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Editorial

Routine House Work May Improve Heart Health

Mohsin Masud Jan

Editor

House work may be as good as formal exercise when it comes in reducing the risk for heart attack and stroke, Swedish researchers say.

For people 60 and older, just keeping busy with daily activities can reduce the risk of cardiovascular problems by nearly 30 percent and even prolong life, they added. Being on your feet and active cuts the time spent sitting around, pointed out lead researcher Elin Ekblom-Bak, of the Swedish School of Sport and Health Sciences and the Karolinska Institute, in Stockholm.

“Sitting is mainly replacing time you spend in daily activity and vice versa,” Ekblom-Bak said. A recent study found long periods of sitting actually resulting to increase the risk for diabetes, cardiovascular disease and death, she noted. “The results of this study showed that activities of daily life are as important as regular intentional exercise for older adults for cardiovascular health and longevity,” she said. But it doesn’t mean formal exercise isn’t important. “We saw that those who exercised regularly and that also had a daily physically active life had the lowest risk of all,” Ekblom-Bak explained.

A time, people spend in exercising, however, is only a small part of the day, which leaves a lot of time for daily activities or sitting, she added. For the new study, researchers collected data on more than 3,800 men and women in Sweden who were born 1937 and 1938. Participants were asked about their lifestyle, which included information on their diet, whether they smoked or drank alcohol, and how physically active they were.

The participants were also asked how often they took part in activities, such as gardening, do-it-yourself projects, car maintenance and blackberry picking over the past year. They were also asked about any exercise they did. To see how heart healthy they were, the researchers examined the participants and took blood samples to assess levels of fat and sugar. They also checked for high levels of blood clotting factor, which is linked to a raised heart attack and stroke risk.

During more than 12 years of follow-up, 476 of the participants died from or experienced a first heart attack or stroke, and 383 died from other various causes. People whose daily activities kept them moving

reduced their risk of a heart attack or stroke by 27 percent and the risk of dying from any causes by 30 percent, compared to people who spent the least amount of time on their feet.

High stress can be associated with increased risk of heart disease.

“The reason for this labor-linked risk is unclear, but might be related to higher stress levels,” Phillips said. In one study, researchers looked at 250 patients who had suffered a first stroke and 250 who had suffered a first heart attack or other type of heart event. They were compared to a control group of 500 healthy people. Stroke and heart patients were more likely to have physically demanding jobs than those in the control group, researchers found. After adjusting for age, sex and a number of lifestyle and health factors, they concluded that having a less physically demanding job was associated with a 20 percent lower risk of a heart event or stroke.

Panagiotakos said the increased risk of stroke and heart events among people with physically demanding jobs may be due to mental stress, while exercise helps reduce stress. He also said people with physically demanding trends to have lower incomes, which might limit their access to health care.

The study suggests that leisure-time exercise might be important to “balanced out” the physical stress encountered in laborious jobs. “This delicate interaction between work and leisure-time activity warrants further research in order to appropriately guide public health,”

In a second study presented at the same meeting, researchers looked at more than 14,000 middle-aged men who did not have heart disease and were followed for about three years on average. The investigators found that physically demanding works was a risk factor for developing coronary heart disease. They also found that men with physically demanding jobs who also did moderate to high levels of exercise during their leisure time had an even greater risk (more than four fold higher) of developing coronary heart disease.

Effectiveness of 1% Versus 0.2% Chlorhexidine Gels in Reducing Alveolar Osteitis from Mandibular Third Molar Surgery: A Randomized, Double-Blind Clinical Trial

Muhammad Farooq¹, Saqib Ghafoor Kayani³, Muhammad Hamza Hashim¹, Faiqa Hassan⁴, Waleed Javaid Toosy² and Syed Ali Asad Raza Naqvi⁵

ABSTRACT

Objective: One of the leading, recurrent and most familiar problem after extraction is alveolar osteitis (AO). This case was designed to compare and publish the effectiveness of chlorhexidine (CHX) gel in concentrations 1% and .2% in combating post-operative complication of AO especially after surgical removal of retained mandibular molars. Moreover, this study also aimed at assessment and analysis of quality of treatment after use of CHX gel on oral wellness.

Study Design: Observational Study

Place and Duration: This study was conducted at the department of Oral Medicine, Avicenna Dental College Lahore from January 2017 to 2019.

Material Methods: This case study was done on basis of practical clinical practice and on patients. The study was randomized. Total patients subjected to treatment were eighty eight. All the patients after post extraction were treated with CHX gel to overcome complication AO in concentration either 1% or .5%. About 41 patients were treated with 1% of CHX gel and 47 remaining were treated with .2% of gel after extraction. The instructions were given to patients to apply this gel twice a day for duration of one week at least. After a week, assessment was made regarding CHX gel application outcomes.

Results: With the assessment and careful observation, it was found that about 13% patient suffered from AO after application of CHX gel in concentration of 0.2% and about 7% patients suffered from AO after application of CHX gel in concentration of 1%. Such difference was not so important with respect to statistics. The pain and inflammation that patients suffered post surgically was almost same during whole one week duration.

Conclusion: In a nutshell, there is no significant difference post surgically found in patients after application of CHX gel either in concentration 1% or .2% in case of extraction of retained mandibular third molar.

Key Words: Alveolar osteitis, chlorhexidine gel, third molar.

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INTRODUCTION

One of the leading and most potent complication post surgically is alveolar osteitis (AO)¹ that has direct effect in damaging oral health quality of patients mouth².

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Another name given to AO is fibrinolytic alveolitis, alveolitis sicca dolorosa, dry socket and and localized osteitis. Dry socket name given to AO by Crawford in 1986. Currently, dry socket is defined as pain that occurs post operatively around the area of alveolus that increase in severity after 1 to 3 days post surgically along with clot displacement completely or partially without or with presence of halitosis. This new definition has been proposed by Blum³. According to different authors, the AO frequency of occurrence varied from percentage 3 to 4 “0%⁴. The cause of occurrence of AO post surgically is still unknown. There were two theories suggested regarding occurrence of AO post surgically that were fibrinolytics⁵ and secondly, the presence of bacterial infection⁶. From epidemiological point of view there were several risk factors involved in occurrence of AO like surgical trauma by dentist, oral contraceptives pills used by patients, patients poor immunity, gender especially in females, inexperience by dentist, faulty method of extraction, smoking, old age and poor oral

hygiene conditions of patients⁷. So prevention accordingly is always better than cure⁸. There were many drugs also suggested to be applied topically like antifibrinolytics, antibiotics and anti septic agents in the prevention of AO post surgically but antibiotics and antiseptics has won the game against anti fibrinolytics agent in combating AO⁴. The antiseptic agent used most commonly in clinical practice in prevention of AO is chlorhexidine (CHX). It has been proven by meta-analysis⁹ that CHX mouthwash usage on following day of extraction of third molar and topically application of CHX gel posts surgically twice a day for a week reduces incidence of AO by great extent. In a recent analysis, it has been shown that application of CHX gel 0.2% post surgically at extraction site twice a day for a week has been considered a best preventive measure against AO¹⁰ since it has no interfere with alveolar hemostasis locally¹¹. The application of CHX gel has shown rapid excellent and extraordinary antiseptics effects against antibacterial infection at extraction site than all the other agents in oral cavity¹². The effectiveness of CHX depends on concentration of CHX used in preparation of CHX gels. The CHX gels with higher percentage of CHX have higher success rates than low concentration gel formulations in treatments like periodontal diseases¹⁴, after the completion of surgical oral treatments¹⁵, in dental implant¹⁶, in controlling and prevention of plaque¹⁷, in prevention of caries¹⁸, and in promoting healing of wound¹⁹. So, this case was designed in order to make comparison of effectiveness between CHX gel in concentration of 1 % and 0.2 % post surgically when use twice a day over a span of 7 days after extraction of retained mandibular third molar and its impact on overall patients oral health quality.

MATERIALS AND METHODS

The results of this current case was based on clinical trials along with consent statement (20). This case study was totally randomized and consists of comparison between two groups. This study took place from January 2017 to 2019 in private dental hospital in Lahore, involving both the genders of age groups from 18 years to 44 years. All the patients presented in these departments had retained mandibular third molar along with difficulty index according to Korean score ranging from 4 through 7 (21). The two expert maxillofacial surgeons rated this difficulty index. Things that were excluded in case study include aids, pregnancy and lactation in women, antibiotics and analgesics taken before procedure, patients allergy to CHX, paracetamol, ibuprofen, articaine, the simultaneous extraction of two third molars, patient's psychological issues, jaw pathologies, or prolonged extraction time (over 30 min). The informed consent was taken from all of the patients as part of ethics. There were two different concentration of CHX gel were used in this case pharmaceutically

these forms were 0.2% (laboratorios kin s.a., barcelona, spain) and secondly, 1% (glaxosmithline consumer healthcare, dublin, ireland). At the start of this extraction assessment, the maxillofacial surgeons taught patients to note following variables during the whole week from day 1 to day 7 by using mill metric ruler that include edema presence during basal and day 1,2 and 7th day post extraction and interincisal aperture basal and at day 1,3 to 7th. In order to measure edema, landmarks that were taken into account by patients were tragus, lateral canthus, mandibular angle, pogonion (at operated site), nasal wing at base, labial commissure. Patients were advised to note pain as well as inflammation that occurred post surgically basal,3 and 7 hourly and at days 1,3 and 7th. The inflammation and pain were noted on special analogical visual scale that ranged from 0 to 100. In order to reduce pain and numb the surgical site local anesthesia (articaine 40mg/ml-epinephrine 0.01%; laboratorios normon s.a., madrid, spain) was given to the lingual, long buccal and inferior alveolar region. In order to gain access to the extraction site a triangular flap was made by maxillofacial surgeon to have an easy access to third molar. Moreover, osteotomy and dental sectioning was performed where requirement was there. After the tooth had been extracted, the alveolar site of third molar was rinsed, sharp bony edges were smooth, the surrounding granulation tissue and follicular remnants were removed and CHX in concentration 0.2% was applied deep inside the alveolar region. At the end of procedure, the wounded site was sutured with 4/0 silk stitches. The patients after extraction were divided into two groups. On one group about 47 patients CHX in 0.2% concentration was applied and in other group about 41 % of CHX was applied. This distribution was made using a simple computer program. All the patients vividly and clearly instructed to apply CHX gel at day of extraction till 7th day post extraction. The patients were also instructed to apply gel at surgical site after cleaning their teeth with soft surgical brush twice a day. In order to reduce pain patients were instructed to take ibuprofen 600 g every 8 hourly along with paracetamol 12 hourly. The physical appearance is of alveolitis was taken as main variable 7 days after extraction. More over diagnostic criteria given by Blum as followed³. All the patients were free to make telephonic communication with doctors for follow ups. The patient's tolerance to treatment was assessed from day 1 to day 7 using analogical scale of 1 to 5. Then finally in end, a questionnaire designed suggested by Savin and Ogden²² was used that had five dimensions and sixteen items. The measurement of sample size was done by simple generalized rule. 0.6 was considered as standardized difference. SPSS windows 15.0 (spss inc., chicago, il) was used to analysis data..

RESULTS

Table No 1: Description and comparison of patients (n=88).

