundibular Width, **LCIUPA:** Lower Calyceal Infundibulo Uretero Pelvic Angle

Frequency distribution of all three observed parameters are described in graphs 1 – 3.

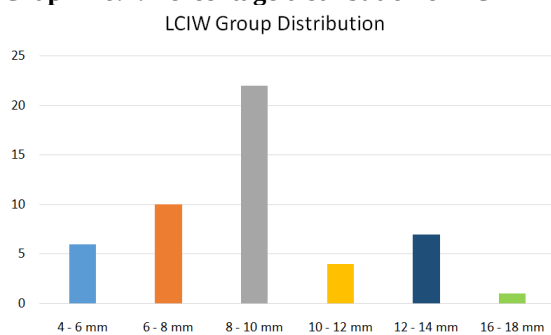
A majority of 33 kidney units (66%) had lower calyceal infundibular length in the range of 20 – 30 mm as depicted in graph 1.

A total of 22 kidney units (44%) had lower calyceal infundibular width in the range of 8 – 10 mm as shown in graph 2.

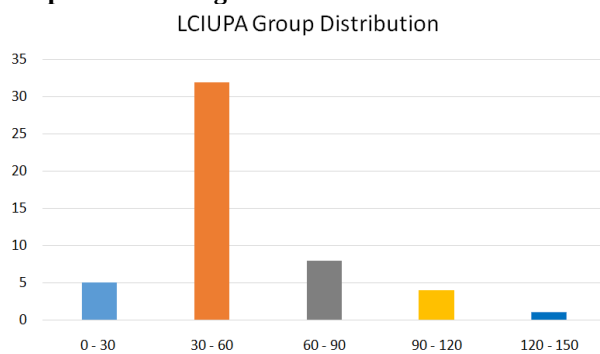
A total of 32 kidney units (64%) had lower calyceal infundibulo ureteropelvic angle in the range of 30 – 60 degree shown in graph 3.



Graph No.1: Percentage distribution of LCIL



Graph 2: Percentage distribution of LCIW



Graph No.3: Percentage distribution of LCIUPA

DISCUSSION

The investigations of the relationship between pelvicalyceal anatomical features and urolithiasis started with the pioneering study of Sampaio & Aragão¹. After that, several studies analysed the pelvicalyceal factors although these studies were generally interested in stone clearance of lower calyceal stones after SWL rather than in its etiologic role^{6,9,12}. In these studies, several anatomical factors, such as infundibular length, width and infundibulopelvic angle were measured and lower pole ratio was calculated on intravenous urogram. Sampaio & Aragão concluded

that an angle of less than 90-degrees between lower pole infundibulum and pelvis, multiple calyces and a calyceal width < 4 mm might lead to retention of residual stones in lower calyceal group after lithotripsy¹. Similarly most studies agreed that the calyceal anatomy was an important risk factor for lower pole stone clearance after SWL^{6,12}, however opposite opinions also exist⁹.

In our present study the mean LCIL was 26.9 mm. It varies from 10.4 – 45.8 mm and it was 20-30 mm in 66% (Graph no. 1). According to Fong Y.K. et al⁶ and Gupta N. P. et al¹³ the mean LCIL was 21.7 ± 6.9 mm in 60.8% & ≤ 30 mm in 77% respectively. Both studies concluded better stone clearance after Lithotripsy in these kidneys. However, in a similar study, Madbouly K. et al⁹ found that the mean LCIL was 20.9 ± 6.56 mm which had no impact on stone clearance after 3 months of lithotripsy.

In our study the mean LCIW was 8.6 mm. It varies from 4.1 – 16.6 mm and it was 8 -10 mm in 44% (Graph no. 2). According to Sampaio F. J. B. et al¹ and Li-ping Xie et al¹¹, the LIW was greater than 4 mm in 60.3% and 67% respectively. Our present findings are comparable with these studies. Similarly, Gupta N. P. et al¹³ found that in 75% of cases the LIW was 5 mm or more and the mean LIW was 6.75 mm.