Variable	CHX 0.2% (n=47)	CHX 1% (n=41)	p-value
Sociodemographics			
Sex (Men-Women) (%) ^a	49-51	49-51	0.845 ^f
Age (14 to 24, 25-44) (%)	54-47	43-57	
Age (mean±sd)	25.7±6.8	26.7±6.2	0.605 ^g
Educational level (Primary-Secondary-University) (%)	21-28-51	21-31-48	0.764 ^h
Clinical chart			
Systemic disease (No-Yes) (%)	95-5	94-5	□1 ⁱ
Contraceptives (only women ^b) (No-Yes) (%) Good oral	78-22	81-19	□1 ⁱ
Hygiene (Yes-No) (%)	71-29	72-29	0.837 ^f
Pre-pericoronaritis (No-Yes) (%)	71-29	82-19	0.445 ^f
Tobacco (No-□10 cig./day->10 cig./día) (%)	75-9-17	75-17-9	0.951 ^h
Surgical procedure			
Molar (38-48) (%)	56-44	54-47	0.962 ^f
Surgeon (MRP-DSL) (%)	76-34	47-53	0.096 ^f
Extraction time min. (mean±sd)	12.5±6.6	10.8±5.8	0.214 ^g
Difficulty in extraction (mean±sd)	5.47±1.06	5.34±1.21	0.557 ^g
Exposure (Included-Semierupted) (%)	30-70	38-62	0.595 ^f
Osteotomy (No-MV-MVD-MVDO) (%)	67-9-15-9	57-3-26-14	0.283 ^j
Odontosection (No-Yes) (%)	86-16	75-25	0.311 ^f
Flap enveloped or triangular (%)	92-8	82-17	0.411 ^f
After surgery			
Alveolitis (No-Yes) (%) Tolerance	86-14 ^d	93-6 ^e	0.487 ⁱ
(mean±sd) ^h	4.36±0.87	4.49±0.76	0.523 ^g

Total patients underwent surgical extraction were 88 for retained mandibular third molar. About 47 patients were treated with 0.2% CHX gel and 41 patients were treated with 1% CHX gel. The age range of patients ranged from 18 to 44 years. Out of total 88 patients, about 41 patients were male and remaining 47 were female. About nine women were on oral contraceptive pills and about 22 patients among males were smokers. the list of risk factors in terms of surgical procedure, clinical variables and sociodemographic variables were listed in table 1 . Statistically no visible difference were found in both these groups as there were 13% patients reported with AO after application of CHX gel in concentration 0.2% and about 7% patients reported AO after application of 1% gel CHX gel (table 1).The variables like inflammation and pain post surgically during a week was found among both groups member. The figure 1 clearly depicts that no significant difference was found among the both groups. The figure 2 depicts the maximum interincisal aperture before surgical removal of retained mandibular molar and at first, second and seventh day post surgically. It was found that no statistically significant differences were seen among both groups when compared. The evolution of edema and baseline levels are shown figure 3 that once again prove no significant differences are there among both groups. There was none adverse effects of treatment shown by patients. The oral health related quality of treated patients over the period of 7 days has been shown by table 2.

There was no significant difference could be marked among two groups in terms of day 1 and day 7. There was improvement in each directions with the use of this treatment in these two groups except psychosocially. The variables like inflammation and pain post surgically during a week was found among both groups member. The figure 1 clearly depicts that no significant difference was found among the both groups. The figure 2 depicts the maximum interincisal aperture before surgical removal of retained mandibular molar and at first, second and seventh day post surgically. It was found that no statistically significant differences were seen among both groups when compared. The evolution of edema and baseline levels are shown figure 3 that once again prove no significant differences are there among both groups. There was none adverse effects of treatment shown by patients. The oral health related quality of treated patients over the period of 7 days has been shown by table 2. There was no significant difference could be marked among two groups in terms of day 1 and day 7. There was improvement in each directions with the use of this treatment in these two groups except psychosocially.

DISCUSSION

Due to the repeated occurrence of AO post surgically specially in mandibular third molars that are retained⁴, and the effect of AO on oral health quality of patients²³, it was necessary to find remedy for AO. prevention from occurrence post surgically. The exact cause of AO has not been identified yet²⁴, but it was

Table No. 2. OHRQoL of patients, at days 1 and 7 After Rsurgery (n=88).

Variable ^a	Day 1				Day 7				Comparisons			
	CHX 0.2% (n=47) [A]		CHX 1% (n=41) [B]		CHX 0.2% (n=47) [C]		CHX 1% (n=41) [D]		A vs B ^e	C vs D ^e	A vs C ^f	B vs D ^f
	% d	mean±sd	%	mean±sd	%	mean±sd	%	mean±sd				
Eating, since your intervention, have you noted any changes in your...?	6-34-37-21 22-44-26-9	2.73±0.86 2.22±0.89	2-35-36-27 19-57-14-10	2.85±0.86 2.14±0.84	28-47-25-2 59-33-6-2	2.00±0.77 1.52±0.72	34-32-31-6 69-19-7-5	2.06±0.91 1.47±0.83	0.571 0.626	0.757 0.450	<0.001 <0.001	<0.001 0.001
ability to chew food	9-48-28-15	2.50±0.86	7-38-31-24	2.71±0.92	56-30-13-0	1.56±0.72	52-31-12-5	1.69±0.86	0.258	0.603	<0.001	<0.001
ability to swallow diet	13-37-26-24	2.61±1.00	10-31-29-31	2.81±0.99	54-28-13-4	1.67±0.87	43-33-19-5	1.85±0.89	0.341	0.285	<0.001	<0.001
enjoyment eating taste	39-41-17-2	1.83±0.80	36-33-14-17	2.12±1.09	65-22-11-2	1.50±0.78	57-26-12-5	1.64±0.87	0.294	0.417	0.033	0.006
speech, since your intervention, have you noted any changes in your... voice?	59-33-4-4	1.54±0.78	60-33-5-2	1.50±0.71	83-13-4-0	1.21±0.51	95-5-0-0	1.04±0.21	0.889	0.060	0.023	<0.001
ability to speak?	26-47-24-4	2.07±0.83	26-45-21-7	2.10±0.88	70-20-9-2	1.43±0.75	69-21-10-0	1.40±0.66	0.936	0.988	<0.001	<0.001
physical effects, since your intervention, have you... experienced pain?	4-47-26-24	2.70±0.89	5-64-24-7	2.33±0.69	33-41-20-6	2.00±0.89	33-45-14-7	1.95±0.88	0.047	0.782	<0.001	0.037
felt ill?	54-22-22-2	1.72±0.89	52-36-12-0	1.60±0.70	67-22-9-2	1.45±0.75	64-19-12-5	1.57±0.88	0.705	0.643	0.031	0.711
appearance, since your intervention	37-44-15-4	1.87±0.83	38-40-19-2	1.86±0.81	67-17-11-4	1.52±0.86	64-29-2-5	1.47±0.77	0.986	0.968	0.030	0.024
has your appearance changed? is it as you expected? ^b	6-26-56-11	2.72±0.75	10-14-60-17	2.83±0.82	2-22-33-44	3.17±0.85	10-29-29-33	2.85±1.00	0.356	0.143	0.005	0.808
psychosocial effects, since your intervention...	83-13-4-0	1.22±0.51	90-7-2-0	1.12±0.40	89-6-4-0	1.15±0.47	93-7-0-0	1.07±0.26	0.286	0.513	0.225	0.500
has your self-confidence changed?	41-26-22-11	2.02±1.04	45-21-10-24	2.12±1.23	65-20-9-6	1.56±0.91	60-19-5-17	1.78±1.13	0.870	0.448	0.004	0.033
have you taken off time at work? has your social life changed?	78-15-6-0	1.28±0.58	69-24-7-0	1.38±0.62	89-9-0-2	1.15±0.51	83-14-2-0	1.19±0.45	0.358	0.444	0.093	0.060
would you undergo surgery again? ^b would you recommend treatment? ^b	15-33-30-22	2.59±1.00	19-38-26-17	2.40±0.99	28-33-13-26	2.37±1.16	26-24-24-26	2.50±1.15	0.384	0.601	0.088	0.449
	21-37-27-16	2.34±0.98	28-34-27-11	2.21±1.00	35-28-15-22	2.23±1.15	31-31-21-17	2.23±1.07	0.534	0.931	0.490	0.852
total score ^c		34.1±7.8		34.0±7.7		27.4±7.7		27.7±8.2	0.891	0.914	<0.001	<0.001

MRP-surgeon 1, DSL-surgeon 2. MV=mesio-vestibular, MVD=mesio-vestibular-distal, MVDO=mesio-vestibular-distal-occlusal.a: Percent distribution rounded to integers for clarity. b: n=24 and n=22 in 0.2%- and 1%-groups, respectively.c: A scale from 1 (low) to 5 (high). d: Corresponds to n=6 alveolitis, with two of them also abscess. e: Corresponds to n=3 alveolitis, with and 2, also with abscess or cellulitis, respectively.f: Chi squared with Yates correction. g: Student t Test for independent samples. h: Mann-Whitney test. i: Bilateral Fisher's exact test. j: chi-squared.

This case study is randomized, double-blindness supported clinically, following consort statements²⁰. The results of this case study showed that no significant difference was found clinically and at patients level from both the concentrations of CHX for AO treatments. So any statement that support any particular treatment was not justified and highly unlikely. One of the short coming for this case study was that no control

group (without any treatment) was selected and observed. The definition of AO given by Blum (3) was mostly used in epidemiological studies¹⁰. Regarding oral health quality of patients a questionnaire was designed that was also used previously in third molar surgery^{22,23}. This questionnaire was simple and easily understandable by patients and researchers^{4,9,10} who worked to find out cure and preventive measure AO occurrence post surgically. Tetracycline is considered very effective as a local antibiotics against AO occurrence⁴, but its use intra alveolar is not recommended to its side effects like systemic toxicity and hypersensitivity reactions²⁴. CHX gel is safe to you for prevention of AO with very less side effects²⁵. Meta-analysis of CHX gel was published by Caso et al which states that use of CHX gel post surgically of retained third molar extraction is associated with no serious side effects and frequency of incidence of AO also appeared to be much less. One of the shortcomings of this meta analysis by Caso was that it only encounter solution form of CHX. One case study

regarding positive effects of CHX gel states that application of CHX gel 0.2% concentration at alveolar site post surgically¹⁵ reduced the occurrence of AO by percentage about 19% (a significant difference) as compare to control group where no treatment was given post surgically at alveolar site after extraction. This is a significant difference. From these conclusions of treatment it has been decided to treat both group of patients with 0.2% CHX gel at alveolar site postsurgically. It becomes protocol to use CHX gel every 12 hourly for seven days by patient at extraction site. CHX in gel form is more expensive than in solution form but it is regarded as best treatment against AO prevention by recent systematic review¹⁰. Our main aim for this case study is that to improve the results of AO prevention by usage of 0.2% of CHX gel²⁶. The effectiveness of CHX is dependent on its dosage. The more the concentration of CHX, the more will be substantivity¹³ and more over more its anti-bacterial effectiveness²⁷. Evidences also show that greater the viscosity of CHX gel harder will be displacement of active agent at extraction site²⁸. It is also noted that use of 1% of CHX gel at extraction site has more positive effects at different clinical level for prevention of AO (14-18). So we can say by increasing concentration of CHX gel by 5% we can more reduce the occurrence of AO post surgically.

CONCLUSION

The difference of AO occurrence by using 1% vs. 0.5% was about half in percentage (7.3% vs. 13%) but from statistics point of view it was not significant. The finding of this case can be found similar to Hita et al.²⁶. Hita et al used the same method and made analysis based on clinical results that AO found after usage of 0.2% was 7.5% as compared to other group where patients suffered 25% from AO after using CHX in concentration 0.12% in mouth rinses. This was a good difference of these two groups when compared but in our case study lack of difference between two groups was due to the others factors that we also observed like inflammation, level of pain, interincisal aperture and secondly in both our groups CHX in gel form (0.5% and 1%) used that it self-reduced the incidence of AO by 19% when applied inside alveolus¹⁵. So it is concluded that clinically 0.2 % concentration of CHX is used in alveolus against AO prevention against 1% CHX gel because of its fewer possible side effects²⁹ and secondly, due to its lower concentration, it can better be retained at extraction site in oral cavity by forming mono layer as compare to high concentration that is just over saturation of CHX concentration³⁰.

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Frequency of Atypical Manifestations of Pediatric Celiac Disease

Muhammad Arshad¹, Ahmad Hassan² and Osama Anwaar³

ABSTRACT

Objective: To determine Frequency of Atypical Manifestations of Celiac Disease in Pediatric age group.

Study Design: Descriptive / cross sectional study.

Place and Duration of Study: This study was conducted at two tertiary care hospitals of Sargodha, Pakistan between September 2014 and March 2019.

Materials and Methods: Total 72 biopsy proven patients of celiac disease were included in the study after informed consent from the parents. Their demographic details as well as clinical, serological and histopathological data was collected on proformas. These statistical variables were analyzed using SPSS 20.

Results: The male to female ratio in our study was 1:1.05, while the mean age of the patients at the time of diagnosis was 5.8 ± 3.12 years. The frequency of chronic diarrhea in these patients was 56.94 % as compared to 40.04% of non diarrheal presentations. The commonest atypical feature in the study was short stature (77.78%). Other significant manifestations included anemia (51.38%), rickets (51.38%), malnutrition (70.8%), abdominal distension (38.89%) and clubbing (12.5 %). Anti TTG was >300 IU in 80.55% patients. The commonest lesion reported on biopsy was Modified Marsh 3b in 39 patients (54.16%) followed by modified Marsh 3c in 21 patients (29.16%) and modified Marsh 3a in 12 patients (16.67%).

Conclusion: The non diarrheal presentations of pediatric celiac disease are increasingly being identified and it is prudent for all pediatricians to keep their threshold very low to screen Celiac disease when dealing patients with such clinical features.

Key Words: Celiac disease, Pakistan, Glutens, Biopsy

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INTRODUCTION

Celiac disease (CD) is a multi-factorial systemic immune dysregulation triggered by consumption of gluten in diet. It primarily affects small intestinal mucosa resulting in progressive villous atrophy.¹ Over the last few decades CD has been more frequently diagnosed all over the world with an estimated prevalence of about 3% in children.² This rising frequency of diagnosis is because of improved understanding of variety of presentations, optimal screening investigations as well as growing burden of the disease.³

Celiac disease has a wide range of clinical manifestations extending from completely asymptomatic forms to obviously symptomatic ones with severe malabsorption syndrome.⁴

However, there has been a pronounced shift in the presenting complaints of pediatric celiac disease towards atypical symptoms during the recent years.⁵ The present-day literature also strongly supports this growing trend of extra intestinal presentations, thus, emphasizing the heterogeneity in clinical spectrum.⁶ This broad spectrum of presentations makes it indispensable for all pediatricians to have an adequate knowledge about the variability in manifestations for an early diagnosis and appropriate management of the disease.⁷

Pakistan is a country with wheat as the main course of weaning diet during early infancy, which makes genetically susceptible children more prone to develop CD. While prompt diagnosis and timely intervention of pediatric CD is critical to avert its complications, unfortunately, there is little local data available regarding the diverse non classical symptoms of CD leading to under diagnosis of the disease.^{8,9}

The rationale of our study is to determine the frequency of atypical manifestations of celiac disease among pediatric population in a low income country with high risk. This will add to the regional evidence regarding pediatric CD presentations and will help to sensitize health professionals for keeping a higher index of suspicion for CD when encountering non-classical symptoms.

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MATERIALS AND METHODS

This was a multi-centered cross-sectional descriptive study carried out in District Head Quarters Hospital and Mubarak Hospital, Sargodha. The study was conducted from September 2014 to March 2019 after taking informed consent from institutional ethical committee. Total 72 children, 41 from District Head Quarters Hospital and 31 from Mubarak Hospital, Sargodha were included in the study after informed consent from their parents. Sample size was calculated by using online open Epi sample size calculator ¹⁰ by taking frequency of non diarrheal manifestations as 17.4 % ¹¹, margin of error as 8.8 % and confidence level as 95%.

A total of 350 patients with clinical suspicion of celiac disease including diarrheal as well as non diarrheal presentations in the form of constipation, anemia, short stature, recurrent abdominal pain, delayed puberty, abdominal distension, rickets and malnutrition were subjected to screening through anti Tissue Transglutaminase IgA levels (TTG) and serum IgA levels. All those children with TTG IgA levels more than 12 IU with normal serum IgA levels for age were considered positive. These patients were total 167 in number. These patients were further evaluated by duodenal biopsies. These biopsies were conducted at Pediatric Gastroenterology department of Children hospital, Lahore. There were 72 such patients in which histopathology (Modified Marsh 3a or above) supported the diagnosis of celiac disease. All these recently labelled celiac patients whose parents gave consent were included in the study by non-random convenience sampling technique. The exclusion criteria of the study included all previously diagnosed cases of celiac disease, children with chronic diseases such as congenital heart disease, chronic kidney disease, tuberculosis, inflammatory bowel disease, endocrinopathies and all patients with dysmorphic features or neurodevelopmental problems.

The data was collected on specially designed proformas which included all the demographic details including age, sex, gender of the subjects, their symptoms, findings of the clinical examination and anthropometric measurements. These proformas were filled by consultant pediatricians and postgraduate residents of the pediatrics department. History was taken from the parents of the patients presenting to opd or admitted in indoor departments, while examination was done according to a set scheme. All examination findings were verified by a second consultant. All children with chronic diarrhea diagnosed as celiac disease according to the aforementioned criteria were categorized as patients with typical presentation of CD, whereas all other manifestations were described as atypical.

The Statistical analysis was done using SPSS version 20. All quantitative variables were represented as mean and their standard deviations (SD) while all categorical

data was represented as frequencies as well as their percentages.

RESULTS

A total of 72 patients, who were finally diagnosed on serological and histopathological basis as having Celiac Disease, were included in the study. Out of these 72 patients 35 (48.6 %) were males while 37 (51.3 %) were females; with male to female ratio of 1:1.05. The mean age at diagnosis was 5.8 ± 3.12 years, with a range of 9 months to 17 years. Majority of the patients were in the age range of >2 to 5 years i.e. 31 patients (43.05%), 29 (40.3 %) were >5 to 12 years, 7 (9.7%) were under 2 years and 5 (6.94%) were > 12 to 17 years.

Most of the patients in our study group presented with chronic diarrhea. These were 41 (56.94 %) in number. Another 13 patients (18.05%) presented with constipation whereas there were 2 patients (2.78%) who presented with delayed puberty. Short stature was present in 56 (77.78%), rickets (defined on the basis of clinical and radiological findings) in 37(51.38%), clubbing in 9 (12.5%) and abdominal distension in 28 (38.89%) patients (Table I). Anemia (haemoglobin below 5th centile for age and gender of the patients) was present in 37 patients (51.38%) and 16 out of these 37 patients (43.24%) required blood transfusion.

There were 60 patients (83.33%) in our study group who presented with multiple presentations while only 12 patients (16.67%) presented with a single clinical feature. Among those with sole clinical feature at presentation; 3 out of 12 patients had (25%) chronic diarrhea. Remaining 9 patients (75%) had atypical presentation; 1 patient out of 12 (8.33%) presented with constipation, 1 (8.33%) with delayed puberty and 1(8.33%) with anemia. However, there were 6 patients (50%) who had short stature as their sole presentation. The one patient who only had delayed puberty as the only presentation was a 17 years old boy and the one who had anemia as the single clinical finding was a 9 months old male.

Table No1: Frequency of Demographic Details and Clinical Manifestations

Variables	Number (%)
Age	5.8± 3.12 years
Gender	
Male	35 (48.62)
Female	37 (51.38)
Diarrhea	41 (56.94)
Constipation	13 (18.05)
Abdominal distension	28 (38.89)
Anemia	37 (51.38)
Rickets	37 (51.38)
Short stature	56 (77.78)
Malnutrition	51 (70.8)
Delayed puberty	2 (2.78)

As regards to malnutrition; 51 (70.8%) were malnourished, with weight falling below 3rd centile when plotted on WHO centile chart for weight for age, 5(6.94%) patients had weight falling between 3rd and 10th centiles, 3 patients (4.16%) were between 10th and 25th centiles, 2 (2.77%) were between 25th and 50th centiles and 1 (1.38%) was above 50th centile. This 1 patient, above 50th centile, was a boy of 17 years who presented with delayed puberty. Among those presenting with a single presenting feature, 8 children (66.67%) were also malnourished with weights falling below 3rd centile.

Anti-TTG IgA was strongly positive in 69 patients (95.83%); 58 patients (80.55% of total) had anti-TTG IgA above 300iu/ml and remaining 11 patients (15.27%) had values in the range of 200 to 300 iu/ml. 3 patients (4.16%) had anti TTG IgA below 200iu/ml. These were diagnosed on the basis of small intestinal biopsy. All the 72 patients underwent small intestinal biopsy and were proven to be patients of celiac disease. The most common histopathological lesion found was Modified Marsh 3b in 39 patients (54.16%), modified Marsh 3c in 21 patients (29.16%) and modified Marsh 3a in 12 patients (16.67%).

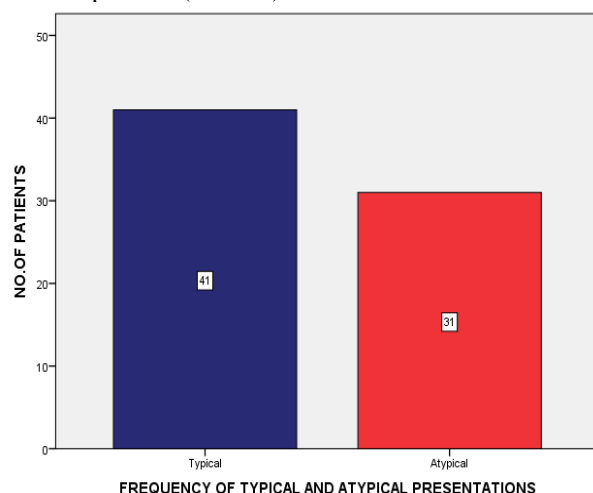


Figure No.1: Frequency of Typical And Atypical Presentations

DISCUSSION

Celiac disease in pediatric age group in Pakistan is still diagnosed after a long delay due to inadequate awareness of various presentations among child health professionals. This delayed recognition of the disease poses a great risk of multiple celiac associated complications in these patients.¹² Our study has evaluated the demographics as well as clinical spectrum of the patients belonging to a peripheral area of Pakistan.

The male to female ratio in our study was 1: 1.05. Although we did not find a significant gender difference among the study subjects, this little female preponderance can be attributed to the autoimmune

nature of the celiac disease. Similar female predominance has been observed in another local study.⁸

In the current study, the mean age of the patients was 5.8 ± 3.12 years which is comparable to another study carried out in Children Hospital Lahore in which the mean age was 6 years.¹³ However, a study conducted in Arab population demonstrated a younger mean age (3.4 years)¹⁴ of the celiac patients, while another Turkish literature reported 8.9 years as the mean age of the celiac patients.¹⁵ These differences might owe to the underlying genetic and environmental factors of the disease.

In our study, the non-diarrheal presentation of the disease was found in a significant proportion of patients (43.06 %) which is in accordance with a study carried out in Agha Khan Hospital, Karachi.¹⁶ Another study by Sharma et al also had 43% celiac patients with atypical presentations. Nevertheless, as discussed earlier there is a wide range of presentations of pediatric celiac disease, in a study by Alvi et al the non diarrheal presentations were only reported to be 17.4% .¹¹

The commonest initial presentation in our subjects was chronic diarrhea which was consistent with the results of a study by cheema et al.¹³ Among the atypical presentations short stature was the most common (77.8%) finding. This result of our study is comparable to the study by Hashmi et al in which there were 81% patients with short stature.⁸ This is why literature now recommends screening for celiac disease in markedly stunted children.¹⁸

Anemia and rickets were the other two significantly reported non- classical manifestations with both reported to be 51.3%. This was concordant with the study by Aziz et al.¹⁵ Similar results with a high percentage of 64% of iron deficiency anemia in another cohort were observed.¹⁹ Anemia and rickets were more common among those who presented with chronic diarrhea than those who presented with atypical features. In our study group none of the patients with sole atypical presentation had rickets while only one had anemia.

In a study by Podder et al 48% patients presented with abdominal distension, which is concurrent with the findings of our study where 38.89% had this manifestation.²⁰ Constipation was another non-classical presentation of patients diagnosed as celiac in our cohort. It was in 18.05% patients which is comparable to 15% reported in a regional study.¹³ There was a significant proportion of patients who were failure to thrive in our study (70.8%) which correlates with the result of another literature.¹⁵ Clubbing was present in 12.5 % of our patients which is slightly lower than what was observed in a study by Ikram et al.²¹

The Modified Marsh 3b was the most common histological finding in the current study (54.16%). Similarly, 55.3% children in a study conducted in

Bangladesh had biopsy with Modified Marsh grade 3b. However, in our study the second most common was grade 3a while in that study Modified Marsh grade 3c was more prevalent.