The mean LCIUPA in our case was 53.6 degree and majority (64 %) were between 30 – 60 degrees (Graph no. 3). According to Zomorodi A. et al¹⁴, the mean infundibulum-uretero-pelvic angle (IUPA) in control subjects and in stone bearing study cases was 53.5 ± 12.7 and 42.6 ± 13.4 , respectively. There was significant correlation between decreased angle and stone formation ($P = \text{or} < 0.001$). In another study by Ahmed E.A. et al¹⁵, the mean infundibulum-uretero-pelvic angle (IUPA) was 52.3 degrees in stone bearing kidney and 54 degrees in normal kidneys ($P = 0.36$). On the other hand, Gökalp et al¹⁶, compared 119 lower calyceal stone forming kidneys with 40 healthy controls and they concluded that lower pole IUPA was not an important factor for stone formation in lower calyx. Similarly, Khan. M et al¹⁷ found no significant effect of lower pole IUP angle on stone free rate after lithotripsy in their series. In another study, Nabi et al¹⁸ evaluated 100 consecutive patients with lower calyceal stones and they found that lower pole IUPA was more acute in 74% of cases in stone-forming side than the normal contralateral kidney. They concluded that IPA was a significant risk factor for lower calyceal stones.

Interpretation of pelvicalyceal anatomy from two-dimensional IVU is very difficult. A large series of three-dimensional endocasts of the kidney collecting system showed that the superior pole was drained by a single calyceal infundibulum in 98% of cases where as the inferior pole was drained by paired calices arranged in two rows in 58% of cases and by a single calyceal infundibulum in only 42% of cases^{19,20}.

Another important point on interpretation of pelvicalyceal variations is the different measurement techniques and interobserver variations. Proper assessment of lower calyceal features seems to be a particular problem because several authors described different methods^{12,13}. A recent study showed that there were high interobserver variations among different techniques²¹. We performed our measurements with the method described by Elbahnasy et al.¹². Additionally, quality of the imaging also bears impact on achieving reliable data.

The 3 major radiographic features of the lower pole calix (infundibulo uretero-pelvic angle, and infundibular length and width) has a statistically significant influence on stone clearance after ESWL. A wide infundibulopelvic angle or short infundibular length and broad infundibular width regardless of infundibulopelvic angle are significant favourable factors for stone clearance following ESWL¹². Conversely, these factors have a cumulatively negative effect on the stone clearance rate after ESWL when they are all unfavourable. In flexible ureteroscopy, particular anatomy of pelvicalyceal system may have a negative impact when there is uniformly unfavourable pelvicalyceal anatomy.

CONCLUSION

Our study was a sincere effort to measure lower calyceal anatomical factors in a local population in order to identify favourable and unfavourable lower pole calyceal anatomical factors in comparison with already published series. Knowledge of these lower calyceal anatomical factors is of immense value in deciding best method of treatment of lower calyceal stones in a patient for a successful outcome.

We believe that the physician should consider these anatomical features when suggesting ESWL to treat calculi in the lower calyces. More detailed studies are needed in a 3 dimensional views of renal pelvicalyceal anatomy in order to reflect the data more accurately.

Author's Contribution:

Concept & Design of Study:	Atika Khurshid
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Final Approval of version:	Atika Khurshid

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

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Assess the Role of Dental Surgeons in Prevention and Early Diagnosis of Oral Cancers

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ABSTRACT

Objective: To determine the role of dentists in early diagnosis and prevention of oral cancers.

Study Design: Observational / descriptive study.

Place and Duration of Study: This study was conducted at the Islam dental College Hospital, Sialkot and various Dental Clinics in Sialkot region during February and March 2017.

Materials and Methods: A questionnaire was designed and distributed among the dentists working in the Islam Dental College hospital as well as in the Sialkot district region to know what role they play in the prevention and early diagnosis of this deadly disease.

Results: Only 18% of the dentists thoroughly examined the entire oral mucosa of their patients. More than sixty percents (60%) of the dentists ask about the use of tobacco, alcohol and other risk factors and only 55% advised and helped their patients to quit these habits. Also about 40% dentists did not ask or asked rarely about the use of cancer risk factors. Even fewer 9% considered the possibility and then searched for incidental finding of oral cancer of which only 6% dentists took biopsy or specialist consideration to confirm the finding of suspicious lesions.

Conclusion: The results of this study indicate that dental surgeons need to do more for the prevention and early diagnosis of oral cancers.

Key Words: Oral Cancer. Diagnosis, Prevention.