The limitation of our study includes small size of the study group. Therefore, larger multi-nation and multi-centre trials are needed to determine the clinical spectrum of CD in children.

CONCLUSION

The atypical presentations of pediatric celiac disease in Pakistan are not very uncommon and our study recommends that the pediatricians and physicians need to lower their threshold for screening CD in patients presenting with clinical manifestations that are recognized as non classical. This will result in early diagnosis and thus better outcomes in patients with CD.

Author's Contribution:

Concept & Design of Study: Muhammad Arshad
 Drafting: Osama Anwar
 Data Analysis: Ahmad Hassan
 Revisiting Critically: Muhammad Arshad
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Efficacy of Ampicillin and Gentamycin Combination Therapy in Children Having Severe Acute Malnutrition Presenting with Acute Diarrhea at Civil Hospital Hyderabad

Efficacy of
Ampicillin and
Gentamycin in
Malnourished
Children with
Diarrhea

Farina Usman¹, Salma Shaikh¹, Muhammad Amir², Muhammad Nadeem Chohan¹ and Muhammad Touseef¹

ABSTRACT

Objective: To assess the Efficacy of Ampicillin and Gentamycin combination therapy in children having severe acute malnutrition presenting with Acute Diarrhea at Civil Hospital Hyderabad

Study Design: Descriptive / case series study

Place and Duration of Study: This study was conducted at the Paediatric Department, Liaquat University of Medical and Health Sciences Hospital Hyderabad from 1st July 2017 to 31st December 2017.

Materials and Methods: This study was done by Non-probability, consecutive sampling technique in 145 children with the diagnosis of severe under nutrition presenting with acute diarrhea. History and physical examination was carried out. Patients were treated as per the standard guidelines by the WHO and Ampicillin+Gentamycin were given. Weight and height was plotted on the standard growth charts and centiles for age and gender for screening of malnutrition.

Results: The average age of the patients was 14.81 ± 7.67 months. Out of 145 under nourished children 85(58.62%) showed satisfactory outcome at the end of 48 hours of therapy

Conclusion: In conclusion, treatment with intravenous ampicillin and gentamycin showed improvement in only 58.6% children at the end of 48 hours of therapy. Further large scale studies are needed to review the response of these antibiotics in children having Severe Acute Malnutrition with acute diarrhea, hence to review for any possible change in the current protocol.

Key Words: Severe Acute Malnutrition, Children, Antibiotics, Response

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INTRODUCTION

Malnutrition causes about 8 million deaths in under five years old children worldwide.¹ It causes almost half of all childhood deaths in developing countries.² Severe acute malnutrition (SAM) is diagnosed if weight-for-height Z-score (WHZ) is < -3 standard deviation in children. SAM is the worst form of malnutrition and it affects 19 million children all over the world.³

As compared to other developing countries, Pakistan has the highest prevalence of child malnutrition.⁴

Infectious Diarrhea is responsible for second leading cause of death among less than 5 years old children

worldwide (about 1,400 children die every day). It causes more death in children comparing to AIDS, malaria, and measles.⁵ The prevalence of diarrhea in Pakistan is 23.8% and its prevalence is more in children under 24 months.⁶ In 2016 the prevalence of diarrhea was 12% in children under age 5 years.⁷

World Health Organization (WHO) recommend parenteral Ampicillin and gentamicin as a first line antibiotic therapy for children having complicated severe acute malnutrition including diarrhea.⁸ This has led to improvement in mortality rates as shown in studies from different parts of the world. There is 50% decrease in mortality after the implementation of WHO antibiotic protocol for complicated SAM.⁹ In some international studies, mortality rates of 4.63% have been observed in malnourished patients treated with recommended oral rehydration formulas and antibiotic regimen recommended by the WHO.^{10,11}

Current studies (low quality evidence) suggest increasing antimicrobial resistance to first line antibiotics (Ampicillin and Gentamycin) but evidence for the efficacy of alternative first-line antibiotics are lacking.¹² Because of bacterial resistance to the currently recommended first-line antibiotics effective

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alternatives should be sought. In a study from Uganda only 30% blood cultures were sensitive to ampicillin and Gentamycin. Resistance is a problem in all geographical areas, but there is a lack of recent high quality studies.¹³

In developing countries infectious diarrhea is very common in children having malnutrition and infection related deaths are also very common.¹⁴ Therefore, the management of infection should be more aggressive in these children. Malnourished children with diarrhea are a special subgroup in which administration of antibiotics gains importance due to the immune-compromised state of the child.^{15,16}

The aim of this study is to determine the outcome (response) of the children having severe acute malnutrition presenting with acute diarrhea and treated with first line antibiotics (Ampicillin and Gentamycin). This study will help us to develop better protocols to treat these children as there is no local data evidence, and thus lead to improvement in morbidity and mortality. This study itself is a new study in determining the outcome of severely under nourished children who present with acute diarrhea and treated with first line antibiotics as there are no previous studies available.

MATERIALS AND METHODS

This Descriptive Case Series study was done by Non-probability, consecutive sampling technique at Department of Paediatrics Liaquat University of Medical and Health Sciences Hospital Hyderabad in 145 children with the diagnosis of severe acute malnutrition presenting with acute diarrhea from 1st July 2017 to 31st December 2017 (total 6 months' duration). Sample size was calculated by taking proportion of efficacy 60%, confidence level 95%, and margin of error 8%.

Patients of either gender, age 6 months to 59 months who were admitted with the diagnosis of severe acute malnutrition presenting with acute diarrhea as defined in the operational definition were included in the study. Children having the history of chronic diarrhea or other co-morbid conditions or known congenital malformation or any child with severe under nutrition presenting with shock and dysentery were excluded from the study.

Written informed consent to participate in the study was taken from the parents/ guardian of the patient. History and physical examination was carried out. Patients were treated as per the standard guidelines by the WHO and antibiotics (as recommended by the guidelines) were given, that is IV ampicillin 50 mg/kg IV every 6 h and gentamicin 7.5 mg/kg IV once daily. Children having treatment failure, were changed to second-line agents like ceftriaxone 75mg/kg/day OD IV or Ciprofloxacin 20mg/kg/day BID IV.

Age, gender, weight, height and duration of diarrhea were noted. Final outcome was noted. Weight and height was plotted on the standard growth charts and centiles for age and gender was noted. Data was collected on a pre-prescribed Proforma and analyzed using Statistical package for social sciences SPSS version 20. Outcome was considered satisfactory if the frequency of stools was < 3 per 24 hours at the end of 48 hours. Frequency and percentage was calculated for nominal data like, gender and outcome. Mean and standard deviation was calculated for age weight, height duration of diarrhea, weight and height centile. Outcome was stratified for age gender and height weight centile and duration of diarrhea groups. Chi² was used and p-value of 0.05 or less was taken as significant.

RESULTS

A total of 145 children with the diagnosis of severe under nutrition presenting with acute diarrhea were included in this study. There were 47.69% children between 6 to 12 months of age, 44.14% were 12.1 to 24 months of age and 8.28% were above 24 months of age as shown in figure 1. The average age of the patients was 14.81 ± 7.67 months similarly mean weight, height, duration of diarrhea and height weight centile is also shown in table 1.

Table1 No1: Demographic Distribution of the Patients n=145

Age	Number	Percentage
6-12 months	69	47.59
13-24 months	64	44.14
>24 months	12	8.28
Gender		
Male	82	56.55
Female	63	43.45
Response to Antibiotics		
Satisfactory	85	58.62
Unsatisfactory	60	41.38
Characteristics	Mean	Std. Deviation
Age (months)	14.81	7.674
Weight (kg)	5.150	1.4747
Height (cm)	66.45	7.816
Duration Diarrhea (days)	3.05	21.11

There were 82(56.55%) male and 63(43.45%) female as shown in figure 2.

Out of 145 under nourished children 85(58.62%) showed satisfactory outcome at the end of 48 hours of therapy as presented in figure 3. Satisfactory outcome was significantly high in 6 to 12 months of age children ($p=0.042$) as shown in table 2. It was also significantly high in female patients as shown in table 3. Stratification was also done with respect to height weight centile and duration of diarrhea and found satisfactory outcome with <3 centile and 1 to 5 days'

duration of diarrhea as shown in table 4 and 5 respectively.

indicators. Wasting is most prevalent in Sindh (23.3%) and KP-NMD (23.1%), whereas Gilgit Baltistan and Islamabad have the lowest proportion 9.4% and 12.1% respectively. The prevalence of underweight among children under five years of age is 19.2% in Islamabad and 41.3% in Sindh. ⁹Malnutrition is aggravated by diarrhea; one of the leading cause of under-five childhood mortality over last two decades. ¹⁷ In malnourished children diarrhea is 5-7 times more common as compared to normal children and it is 3 to 4 times more severe in malnourished children as compared to normal children. Diarrhea continues to be a serious problem in our children

Table No.2: Outcome in Severely Undernourished Children Treated with Intravenous Ampicillin And Gentamycin According to Age Groups

Age Groups (Months)	Outcome		Total
	Satisfactory	Unsatisfactory	
6 to 12	44(63.8%)	25(36.2%)	69
12.1 to 24	38(59.4%)	26(40.6%)	64
>24	3(25%)	9(75%)	12

Chi-Square=6.36 p=0.042

Table No.3: Outcome in Severely Undernourished Children Treated with Intravenous Ampicillin And Gentamycin According to Gender

Gender	Outcome		Total
	Satisfactory	Unsatisfactory	
Male	42(51.2%)	40(48.8%)	82
Female	43(68.3%)	20(31.7%)	63

Chi- Square=4.26 p=0.039

Table No.4: Outcome in Severely Undernourished Children Treated with Intravenous Ampicillin And Gentamycin According to Gender

Height Weight Centile	Outcome		Total
	Satisfactory	Unsatisfactory	
-3	42(73.7%)	15(26.3%)	57
-4 to -5	43(48.9%)	45(51.1%)	88

Chi-Square=8.78 p=0.003

Table No5: Out Come in Severely Under-nourished Children Treated with Intravenous Ampicillin and Gentamycin According to Duration of Diarrhea

Duration of diarrhea	Outcome		Total
	Satisfactory	Unsatisfactory	
1 to 5 days	85(68%)	40(32%)	125
>5 days	0(0%)	20(100%)	20

Chi- Square=32.86 p=0.0005

DISCUSSION

According to 2018 Pakistan National Nutrition Survey (NNS 2018), 40.2% children under five years of age are

stunted while 17.7% are wasted and 28.9% are underweight. Boys are more affected than girls by all forms of malnutrition. Children living in rural areas suffer more from under nutrition than children living in urban areas. Since 1997, the prevalence of wasting among young children is increasing, it was 8.6% in 1997, 15.1% in 2011 and it increased to 17.7% in 2018 (highest rate in Pakistan history). Acute malnutrition remains a nutrition emergency despite the improvement in socioeconomic and is fatal when superimposed upon malnutrition. ¹⁸

Increasing antibiotic resistance is an issue of international concern. ¹⁹ In a study from Bangladesh, only 6 (1.4%) children blood culture isolate was resistant to ampicillin and gentamicin. On the other hand, 3 (0.7%) children blood culture isolates were resistant to ceftriaxone, and 1 (0.2%) was resistant to ciprofloxacin. ²⁰ High rates of non-susceptibility have been documented in several epidemiological studies in children with SAM. ²¹

Our Pediatric department has functional nutritional stabilization center for last 10 years and we are dealing with lot of children with Severe Acute Malnutrition having acute diarrhea. Number of Children with acute diarrhea is increasing so no response with first line antibiotics (Ampicillin and Gentamycin) is prolonging the hospital stay of these children and increasing the burden of inpatient children. WHO recommendations regarding the first line antibiotics in complicated SAM should be reviewed to prevent the delay in response in these children.