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INTRODUCTION

The incidence of oral cancers especially the squamous cell carcinoma accounts for 3% of all the cancers worldwide¹. Most of the cancer cases are found in the developing countries like Pakistan, Brazil and India and one developed country; France. Smoking, pan chewing and alcohol consumption makes the most recognized risk factor for such cases. Betel quid and smokeless tobacco chewing are also important risk factors in some populations^{2,3} and human papillomavirus (HPV) infection appears to be a risk factor for younger populations⁴. Even though the oral cavity is the most accessible area for examination, up to 50% of oral cancers are not detected until the disease is well established⁵. Due to lower literacy rate, socio-economic status, and life style, it is growing every year and carries a poor prognosis with overall survival around 50%⁶.

Oral cancers can easily be prevented by making an early diagnosis and by creating awareness about its risk and the causative factors.

Total lack of awareness, low literacy rate, poverty and the unavailability of the specialist are some of the major causes of the high incidence and late diagnosis in Pakistan. All the health care providers can play a very important role in the diagnosis and early treatment of oral cancers but the dental professionals are directly responsible for the oral health, prevention, diagnosis and timely management of oral and dental diseases including oral cancers or any suspicious lesions in oral and head and neck regions including oral cancers⁷. The main purpose of this study was to see the role played by the dental surgeons in the prevention and timely diagnosis of oral cancers. Many similar researches have already been done in Pakistan and other countries and are very helpful in determining the deficiencies on the part of dental surgeons. It is hoped that this study will help dental surgeons to become aware of their responsibility in preventing and diagnosing such lesions to enhance healthy growth of community.

MATERIALS AND METHODS

This study was conducted mainly at Islam Dental College Hospital, Sialkot and at different dental clinics in Sialkot district in the months of February and March, 2017. A questionnaire was given out to around 250 male and female dental surgeons randomly who were ready to fill it. The questionnaire contained the

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information about the patient's examination, history especially about use of risk factors like tobacco, paan, gutca, and of other cancerous lesions in head and neck region. Instructions were given out to the patients to leave such habits. Also, diagnosis of any suspicious oral lesion or cancer was made.

The questionnaire was distributed personally making confidentiality of the patient of prime importance and was kept secret during the study. It was later collected after 2-3 days and the dental surgeons who filled the forms on time and completely were also included in the

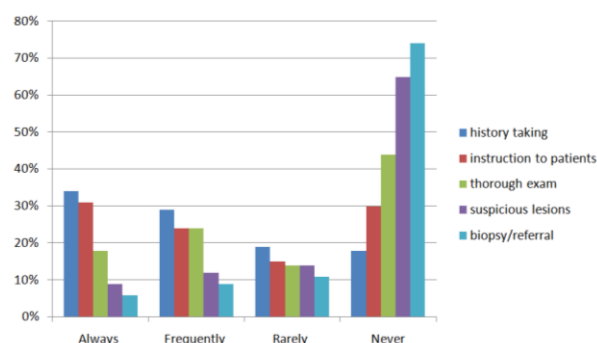
results. All the questionnaires which were ill-filled or incomplete were excluded from the study. Simple percentages and calculation of the results were made.

RESULTS

Out of 250 questionnaires that were distributed amongst the dentists 230 were completed on time and returned and out of that 170(74%) were male and 60 (26%) were female dentists.

Table 1: Oral Cancers Diagnosis and Prevention by Dental Surgeons

Variables	Always	Frequently	Rarely	Never	Total
History of Tobacco, Paan, Gutca, Alcohol	78(34%)	66(29%)	44(19%)	42(18%)	230
Thorough Examination of oral and head and neck region	40(18%)	56(24%)	32(14%)	102(44%)	230
Instruct patient to quit habits	72(31%)	56(24%)	34(15%)	68(30%)	230
Consideration of any suspicion of oral cancer	20(9%)	28(12%)	32(14%)	150(65%)	230
Biopsy/ refer for specialist	14(6%)	22(9%)	26(11%)	172(74%)	230



Picture No.1: Graphical Presentation of the Dental Surgeons Performing Specific Procedure for Prevention and Early Diagnosis of Oral Cancer/Oral Lesions.

About 37% dentists rarely or never asked about use of tobacco, paan, alcohol habits. Only about 55% Dentists gave instructions to their patients to leave such habits which may cause oral cancers. Eighteen percent (18%) of the dentists always did a thorough oral and head and neck examination. Only 9% took great care to consider lesions suspicious leading to oral cancer and only 6% took biopsies or referred to specialists to confirm their findings. Results are shown in table 1 and graphically shown in picture 1.

DISCUSSION

Squamous cell carcinoma is one of the most common cancer in the world mainly because of the smoking habits among the populations. All the health professionals especially the dentists are very well aware that the usages of any form of tobacco, alcohol, pan or betel chewing are the main concerning factors for oral cancers. The lack of public awareness is the main issue that we have to deal it. The study that was conducted was mainly done to enhance the awareness of the dental

professional to be careful and responsible in the prevention and correct diagnosis of lesions so that there can be a decrease in the morbidity and mortality rate due to oral cancers.

The results clearly showed us that only 34% dentists did take complete history of patients and asked the important questions about smoking, the use of tobacco, pan and alcohol but only about one third (31%) of dentists did advise their patients to stop using such pre-cancerous agents. The study clearly showed that the dentists do not take complete patients history about the use of tobacco as frequently as required which is also mentioned in other studies^{7,8}. Another study also indicated that many dentists don't take serious parts in preventing and cessation of such habits when compared to other health professionals^{9,10,11,12}.

Prevention and diagnosis of early cancerous lesions in majority of patients is possible simply by careful examination of the oral and head and neck area of the patient, taking detailed history about risk factors and identifying any suspicious lesions. Any lesion **which does not resolve within two weeks period on its own, with or without treatment**, should be considered suspect and worthy of further examination or referral to a specialist. Early diagnosis and initial stage are the most significant factors affecting the treatment and survival rate of oral cancer patients. As five year survival for a localized stage 1 oral cancer is 80% that can decline to 51 % with regional spread and deteriorates further to 29.5% with distant metastasis¹³.

The results of present study show that majority of the dentists just pay attention to the dental treatments and do not seriously make efforts to prevent or diagnose oral cancers at an early stage. It is why most of the oral cancers are diagnosed at late stage with advanced lesions having significantly poorer survival rate as also mentioned in a study by Shah et al⁷. General Medical

Practitioners and dental surgeons can have an important role in the early detection of oral cancer. Research has shown that GMPs do not opportunistically screen high-risk individuals¹⁴.

CONCLUSION

Oral cancer claims hundreds of thousands of lives every year around the world. It can be prevented and diagnosed easily. Health professional and especially dental surgeons should be careful when treating patients. Education and the development of patient awareness regarding the risk factors leading to oral cancer are primary responsibilities of the dental surgeons. They should play their active role in the prevention, early diagnosis and management of oral cancers and other fatal conditions.

Author's Contribution:

Concept & Design of Study: Sana Zafar
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Descriptive Study on Presentation of the Stroke

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ABSTRACT

Objective: To see the clinical presentation of Stroke and risk factors

Study Design: Descriptive / Cross Sectional Study

Place and Duration of Study: This Study was conducted in the department of Medicine at PMCH Nawabshah from November 2015 to February 2017.

Materials and Methods: 115 patients were enrolled for this study 67 were males and 53 were females, informed consent was taken from all the relatives of patients using Questionnaire translated into local languages, statistical analysis was done using SPSS 15 version.

Results: Age range from 47 to 76 years mean age was 63.91±8.05. 38 patients were drowsy or unconscious. Out of 115 patients 70 patients were diagnosed as Ischemic Stroke and 45 as Hemorrhagic Stroke diagnosed using CT Scan Brain. 84 patients were diabetic, 95 patients were hypertensive and 31 patients were non diabetic and 20 patients were non hypertensive, cholesterol level ranged 153-294 mg/dl, RBS ranged 120-452 mg/dl. 96 patients were discharged and 19 patients expired due to severity of disease and complications.

Conclusion: Stroke is a major problem in our country, main risk factor noted was diabetes, hypertension, hyperlipidemia and old age. Proper treatment of diabetes, hyperlipidemia, hypertension and counseling about disease mortality and morbidity can be reduced.