In our study a total of 145 children with the diagnosis of severe under nutrition presenting with acute diarrhea were included. Gender based provision of medical care is an issue in various developing countries, emphasizing the provision of equal medical care and facilities to boys and girls. ¹⁶ Various studies show that South Asian countries has the gender discrimination in health, education nutrition and immunization. ^{22,23} According to World Bank survey in 2005, there were less health care facilities to girls as compared to boys. ²⁴ In our study we found that there were 56.55% male and 43.45% female showing less number of malnourished female patients as compared to males. This is also supported by the literature which showed food decimation among males and females. ²⁵ An Indian study did not show any gender difference regarding food. ²⁶ The gender of the child was a statistically significant predictor of childhood diarrhea, with boys more likely to be affected by diarrheal disease than girls. This was also supported by various other international studies. ^{27,28}

In our study the outcome was labeled satisfactory if the frequency of stools was <3 per 24 hours at the end of 48 hours. We found that out of 145 under nourished children 58.62% showed satisfactory outcome at the end of 48 hours of therapy. This satisfactory outcome was significantly high in children between 6 to 12

months of age. Our results are supported by few other studies showing 67% antimicrobial sensitivities of blood culture to the first line combination of ampicillin and gentamicin.²⁹ While another study showed that 73% organisms were sensitive to gentamicin.³⁰ Another observational study in Niger done in 311 children aged 6–59 months with complicated SAM. Most isolated Enterobacteriaceae causing diarrhea were resistant to amoxicillin and co-trimoxazole but susceptible to ceftazidime/ceftriaxone, gentamicin and quinolones.³¹

CONCLUSION

In conclusion, treatment with intravenous ampicillin and gentamycin showed improvement in only 58.6% children at the end of 48 hours of therapy. Further large scale studies are needed to review the response of these antibiotics in children having Severe Acute Malnutrition possible change in the current treatment national protocol in SAM children with diarrhea.

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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Testosterone with Lipid profile in Healthy Middle Aged Males

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ABSTRACT

Objective: To construct a foreseeable connection of total testosterone with lipid profile in middle aged healthy men.

Study Design: Analysis / cross sectional study.

Place and Duration of Study: This study was conducted at the Dow University of Health Sciences Karachi for duration of nine month from April 2012 to January 2013.

Materials and Methods: Two hundred disease free nonsmoker males of 30 to 50 years of age were enrolled for this study, total testosterone value was estimated by Chemiluminescence assay method and fasting lipid profile which includes cholesterol, triglyceride, high density lipoprotein (HDL) and low density lipoprotein (LDL) were tested in Hitachi 902 auto analyzer by photometry technique. Mean differences of all the lipid parameters in between the two groups of testosterone were computed by independent sample T test. Correlation between total testosterone and fasting lipid parameters was assessed by Pearson correlation. Multivariable linear regression was also applied to predict the change in the levels of lipid profile parameters on the basis of per unit rise in total testosterone level.

Results: In this study the mean (\pm SD) value of total testosterone was 15.92 (\pm 6.322) nmol/L, while the mean (\pm SD) values of cholesterol, triglyceride, HDL and LDL were 182.71 (\pm 40.673), 134.02 (\pm 55.407), 41.37 (\pm 8.018) and 118.13 (\pm 33.451) mg/dl respectively. Statistically significant difference ($P = 0.021$) was observed in the mean value of serum triglyceride when compared with the two testosterone groups. Significant negative ($P = 0.000$) and positive ($P = 0.001$) association of testosterone with triglyceride and HDL respectively were also documented. Multivariable linear regression model showed significant decrease in triglyceride level by 2.742 mg/dl and significant increase in HDL level by 0.304 mg/dl for each additional nmol/L of age adjusted testosterone.

Conclusion: Convincing negative and positive associations of total testosterone with triglyceride and HDL respectively in this study suggest a promising link between low total testosterone and obesity.

Key Words: Serum Total Testosterone, Lipid Profile, Cholesterol, Triglyceride, HDL, LDL

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INTRODUCTION

With the inception of furtherance life in the emerging countries, decreased athletics and ferocious eating habits, (especially the fast food) were noticed, which is the root cause of obesity and overweight.¹ As a consequence, risk factors like increased accumulation of abdominal fat, abnormal lipids mainly high density lipoproteins (HDL) and triglycerides which later leads

to cardiovascular and many metabolic diseases.^{2,3}

Persons having dyslipidemia leads to metabolic syndrome and are more likely to die due to cardiovascular and many metabolic diseases.^{2,3}

Persons having dyslipidemia leads to metabolic syndrome and are more likely to die due to cardiovascular diseases and have risk of developing stroke and heart attack three times as compared to those who are not suffering from it.⁴

Along with the manifested effects of low levels of serum total testosterone in men ^{5,6} low testosterone levels are also associated with altered lipid profile which will lead to various metabolic disorders.^{7,8}

The exact mechanism that how low total testosterone causes dyslipidemia remains unclear, however some possible mechanisms suggests that testosterone modifies the metabolism of proteins and fat, according to researches testosterone under normal conditions reduces fat by inhibiting lipoprotein lipase⁹ and glyceraldehyde 3-phosphate dehydrogenase.¹⁰

Active for of testosterone also reduces lipid levels by breakdown of fats inside the cells.¹¹ Testosterone also

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inhibits adipocytes differentiation in such a way that adipogenesis is impaired.¹² Studies have also suggested that testosterone replacement has also favorable effects on lipid profile.¹³

The basic aim behind the study was to construct a foreseeable connection of total testosterone with lipid profile. However most of the previous studies on low total testosterone & lipid profile were conducted on subjects belongs to elder age group and also has cardiovascular complications. We conducted this study in disease free middle aged men.

MATERIALS AND METHODS

This study was a cross sectional analysis which was conducted in duration of nine month April 2012 to January 2013. Dow University of Health Sciences Karachi, for which two hundred disease free nonsmoker males of 30 to 50 years of age were enrolled. Sample size estimation was done with the prevalence of androgen deficiency in Massachusetts Male Aging Study, which was 12.3 %.¹⁴ The study inclusion criteria was based on healthy, nonsmoker males aged between 30 to 50 years, so individuals with any systemic disease acute and chronic disease, those taking any testosterone supplementation or suffering from hypogonadism & smokers as altered levels of testosterone were reported in smokers¹⁵ were excluded from the study. A total of 323 subjects were approached for sampling, out of which 123 subjects were eliminated as they were not met with the study inclusion criteria. Detailed medical history and complete general physical examination and systemic clinical examination were carried out. Blood samples were collected at early morning in a fasting state of (12 -14 hours). Early morning samples were required for Serum total testosterone due to its diurnal variation¹⁶ and fasting was required for Lipid profile measurements. Total testosterone was tested in Cobas e 411 by chemiluminescence assay. Fasting lipid profile which includes cholesterol, triglyceride, high density lipoprotein (HDL) and low density lipoprotein (LDL) were tested in Hitachi 902 auto analyzer by photometry technique followed by enzymatic colorimetric and homogeneous enzymatic colorimetric test principles.¹⁷ Reference values taken for all bio chemical assays are according to DDRRL.¹⁸⁻²⁰

Data analysis was carried out by SPSS software. Testosterone values were divided into two groups. Group I having low testosterone levels (< 9.7 nmol/L) and group II having normal or above normal testosterone levels (≥ 9.7 nmol/L). Mean comparison between the two testosterone groups were analyzed by independent sample T test, whereas correlation between total testosterone and fasting lipid parameters was assessed by Pearson correlation. Multivariable linear regression model was then also applied to predict the change in the levels of serum cholesterol, triglyceride,

HDL and LDL on the basis of per unit rise in testosterone value adjusted with age.

RESULTS

Table I shows mean values of total testosterone, cholesterol, triglyceride HDL and LDL of 200 healthy subjects having mean age of 38.72 ± 6.56 years.

Table No. 1: Descriptive Statistics.

Variables	Mean	Standard Deviation	Minimum	Maximum	Range
Testosterone nmol/L	15.92	6.322	5.63	43.64	38.01
Age (Years)	38.72	6.563	30	50	20
Cholesterol (mg/dl)	182.71	40.673	96	305	209
Triglyceride (mg/dl)	134.02	55.407	43	297	254
HDL (mg/dl)	41.37	8.018	24	75	51
LDL (mg/dl)	118.13	33.451	44	207	163

Table No. 2: Mean Differences.

Variables	Low Testosterone Group (n = 27)	Normal Testosterone Group (n = 173)	P Value
Mean \pm SD Cholesterol	192.81 \pm 38.058	181.13 \pm 40.945	0.166
Mean \pm SD Triglyceride	142.19 \pm 38.368	132.75 \pm 57.595	*0.021
Mean \pm SD HDL	40.48 \pm 8.021	41.51 \pm 8.032	0.537
Mean \pm SD LDL	125.48 \pm 32.328	116.98 \pm 33.568	0.220

*Significant (p < 0.05)

Table No. 3: Correlation of Testosterone with Lipid Parameters.

	Correlation Coefficient	P Value
Cholesterol	-0.112	0.114
Triglyceride	-0.314	*0.000
HDL	0.243	*0.001
LDL	-0.047	0.512

*Significant (p < 0.05)

Table No. 4: Multivariable Linear Regression Model of Age adjusted Testosterone with Lipid Profile.

	Unstandardized Coefficients (β)	P Value
Cholesterol	-0.746	0.099
Triglyceride	-2.742	*0.000
HDL	0.304	*0.001
LDL	-0.265	0.479

*Significant (p < 0.05)

Out of 200 study subjects 13.5% had low total testosterone and categorized into low testosterone group, whereas 86.5% had normal testosterone and categorized into normal testosterone group.

Differences of mean in between the two groups was computed by Independent Sample T Test, showed significant (P = 0.021) changes in mean values of triglyceride as shown in table 2.

Correlation between serum total testosterone and lipid profile was analyzed by Pearson correlation, showed statistical significant inverse correlation with

triglyceride ($P = 0.000$) and statistical significant positive correlation ($P = 0.001$) with HDL as shown in table 3.

Multivariable linear regression model was applied to find the unit change in dependent variable due to unit change in independent variable. The independent variables were testosterone and age and the dependent variables were cholesterol, triglyceride, HDL and LDL in this study.

A significant decrease in triglyceride level by 2.742 mg/dl for each additional nmol/L of age adjusted testosterone and a significant increase in HDL level by 0.304 mg/dl for each additional nmol/L of age adjusted testosterone were recorded as shown in table 4.

The interaction between testosterone and age for each study variable was also analyzed which was insignificant for each study variable, hence testosterone and age were not associated with each other for any change in cholesterol, triglyceride, HDL & LDL.

DISCUSSION

This study was designed to record the effects of total testosterone levels on lipid profiles of disease free middle aged men.

Total testosterone deficiency has been reported throughout the world in different studies. Frequency of low testosterone recorded in this study was 13.5%. Araujo and his fellows in an observational cohort study found the crude prevalence of low androgen to be 12.3%.¹⁴ Similarly Goel and his colleagues found lower testosterone frequency in 40 to 60 years old diseased free Indian men as 24.2%.²¹ Mean value of serum total testosterone recorded in this study was 15.92 ± 6.322 nmol/L, whereas Eendebak and fellows in a study recorded a mean testosterone value of 14.0 ± 0.4 nmol/L in South Asian males aged between 40 to 84 years suggesting the role of ethnicity in testosterone.²²

Fasting triglyceride levels ≥ 150 mg/dl and HDL cholesterol levels in male < 40 mg/dl or on specific treatment for such an abnormal value are also included in the diagnostic criteria for metabolic syndrome by IDF.²³ Current study showed (according to DDRRL reference ranges)^{19,20} overall 31.5% of the study population ($n = 200$) (in both TT groups) had high triglyceride levels and 47% of all the subjects had low HDL cholesterol levels. Similarly Ray et al., in 767 healthy military adults aged between 18-50 years in India found the prevalence of high triglyceride and low HDL as 14% and 67% respectively.²⁴ Moreover 37% and 30.6% of the present study subjects belonged to low ($n = 27$) and normal ($n = 173$) TT groups respectively had high triglyceride levels whereas 52% and 48% of the current study population had low levels of HDL cholesterol were from low ($n = 27$) and normal ($n = 173$) TT groups respectively. Significant negative correlation ($\beta = -2.742$) of TT with triglyceride, while significant positive correlation ($\beta = 0.304$) of TT with HDL was recorded in the present study, which is consistent with the findings of Akishita and his colleagues, who also revealed that TT was significantly

related to triglyceride ($\beta = -0.242$) and HDL ($\beta = 0.228$).²⁵ Further Haffner et al., also determined the relationship of sex hormones to lipid profile in 178 non diabetic men and found significant negative association between total testosterone and triglyceride and significant positive association between total testosterone and HDL levels²⁶ which is again consistent with the present study findings. However Haffner also found significant correlation between TT, total cholesterol and LDL cholesterol levels, which is in contrast with the current study results as TT was not correlated significantly with total cholesterol and LDL cholesterol in the present study, though overall 33.5% and 36% of the study population ($n = 200$) (in both TT groups) had high total cholesterol and LDL levels respectively, while Ray et al.²⁴ found the prevalence of high total cholesterol and LDL as 22% and 22% in 767 young healthy military adult officers respectively. Laouali and colleagues examined the correlation of low TT and mortality in older men, and found significant negative ($P < 0.01$) association of total testosterone with triglyceride²⁷ which is quite analogous ($P = 0.000$) with the current study findings.