Key Words: Stroke, Ischemia, hemorrhage, Diabetes Mellitus, Hypertension

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INTRODUCTION

Stroke is a disease characterized by decreased blood flow to brain resulting cell death. There are two types of stroke ischemic and hemorrhagic. WHO reported 15 million patients of stroke worldwide per year. Out of these 5 million are disabled and 5 million die.¹ Yearly incidence of stroke in USA is 800,000, 82-92% of these strokes are ischemia. Stroke is the 5th main cause of mortality and morbidity.² With disturbance of brain function patient can not move one side of body with loss of sensation and in some cases aphasia.³ Few patients present with facial palsy and loss of vision to one side. Severe headache associated with hemorrhagic stroke.³ Patient may develop complete paralysis or recover within 24 hours, if recover within 24 hours termed as a TIA.³ Main risk factors of stroke are diabetes mellitus, hypertension, hyperlipidemia, smoking, atrial fibrillation, mitral or aortic stenosis and atherosclerosis or old age.³ Ischemic stroke caused by thrombosis or embolism.⁴

Ischemia due to particular vessel involvement release of excitatory and other neuropeptides, resulting calcium flux into neurons, cell death and neurologic deficit is increased. Hypoxia and depletion of ATP caused by ischemia, due to lack of energy is not available for maintenance of ionic gradients across the cell membrane and cell depolarization. Influx of calcium and sodium ions and inflow of water into cell resulting cerebral edema.⁵ In ischemic stroke local blood flow is limited in cerebral arteries, affected cerebral blood flow lower than 10 ml/100 gm of tissue/minute. Stroke resulting within minutes due to cell death.⁶ Ischemic stroke is subdivided into 3 sub types,⁷ large artery, small vessel or lacunar and cardioembolic infarction. Arteries involved are carotid, vertebrobasilar and cerebral arteries. Recurrent stroke is mainly due to cardioembolic emboli, with high mortality. Intracerebral hemorrhage occurs in arteries and arterioles,⁸ secondary hemorrhage occurs due to AV malformation, in subarachnoid hemorrhage bleeding occurs outside the brain tissue but in skull, mortality rate is high in intracerebral hemorrhage. Cocaine causes spasm of an artery. Stroke is diagnosed with CT Scan, MRI, Doppler ultrasound and arteriography. Blood test commonly used for the diagnosis of stroke.⁹ MRI is useful in chronic hemorrhages.¹⁰ Medication recommended for ischemic stroke is Alteplase or rt-PA, if needed anti hypertensive, anticonvulsants and osmotic agents are recommended. Treatment of comorbid disease if present. Criteria for treatment of ischemic stroke are, 1. Anticoagulation 2. Reperfusion 3. Antiplatelets.

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Conservative and supportive treatment is better for intracerebral hemorrhage. Intraventricular hemorrhage and hydrocephalus require ventricular drainage. evacuation of hematoma in cerebellar hemorrhage is necessary. Survival is improved with recombinant factor 7. Aim of treatment in SAH is to prevent hemorrhage and surgical clipping.cmdt

MATERIALS AND METHODS

This descriptive cross sectional study was carried out in the department of Medicine PMCH Nawabshah from November 2015 to February 2017. After taking informed consent to relatives of patients and well conscious patients a written Questionnaires translated in Sindhi and Urdu languages was given and study was done using Questionnaires. Detailed history was taken. Clinical examination was done with all routine investigations, CT Scan, ECG, Echocardiography and specific investigations according to cause. Statistical analysis was done using SPSS 15 version.

Inclusion criteria

All patients with hemiplegia

CT Scan positive with infarction or hemorrhage

Exclusion criteria

Uncooperative patient

CT Scan negative for infarction or hemorrhage

Intracranial tumor

RESULTS

Total patients selected for this study were 115, 67 males, 53 females, age ranged 47 to 76 years mean age was 63.91 $\pm$ 8.05, right sided hemiplegic were 87, left sided hemiplegic were 28, aphasia noted in 46 patients, CT Scan was done all patients, infarction was noted in 70 patients, hemorrhage in 45 patients. GCS scale 7/15 in 63 patients, 12/15 in 18 patients, 9/15 in 10 patients, 3/15 in 17 patients and 15/15 in 7 patients. 47 patients admitted with altered level of consciousness.

Table No.1: Type. Stroke

Variable	Frequency	Percent	Valid Percent	Cumulative Percent
Valid 1	70	60.9	60.9	60.9
2	45	39.1	39.1	100.0
Total	115	100.0	100.0	

Table No.2: Occupation

Variables	Frequency	Percent	Valid Percent	Cumulative Percent
Valid 1	50	43.5	43.5	43.5
2	52	45.2	45.2	88.7
3	8	7.0	7.0	95.7
4	5	4.3	4.3	100.0
Total	115	100.0	100.0	

Table No.3: Sex

Variables	Frequency	Percent	Valid Percent	Cumulative Percent
Valid 1	62	53.9	53.9	53.9
2	53	46.1	46.1	100.0
Total	115	100.0	100.0	

Table No.4: Type. Stroke

Variables	Frequency	Percent	Valid Percent	Cumulative Percent
Valid 1	80	69.6	69.6	69.6
2	15	13.0	13.0	82.6
3	13	11.3	11.3	93.9
4	7	6.1	6.1	100.0
Total	115	100.0	100.0	

Table No.5: Paired Samples Statistics

		Mean	N	Std. Deviation
Pair 1	Type.Stroke	1.39	115	.490
	RBS	281.17	115	87.947
Pair 2	Type.Stroke	1.39	115	.490
	Age	63.91	115	8.053
Pair 3	Type.Stroke	1.39	115	.490
	Cholesterol	248.18	115	31.939
Pair 4	Type.Stroke	1.39	115	.490
	Sys.BP	172.7391	115	32.88232
Pair 5	Type.Stroke	1.39	115	.490
	Dia.BP	99.3478	115	13.08745

Table No.6: Paired Samples Correlations

	Variables	N	Correlation	Sig.
Pair 1	Type.Stroke& RBS	115	.126	.181
Pair 2	Type.Stroke& Age	115	-.414	.000
Pair 3	Type.Stroke& Cholesterol	115	-.014	.881
Pair 4	Type.Stroke&Sys.BP	115	.123	.189
Pair 5	Type.Stroke&Dia.BP	115	.081	.389

Table No.7: Statistics

	Type Stroke	Age	Occupation	Sex	Education
N Valid	115	115	115	115	115
Missing	0	0	0	0	0

Facial palsy noted in 27 patients .At the time of admission motor power was 0/5 in 78 patients, 4/5 in 23 patients, 3/5 in 11 patients, 2/5 in 3 patients, planters up going in 97 patients, equivocal in 18 patients all the patients. 84 patients were diabetic, random blood sugar level ranged 120-452 mg. 95 patients were hypertensive, systolic BP ranged 120-230 mmHg, diastolic BP ranged 70-130 mmHg. 28 patients were non diabetic nonhypertensive. Cholesterol was

increased 104 patients, ranged 153-294mg. Hb ranged 7-12, Leukocyte count ranged 8967-15725. Platelets count ranged 80218-222042. Urea ranged 23-280, creatinine ranged 0.8-19. PT ranged 12-24. In statistical analysis males denoted by 1, females denoted by 2,

uneducated by 1, primary by 2, middle by 3, matric by 4, farmer by 1, housewife by 2, unemployed by 3, self business by 4. Out of 115 patients 96 discharged and 19 expired due to severity of disease and complications.

Table No.8: ANOVA

Variables		Sum of Squares	Df	Mean Square	F	Sig.
Age	Between Groups	1264.210	1	1264.210	23.308	.000
	Within Groups	6128.921	113	54.238		
	Total	7393.130	114			
Sex	Between Groups	.663	1	.663	2.683	.104
	Within Groups	27.911	113	.247		
	Total	28.574	114			
Occupation	Between Groups	18.518	1	18.518	41.372	.000
	Within Groups	50.578	113	.448		
	Total	69.096	114			
Education	Between Groups	39.131	1	39.131	76.978	.000
	Within Groups	57.443	113	.508		
	Total	96.574	114			
RBS	Between Groups	13906.006	1	13906.006	1.811	.181
	Within Groups	867840.516	113	7680.005		
	Total	881746.522	114			
Cholesterol	Between Groups	23.216	1	23.216	.023	.881
	Within Groups	116269.949	113	1028.938		
	Total	116293.165	114			
Hemoglobin	Between Groups	39.862	1	39.862	42.486	.000
	Within Groups	106.021	113	.938		
	Total	145.883	114			
L.Count	Between Groups	4922418.962	1	4922418.962	3.049	.083
	Within Groups	182406952.986	113	1614220.823		
	Total	187329371.948	114			
Platelets	Between Groups	1255166843.494	1	1255166843.494	1.184	.279
	Within Groups	119781080338.071	113	1060009560.514		
	Total	121036247181.565	114			
PT	Between Groups	12.524	1	12.524	1.580	.211
	Within Groups	895.771	113	7.927		
	Total	908.296	114			
Urea	Between Groups	655.962	1	655.962	.204	.653
	Within Groups	363722.421	113	3218.782		
	Total	364378.383	114			
Creatinine	Between Groups	2.651	1	2.651	.198	.657
	Within Groups	1514.780	113	13.405		
	Total	1517.432	114			
Sys. BP	Between Groups	1876.896	1	1876.896	1.747	.189
	Within Groups	121385.278	113	1074.206		
	Total	123262.174	114			
Dia.BP	Between Groups	128.587	1	128.587	.749	.389
	Within Groups	19397.500	113	171.659		
	Total	19526.087	114			