CONCLUSION

Significant negative and positive associations of total testosterone with triglyceride and HDL respectively in this study suggests a promising link between low total testosterone and obesity, as low total testosterone probably causes alteration in fat metabolism leading to dyslipidemia..

Author's Contribution:

Concept & Design of Study:	Muhammad Omar Shamim
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Data Analysis:	Aaqiba Rasheed Atif Mahmood
Revisiting Critically:	Farooq Munfaet Ali
Final Approval of version:	Muhammad Omar Shamim

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

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To Compare the Outcomes of Laparoscopic and Open Appendectomies

Laparoscopic
and Open
Appendectomy

Ahmad Shah, Samina Karim and Nazir Ahmed Sasoli

ABSTRACT

Objective: To compare the surgical site infection, hospital stay and time duration of procedure in patients undergoing laparoscopic and open appendectomies.

Study Design: Prospective study.

Place and Duration of Study: The study was conducted at the Department of Surgery, Bolan University of Medical & Health Sciences, Quetta from January 2017 to February 2019.

Materials and Methods: Two hundred male/female patients with ages >10 years presented with acute appendicitis were included. Patients demographic including age, sex and body mass index were recorded after written consent. Equally divided all the patients into two groups. Group-I (Laparoscopic appendectomy) consist of 100 patients and Group II (Open appendectomy) with 100 patients. Outcomes such as surgical site infection, hospital stay and time duration of procedure were examined and compare the results between both groups. SPSS 24.0 was used for analyzing the data.

Results: here were 110 (55%) patients (52 Group I, 58 Group II) were male with mean age 24.3 ± 7.45 years while 90 (45%) patients (48 Group I, 42 Group II) were females with mean age 25.2 ± 8.2 years. No significant difference regarding BMI between both groups $p > 0.05$. Significant difference was observed in term of surgery time duration between both groups 45.42 ± 10.95 minutes Vs 30.48 ± 9.68 minutes ($P = 0.001$). No significant difference observed in term of hospital stay ($p = 0.345$). 10 (10%) patients in Group II and 6 (6%) patients in Group I had developed surgical site infection with no significant difference ($p = 0.41$).

Conclusion: Open appendectomy is better in term of operative time as compared to laparoscopic appendectomy. We found no significant difference regarding surgical site infection and hospital stay.

Key Words: Acute appendicitis, Appendectomy, Laparoscopic, Open, Outcomes.

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INTRODUCTION

In 1984, McBurney introduced open appendectomy and the procedure becomes a method of choice for acute appendicitis.¹ Globally, acute appendicitis is one of the most common disorders with a risk of 6%. The incidence rate of acute appendicitis is quite high as compared to other abdominal diseases.^{2,3} In recent years there are many technique applying for the treatment of acute appendicitis but laparoscopic and open appendectomy are the most performing surgical techniques because of fewer rate of complications. A German gynaecologist firstly introduced laparoscopic appendectomy in 1983.⁴

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There is still a controversy between both open and laparoscopic. Some of studies reported laparoscopic technique for acute appendicitis is and better in term of surgical site infection as compared to open appendectomy techniques regarding surgical site infection.⁵ Nosocomial infections are directly associated with surgical treatments but surgical site infection is one of the most common complication associated with open and laparoscopic procedures.⁶ The incidence rate of surgical site infection is approximately 60% after surgical treatment and it leads to severe complications, mortality and increase length of hospital stay.⁷⁻⁸ Many op studies regarding acute appendicitis demonstrated that the open appendectomy procedure has high rate of surgical site infection as compared to laparoscopic appendectomy and some of studies reported no significant difference between both techniques. However, laparoscopic appendectomy considered a method of choice for the treatment of acute appendicitis.⁹⁻¹⁰ Many of factors are involved for increased incidence of surgical site infection between laparoscopic and open appendectomies.¹¹ The present study was conducted to determine the outcomes of laparoscopic and open appendectomy in term of Surgical site infection, hospital stay and operative duration.

MATERIALS AND METHODS

This prospective study was carried out at Department of Surgery, Bolan University of Medical & Health Sciences, Quetta from 1st January 2017 to 28th February 2019. A total of 200 patients of both genders with ages >10 years presented with acute appendicitis were included. Patients demographic including age, sex and BMI were recorded after written consent. Histopathology findings of the patients were recorded. Pregnant women, patients with history of abdominal surgery, patients with recurrence and those with no consent were excluded. Patients were equally divided into two groups. Group I consist of 100 patients and treated with laparoscopic technique and Group II with 100 patients treated with open technique. Outcomes such as surgical site infection, hospital stay and time duration of procedure were examined and compare the results between both groups. Computer statistical software SPSS 24.0 was used to analyze the data. Student t' test and chi-square test was applied to analyze the finding between both procedures with P-value set at <0.05 as significant.

RESULTS

There were 110 (55%) patients (52 Group I, 58 Group II) were male with mean age 24.3 ± 7.45 years while 90 (45%) patients (48 Group I, 42 Group II) were females with mean age 25.2 ± 8.2 years. No significant difference regarding BMI between both groups, Group I and II (24.5 ± 4.2 vs 24.3 ± 3.6). According to the histopathology findings 85% patients had inflammation, 3% had phlegmonous, 1% had gangrenous, 8% had perforated and 3% had normal appendicitis in Group I. In Group II 79% had inflamed 5% had phlegmonous, 2% had gangrenous, 10% had perforated and 4% had normal

Table No.1: Demographic information of the patients

Variable	Group I	Group II	Total
Mean age (yrs)	24.3±7.45	25.2±8.2	
Gender			
Male	52 (52%)	58 (58%)	110 (55%)
Female	48 (48%)	42 (42%)	90 (45%)
BMI	24.5±4.2	24.3±3.6	
Histopathology			
Inflamed	85 (85%)	79 (79%)	164 (82%)
Phlegmonous	3 (3%)	5 (5%)	8 (4%)
Gangrenous	1 (1%)	2 (2%)	3 (1.5%)
Perforated	8 (8%)	10 (10%)	18 (9%)
Normal	3 (3%)	4 (4%)	7 (3.5%)

P-value >0.05

in term of surgery time duration between both groups 45.42 ± 10.95 minutes Vs 30.48 ± 9.68 minutes; $P=0.001$. appendicitis (Table 1). There was a significant difference No significant difference observed in term of hospital stay between both groups 2.01 ± 1.12 vs 2.32 ± 1.05 days. 10 (10%) patients in Group II in which 7% had Superficial SSI and 3% had Deep SSI. 6 (6%) patients

4% superficial and 2% Deep SSI in Group I had developed surgical site infection with no significant difference ($p=0.41$) (Table 2).

Table No.2: Comparison of outcomes

Outcome	Group I	Group II	P value
Operative time	45.42±10.95	30.48±9.68	0.001
Hospital stay	2.01±1.12	2.32±1.05	0.89
Surgical site infection			
Superficial	4 (4%)	7 (7%)	0.41
Deep	2 (2%)	3 (3%)	

DISCUSSION

Surgical Site Infection (SSI) is the most common complication after all the performing surgeries whether it is laparoscopic or open technique.¹² We found that 110 (55%) patients (52 Group I, 58 Group II) were male with mean age 24.3 ± 7.45 years while 90 (45%) patients (48 Group I, 42 Group II) were females with mean age 25.2 ± 8.2 years. These results were similar to some previous studies in which male patients were high in numbers as 52 to 75% as compared to females and majority of patients were ages 20 to 35 years.^{13,14} Some of studies reported female patients population was high as compared to males.¹⁵ In present study we found no significant difference regarding Body Mass Index (BMI) between both groups. We found that 85%, 3%, 1%, 8%, 3% patients had inflamed phlegmonous, gangrenous, perforated and normal appendicitis in laparoscopic treated patients according to the histopathology findings. In Group II 79% had inflamed, 5% had phlegmonous, 2% had gangrenous, 10% had perforated and 4% had normal appendicitis. These results were comparable to some other studies.^{16,17} In our study significant difference in term of surgery time duration between both groups 45.42 ± 10.95 minutes vs 30.48 ± 9.68 minutes; $P=0.001$. A study conducted by Jawad et al¹⁸ reported laparoscopic appendectomy take more time to perform as compared to open appendectomy (47.54 ± 12.82 minutes versus 31.36 ± 11.43 minutes; < 0.001). In present study we found no significant difference observed in term of hospital stay between both groups 2.01 ± 1.12 vs 2.32 ± 1.05 days. Many of studies showed similar results to our study in term of hospital stay and demonstrated no difference between both open and laparoscopic procedures.^{19,20} We found in our study that 10 patients in open appendectomy group develop surgical site infection in which 7% patients had superficial and 3% patients had deep SSI. 6% patients develop SSI in patients received laparoscopic technique in which 4% had superficial and 2% had deep SSI. Between both groups no significant difference was observed ($p=>0.05$). These results were similar to many other studies in which no significant difference reported in term of SSI between laparoscopic and open technique.^{21,22} Khan et al²³ reported 11% intra-abdominal infection in laparoscopic group and 3% in

open group. Some other studies reported that laparoscopic technique had increase incidence of intra-abdominal abscess as compared to open appendectomy.²⁴⁻²⁶

CONCLUSION

Surgical site infection is one of the most common complication resulted after surgical treatment. We concluded that there is no significant difference found between open and laparoscopic technique in term of surgical site infection while open appendectomy is better in term of operative time as compared to laparoscopic appendectomy.

Author's Contribution:

Concept & Design of Study: Ahmad Shah
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 Data Analysis: Nazir Ahmad Sasoli
 Revisiting Critically: Ahmad Shah, Samina Karim
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Compare the Outcomes of Antibiotic Therapy with Appendectomy in Patients with Acute Appendicitis

Samina Karim, Ahmed Shah and Muhammad Ishaq Durrani

ABSTRACT

Objective: To compare the outcomes such as recurrence, complications, hospital stay and pain of antibiotic therapy and appendectomy in patients presented with acute appendicitis.

Study Design: Comparative study.

Place and Duration of Study: The study was conducted Department of Surgery, Bolan University of Medical & Health Sciences, Quetta from July 2017 to August 2019.

Materials and Methods: Eighty patients of both genders presented with acute appendicitis were included. Patient's demographical details were recorded after written consent. Patients were equally divided into two groups i.e. Group I consist of 40 patients and received appendectomy, Group II consist of 40 patients and received antibiotics. Outcomes such as recurrence, pain, hospital stay and complications were examined and compare the findings between both groups. SPSS 21.0 was used to analyze the data.

Results: Fifty three (66.25%) were male (Group I 28, Group II 25) with mean age 32.2 ± 7.6 years and 27 (33.75%) were females (12 Group I, 15 Group II) with mean age of 31.5 ± 9.1 years. Group I patients had less hospital stay, recurrence rate and pain score as compared to Group II patients (p -value < 0.05). In Group I patients wound infection was the most common complication found in 10 (25%) patients and in Group II appendicular mass was most common complication found in 12 (30%) patients.

Conclusion: Appendectomy is very effective and better treatment modality as compared to antibiotic therapy for acute appendicitis.

Key Words: Acute Appendicitis, Appendectomy, Antibiotic Therapy, Outcomes

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INTRODUCTION

Acute appendicitis is most common abdominal emergency, world wise.¹ Acute appendicitis is associated with 40000 hospital admissions per years in United Kingdom.² Acute appendicitis is common in early ages from 10-20 years of age. However, it may occur at any age. Males are at high risk of developing acute appendicitis as compare to female (life time risk 8.6% vs 6.7%) in United States.³ An estimated decline in acute appendicitis has been reported after 1980s. Prevalence of acute appendicitis was 48% in 2008 at Pakistan Ordinance Factories, Wah Cantt.⁴

Clinically acute appendicitis is defined as acute inflammation associated with vermiform appendix.⁵ Moreover, the inflammation is due to obstruction of appendicular lumen. The obstruction might be due to infective agents, stools, lymphoid hyperplasia and faecolith.⁶ Acute appendicitis is presented with abdominal pain in peri-umbilical region followed by localization in the right lower abdomen, vomiting, nausea, loss of appetite and constipation. Murphy described migration of pain to right iliac fossa in 50% of patients as diagnostic sequence (colicky central abdominal pain).⁷ Literature reported that initial pain is termed as referred pain while the pain intensifies within 24 hours and become sharp or constant within this duration. Visceral innervations of midgut are responsible for referred pain while parietal peritoneum is responsible for localization of pain in acute appendicitis patients.⁸

Acute appendicitis treatment includes medical and surgical treatment.⁹ Medical treatment includes antibiotics and analgesics use, while surgical treatment consists of open and laparoscopic procedures. Evidence exist that laparoscopic approach is associated with early recovery, abdominal exploration through small incision and lower pain level, while antibiotic

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treatment resulted more hospital stay, pain and recurrence rate. Wound infection, post-operative abscesses and hematoma formation are common complications of surgery.¹⁰⁻¹¹

Present study was conducted aimed to examine the outcomes of appendectomy and antibiotic therapy in term of hospital stay, recurrence, pain and complication in patients presented with acute appendicitis.

MATERIALS AND METHODS

This comparative study was conducted at Department of Surgery, Bolan University of Medical & Health Sciences, Quetta from 1st July 2017 to 31st August 2019. A total of 80 patients of both genders with ages 15 to 50 years presented with acute appendicitis were included. Patient's demographical details were recorded after written consent. Pregnant women, patients with irritable bowel disease, allergic to antibiotic and those not willing to sign consent were excluded from the study. Patients were equally divided into two groups i.e. Group I consist of 40 patients and received appendectomy, Group II includes 40 patients and received antibiotics treatment (ciprofloxacin 250mg, metronidazole 500mg) thrice a day for three days. Outcomes such as recurrence, pain, hospital stay and complications were examined and compare the findings between both groups. Pain score was examined by visual analogue score VAS. Data was analyzed by SPSS 21. Chi-square test and students 't' test was used to compare the findings between both groups. Data was recorded in the form of table. P-value <0.05 was considered as significant.

RESULTS

There were 53 (66.25%) males (Group I 28, Group II 25) with mean age 32.2 ± 7.6 years and 27 (33.75%) were females (12 Group I, 15 Group II) with mean age of 31.5 ± 9.1 years (Table 1). In Group I 30 (75%) patients had hospital stay less than 7 days and 10 (25%) patients had hospital stay >7days. In Group II 9 (22.5%) had stay <7 days while 31 (77.5%) patients had hospital stay >7 days. Recurrence rate was high in Group II patients 12 (30%) as compared to Group I 7.5%. According to the pain, In Group I 34 (85%) patient had no pain, 5 (12.5%) had mild pain and 1 (2.5%) had moderate pain while no patient had severe pain. In Group II 8 (20%) patients had no pain, 1 (2.5%) patient had mild pain, 21 (52.5%) patients had moderate pain and 10 (25%) patients had severe pain (Table 2).

In Group A patients wound infection was the most common complication found in 10 (25%) patients followed by peritonitis 6 (15%) and perforation 2 (5%). In Group II appendicular mass was most common complication found in 12 (30%) patients followed by

perforation 7 (17.5%) and appendicular abscess 5 (12.5%) (Table 3).

Table No.1: Age and gender wise distribution among both groups (n=80)

Variable	Group I	Group II
Mean age (years)	32.2 ± 7.6	31.5 ± 9.1
Gender		
Male	28 (70%)	25 (62.5%)
Female	12 (30%)	15 (37.5%)

P-value >0.05

Table No.2: Outcomes in term of hospital stay, recurrence and pain score

Outcome	Group I	Group II	P value
Hospital stay (days)			
<7	30 (75%)	9 (22.5%)	0.001
> 7	10 (25%)	31 (77.5%)	
Recurrence			
Found	3 (7.5%)	12 (30%)	0.001
Not Found	37 (92.5%)	28 (70%)	
Pain (VAS)			
No Pain	34 (85%)	8 (20%)	0.001
Mild	5 (12.5%)	1 (2.5%)	
Moderate	1 (2.5%)	21 (52.5%)	
Severe	0 (0%)	10 (25%)	

Table No.3: Comparison of complication among both groups (n=80)

Complications	Group I	Group II
Wound Infection	10 (25%)	-
Peritonitis	6 (15%)	-
Perforation	2 (5%)	7 (17.5%)
Appendicular Mass	-	12 (30%)
Appendicular Abscess	-	5 (12.5%)

DISCUSSION

Acute appendicitis is one of the most common disorders in all over the world and appendectomy is the most common surgical treatment performing worldwide.¹² Appendectomy and antibiotic therapy are the two main treatment modalities for acute appendicitis but appendectomy consider as a treatment of choice for this malignant disorder.¹³ Present study was conducted to examine the outcomes of appendectomy and antibiotic therapy in patients with acute appendicitis and compare the findings between both methods. In this regard 80 patients were enrolled and equally divided into two groups i. e. Group I consist of 40 patients and received appendectomy, Group II consist of 40 patients and received antibiotics treatment (ciprofloxacin 200mg, metronidazole 500mg) thrice a day for three days. Out of 80 patients, 53 (66.25%) were male (Group I 28, Group II 25) with mean age 32.2 ± 7.6 years and 27 (33.75%) were females (12 Group I, 15 Group II) with mean age of 31.5 ± 9.1 years. These results showed

similarity to many of previous studies in which male patients were high in number 55 to 75% as compared to females and majority of patients were ages 25 to 40 years.^{14,15}

In this study we found that 75% patients whom were received appendectomy had hospital stay less than 7 days while 22.5% patients whom were received antibiotics had hospital stay less than 7 days. There was significant difference in term of hospital stay ($p=0.001$). These results were similar to some other studies in which patients treated with appendectomy had less hospital stay as compared to those who received antibiotic therapy.^{15,16}

In the present study, we found a significant difference in term of recurrence and pain score ($p<0.05$). We found recurrence rate was high in Group II patients 12 (30%) as compared to Group I 7.5%. According to the pain score appendectomy group had high rate of no pain 85% as compared to antibiotic group 20%. A study conducted by Farzana et al¹⁷ regarding efficacy of appendectomy and antibiotic treatment for acute appendicitis reported antibiotic group had high recurrence rate 13.3% as compared to appendectomy patients 3.3%.

In present study In Group A patients wound infection was the most common complication found in 10 (25%) patients followed by peritonitis 6 (15%) and perforation 2 (5%). In Group II appendicular mass was most common complication found in 12 (30%) patients followed by perforation 7 (17.5%) and appendicular abscess 5 (12.5%). These results were comparable to some other studies.^{13,16,18}

CONCLUSION

Appendectomy is safe and effective treatment modality for acute appendicitis as compared to antibiotic therapy in term of hospital stay, recurrence and pain. It is also concluded that appendectomy resulted low complications rate as compared to antibiotic therapy.

Author's Contribution:

Concept & Design of Study:	Samina Karim
Drafting:	Ahmad Shah
Data Analysis:	Muhammad Ishaq Durani
Revisiting Critically:	Samina Karim, Ahmad Shah
Final Approval of version:	Samina Karim

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

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Role of Testosterone in Male Fertility/ Infertility in Tertiary Care Hospital of Karachi

Fareena Khalil, Intesar Burney and Abdul Shakoor Memon

ABSTRACT

Objective: To determine the effect of testosterone in male fertility in a tertiary care hospital of Karachi.

Study Design: Case Control study.

Place and Duration of Study: This study was conducted at the Gynecology and Obstetrics Department, Jinnah Post Graduate Medical Center Karachi from October 2016 to May 2018.

Materials and Methods: This study was conducted on 100 married males in collaboration with RHS centre (Male infertility clinic) at JPMC, Karachi. The male patients were divided into two major groups Group A (control group of fertile males) and Group B (case group of infertile males), Group B is further subdivided into three subgroups of Azoospermia, Oligospermia and Others causes of infertility. Semen Analysis was done following WHO criteria and the Quantitative measurement of testosterone in the serum was carried out by ELISA kit.

Results: The serum levels of testosterone was found out to be lower in infertile male group B1 (Azoospermia) and higher in group B2 (Oligospermia) and remains normal in Group A (Proven fathers) and Group B3 (Others).

Conclusion: Testosterone is lower in Azoospermia, Normal in Proven Fathers and higher in Oligospermia patient.

Key Words: Azoospermia, Fertile, Infertile, Oligospermia, Semen Analysis, Testosterone.

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INTRODUCTION

Infertility is when a married couple is unable to conceive a child after one year of regular unprotected sexual intercourse . It affect 15-20 % population worldwide ^[1]Male infertility is define as when a male is unable to achieve pregnancy with fertile female and there is an equal participation of both the partners in infertility i.e 40% due to male and 40% due to female and 20% is combination of both ^[2]However the exact cause of male infertility sometimes, is not ruled out and 20-50% of males present with idiopathic infertility ^[3]The quality of human sperm is declining world wide due to the lifestyle, enviornmental and nutritional factors ^[4]Endocrine problems leads to decrease sperm production , drug reactions and exposure to radiations may leads to male infertility ^[5] Testosterone is a principle sex hormone and maintains reproductive functions in males ^[6] activating the membrane bound androgen receptors after binding.^[7]

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The decrease production of sperm is due to impaired spermatogenesis and is due to hormonal imbalance of pituitary hormones i.e. FSH, LH and testosterone due to various drug, hormones and surgical procedures ^[8] Detoriation in the quality of semen occurs after about fifteen years of infertility treatment and there is an increase in LH hormone and decrease in testosterone/LH ratio ^[9]Testosterone plays a key role as an androgenic like development of secondary sex characters and maturity of sex organs ^[10]and anabolic hormone in the body before birth, during early infancy ,pre-pubertal, pubertal and in adult age by regulating hypothalamic-pituary-adrenal axis response ^[11]as it is mainly secreted from the testes and also from adrenal glands ^[12]Low or high levels of testosterone may impaired the functioning of reproductive system in males and may leads to male infertility by decreasing the sperm production to less than 20 million sperms/ml as compared to normal semen volume and other normal semen parameters and causing infertility in males.