DISCUSSION

Stroke is a major problem in our country. In our study major risk factors found were diabetes mellitus and

hypertension. Majority of the patients reported in acute stroke.¹¹ Diagnosis of acute stroke is a challenge. Training about stroke management for physicians and nursing is important. Stroke patients present weakness of arm and leg, most of the patient are obese, having

atrial fibrillation at the time of hospitalization. Previous observations of stroke with history of atrial fibrillation in hospitalized patients.¹² As compared to community stroke patients cardioembolic risk is more in hospital stroke patients.¹² Withdrawal of anticoagulation treatment in atrial fibrillation patients develop ischemic stroke. Poor prognosis was noted in cardioembolic stroke with atrial fibrillation in previous studies.¹³ Early anticoagulation in these patients is helpful. Patients awaiting i/vtPA, CT, MRI and EEG are recommended.¹³ After anterior circulation ischemic stroke is associated with worse neurological outcome with elevated systolic blood pressure, systolic blood pressure is better predictor of neurologic outcome.¹⁴ In normal circumstances cerebral blood flow is maintained by cerebrovascular bed autoregulation.¹⁵ After severe to moderate ischemic stroke autoregulation is lost.¹⁶ No benefit or worse outcome stroke with antihypertensives in a study.¹⁷ For ischemic stroke labetalol was superior than calcium channel blockers.¹⁸ Vasopressor in ischemic stroke increases neurological outcome without any side effect in a randomized controlled trial.¹⁹ There is increased chances of ischemic and hemorrhage stroke in diabetes.²⁰ In acute stroke hyperglycemia is common, may be due to stress or impaired glucose metabolism. In a study on rats cerebral blood volume in cerebral hemisphere is reduced 37% in hyperglycemic as compared to normal glucose level.²¹ Behavioral risk factors like obesity, heavy drinking and smoking should be reduced. Incidence of stroke is increased in males as compared to females. In European countries risk increased in females less than 30-35 years of age in studies. Due to genetic susceptibility premature atherosclerosis can occur. For prevention of stroke knowledge about risk factors is important, most of the patients know about risk factors.²¹ Hypertension was most commonly identifiable risk factor second obesity, consumption of high food, smoking and alcohol consumption were known risk factors.²² These are modifiable risk factors, other known non modifiable risk factors are old age and family history. In another study it was found that peoples who were graduate or master in their educational qualification know well about risk factors as compared to non educated and primary or secondary education,²³ same was observed in this study. 80% patients of stroke were hypertensive, diabetic or both a study in Nigeria.²⁴ Stroke prevention is best than treatment in poor countries, knowledge of risk factors and health education are good measures to prevent stroke.²⁵

CONCLUSION

Stroke is a major problem in our country, major risk factors noted was Diabetes mellitus, Hypertension, hyperlipidemia and old age. Ratio in male sex is increased, avoiding cigarette smoking, weight reduction

in obese people, education of the people about risk factors, increase physical activity, avoidance of saturated fat intake, morbidity and mortality can be reduced. Diabetes is a modifiable with oral hypoglycemic and insulin therapy. Poor outcome of stroke in ischemic and hemorrhagic stroke noted in hyperglycemia. People give up antihypertensive after BP control and chances of stroke are increased and there is a need of education about BP control.

Author's Contribution:

Concept & Design of Study:	Jeando Khan Daidano
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Data Analysis:	Nazia Azam Yusufani, Ahmed Ali Kanher
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