In this study we compared the effects of testosterone on fertile i.e. Proven fathers and infertile males like Azoospermia (no sperm in ejaculate), Oligospermia Sperm count is very low) and others causes infertility

MATERIALS AND METHODS

This case control study was conducted on total 100 married fertile and infertile male subjects presenting to RHS centre (Male infertility Clinic) Department of Gynaecology and Obstetrics, JPMC , Karachi during

October 2016- May 2018 and the following data and results were collected. The subject included in our study were divided into two major groups of fertile and infertile males. Group A (control group) of 25 normal fertile males and Group B (case group) of 75 infertile males which were further subdivided into three groups Azoospermia (B 1) = 25 , Oligospermia (B 2) = 25 and others

(B3) = 25 categories of male infertility like Asthenospermia, Aspermia, Necropermia, Oligoasthenospermia, Teratospermia. All married males of age 18-45 years with no restriction of socioeconomic status are included in this study. Group A includes 25 fertile males (Proven Fathers) with a baby of one day to one year and Group B includes 75 infertile married males living with their physiologically normal (investigated by Gynaecologist) wives of child bearing age for a year and having regular intercourse without protection and wives are not

becoming pregnant and they are subdivided into (Group) B1) = 25 Azoospermia (zero sperm count (Group B2) = 25 Oligospermia (low sperm count), (Group B3) = 25 Others categories of male infertility confirmed by their Semen Analysis. Unmarried males above 45 years of age and suffering from chronic disease e.g liver and renal diseases and hypogonadism are excluded from this study .A detailed history was taken on a questionnaire with their informed consent and two types of samples (Blood and Semen) were collected and Semen was analysed according to WHO procedure as prescribed in WHO manual ¹(WHO,2010) i.e Semen sample were obtained by masturbation after 3-4 days of sexual abstinence not more than 7 days and the sample was taken by providing an isolated place and a sterile plastic jar to the patients and control and analysis was performed for semen parameters within half an hour of collection of semen at room temperature. The quantitative measurement of testosterone in serum was carried out by enzyme immunoassay using testosterone –ELISA kit no KAPD1559 DIA source Belgium

RESULTS

A total of 100 male subjects included in this case control study were divided in two major groups A (proven fathers) and B (infertile) males and group B is further subdivided into three subgroups of Azoospermia B1, Oligospermia B2 and Others B3 of different categories of male infertility .

Our result in Table 1 gives the multiple comparison of means for serum testosterone across group, it was seen that, serum testosterone in azoospermia patients 1.63 units lesser as compare to oligospermia, 1.19 unit lesser as as compare to others, and 1.22 unit lesser as compare to proven father, they all differences were significant with $p < 0.01$ obtained using LSD test.

Comparison of oligospermia with others tell us that mean of serum testosterone was 0.44 unit higher in oligospermia, 0.4 unit higher in proven father, but these differences cannot be consider significant as p was obtained more than 0.05.

Table No.1: Comparisons of Serum Testosterone of case and control

Serum Testosterone				
Groups Cases and controls		Mean Difference	Standard Error	p-value
Group B1 Azoospermia	Group B2 Oligospermia	-1.63	0.52	<0.01*
	Group B3 Others	-1.19	0.52	0.026*
	Group A Proven Father	-1.22	0.52	0.02*
Group B2 Oligospermia	Group B3 OTHERS	0.44	0.52	0.406
	Group A Proven Father	0.4	0.52	0.445
Group B3 Others	Group A Proven Father	-0.03	0.52	0.945

* The mean difference is significant at the 0.05 level.

Table No.2: Comparison of Serum Testosterone between case and control groups

Case and control groups		Cases			P value
Parameters	Control Group A (Fertile) n=25	Group B (Infertile) n=75			
	Group A n=25 Proven Father	Group B1 n=25 Azoospermia	Group B2 n=25 Oligospermia	Group B3 n=25 Others	
		Mean \pm S.D			
Serum Testosterone (ng/ml)	4.56 \pm 1.25	3.33 \pm 1.78	4.9 \pm 1.93	4.53 \pm 2.36	0.017*
*p<0.05 was considered significant using ANOVA					

* $p < 0.05$ was considered significant using ANOVA

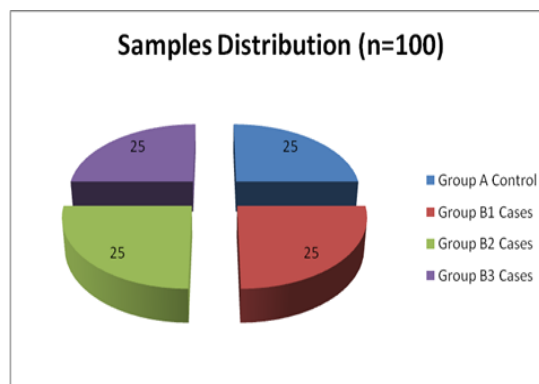


Figure No.1: Sample Distribution of case and control groups

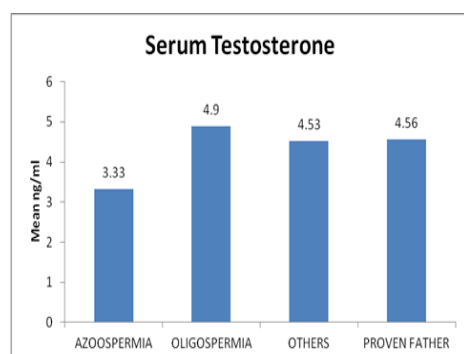


Figure No.2: Serum Testosterone of case and control groups

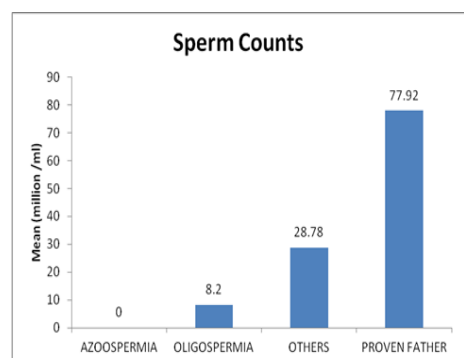


Figure No.3: Sperm Count of case and control group

Serum levels of testosterone in Azoospermia patients was getting down, it was also gives significant p-value , 0.017 that tell us that mean of serum testosterone was not same across four groups.

DISCUSSION

In this case control study we had investigated the male patients for their fertility status attending the male infertility clinic at RHS A centre, JPMC, Karachi. The aim of our present study was to found out the effect of testosterone on male fertility and infertility. In the previous studies, we have found that the testosterone had a potent effect on male fertility parameters and a very few studies had been conducted with reference to testosterone level in different groups of infertility like Azoospermia, Oligospermia and others groups of infertility. Although testosterone is not a factor for infertility because the production of sperm is stimulated by hormones other than testosterone .Testosterone is responsible for sperm maturation and its level is higher in the testes where sperm are produce as compared to in blood and therefore a small amount of it can cause sperm production. ^[13]In Egypt , a study was done ^[14]showed a negative correlation between serum testosterone and Azoospermia patient and this was in agreement with our study.

A similar study was conducted in China by ^[15]which was in favour of our present study that serum

testosterone had negative correlation with sperm motility as seen in our group B3 patients i.e Asthenozoospermia. According to the study done by ^[16] in Mansehra ,Pakistan serum testosterone was found out to be lower in Azoospermia patients ,oligospermia and others group patients and there was also a differences in the level of testosterone in fertile patients. The study done by ^[17,18]showed that the level of testosterone in serum was higher in Oligospermia males than in other groups of infertility and it also improves spermatogenesis even in fertile males and this is also proved in our study. In a study conducted by ^[19,20] evealed the role of testosterone on semen parameters and its influenced on the fertility status of male.

Testosterone is supposed to be an important parameter while diagnosing male fertility and it plays a vital role in male reproduction. In a present study we found that the level of testosterone in different study groups were variable and while comparing the groups we found that the level of testosterone in proven fathers (control group A) is less than the infertile groups (case groups B) like Oligospermia (B2) ,but in Azoospermia (B1) the level of testosterone is lower than the others (B3) group which shows that there must be a malfunctioning of the testes either in their physiological or anatomical structures.

CONCLUSION

In this study we found out that testosterone was not solely responsible for the fertility regulation in males because the level of testosterone was higher in infertile group as compared to the proven fertility.

Author's Contribution:

Concept & Design of Study: Fareena Khalil
 Drafting: Intesar Burney
 Data Analysis: Abdul Shakoor
 Revisiting Critically: Fareena Khalil, Abdul Shakoor
 Final Approval of version: Fareena Khalil

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

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Tuberculosis as a Predictor of Childhood Malnutrition in Sindh, Pakistan

TB in
Malnourished
Children

Shafi Muhammad Khuawar¹, Arshad Hussain Laghari² and Ghulam Sarwar Shaikh³

ABSTRACT

Objective: To assess the prevalence and identify risk factors associated with Mycobacterium tuberculosis infection in Sindh, Pakistan.

Study Design: Quantitative and cross-sectional study.

Place and Duration of Study: This study was conducted at the Department of Pulmonology, and Department of Biochemistry Ghulam Muhammad Mahar Medical College, Sukkur from January 2016 to May, 2019.

Materials and Methods: Diagnosis of TB was performed by AFB smear and X-ray chest. For the screening of malnutrition, blood sample were collected and Total Protein, Albumin and A/G ratio were analyzed. Body Mass Index (BMI) were estimated by analyzing data from questioners.

Results: Overall 170 children were recruited in this study, 81 were male and 89 were female. It was estimated that 13% children were infected with Tuberculosis every year. Malnutrition was highly prevalent in TB infected children.

Conclusion: This seems to be a relationship between malnutrition and an increased risk of TB in children belong to remote areas of Sindh, Pakistan.

Key Words: Mycobacterium Tuberculosis, Malnutrition, Childhood Malnutrition.

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INTRODUCTION

TB is one of the leading infection cause mortality as weigh against to other infections disease of humankind particularly in rustic areas of developing countries¹. TB is most spreading and has high mortality rate. It is reported that the rate of deaths due to TB is very high in developing countries². As for as Pakistan is concern, it is not probable to present precise data of TB and TB related deaths due to the dearth of disease surveillance³. Tuberculosis (TB) remains a significant source of morbidity and mortality amid children in resource-limited areas. It was estimated in a study that 11% children are infected with TB among new TB infections each year. Malnutrition is also highly prevalent in children belong to tuberculosis endemic countries and contributes to 2.2 million deaths in children under 5 years of age worldwide⁴. There is multiple reasons contributed both malnutrition and poor TB control like poverty, overcrowding, food insecurity and human immunodeficiency⁵.

Although the World Health Organization (WHO) states that malnutrition is a significant risk factor for childhood tuberculosis, there are limited studies to explain the mechanisms underlying this association⁶. This may be due to the challenges in diagnosing pediatric tuberculosis, difficulty in establishing a causal role of malnutrition on tuberculosis, and an overall low research priority because of the limited infectivity of children⁷. We will review 4 lines of support that serve as the foundation of our understanding of the interaction between pediatric tuberculosis and nutritional status, namely, (1) gene polymorphisms involving vitamin metabolism to danger of tuberculosis, (2) studies investigating immune development amid malnourished children, (3) links between malnutrition and respiratory tract infections in children, and (4) associations among nutritional status and tuberculosis in both animal model and children^{8,9}. Taken jointly, the proof suggests that malnutrition affects genetic expression and immune function that predisposes children to tuberculosis progression, and the resulting disease and inflammatory response further worsens the nutritional state¹⁰. Because of this devastating cycle, understanding the mechanisms that contribute to this precise interaction in children is necessary to addressing both epidemics and ascertaining whether nutritional interventions. Eventually, we want to recognize if nutritional supplementation can recover immune function and clinical outcomes in tuberculosis¹¹. Early ecological studies found that during times of food restriction, such as war, tuberculosis morbidity rose significantly and then sharply declined after food supplies returned¹².

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However, clinical trials face large challenges, because tuberculosis therapy will cause a rapid drop in bacillary load and improve nutritional status. Consequently, this can overshadow any modest change after supplementation¹³. One promising randomized trial among adults with tuberculosis in Indonesia found that supplementation of zinc and vitamin A resulted in faster sputum conversion time and resolution of lung lesions on chest X-ray^{13,14}. However, more recently, the same group was unable to repeat the results in a more malnourished population with a combined or individual addition of vitamin A and zinc. The few trials on nutritional supplementation for pediatric tuberculosis do not suggest a significant benefit¹⁵. A study in Brazil showed that zinc supplementation at the time of purified protein derivative (PPD) placement in malnourished children increased the size of induration, suggesting an improvement in cell-mediated immunity¹⁶. However, an in-vitro study found that in HIV-positive patients, zinc was unable to improve IFN- γ response or increase lymphocyte levels after PPD stimulation^{16,17}. Clinical trials have shown mixed results. Hanekom et al evaluated the response to vitamin A supplementation in 85 South African children at baseline, 6 weeks, and 3 months after initiation of tuberculosis therapy. Supplementation was not associated with a significant improvement in outcomes, including weight change or improvement in respiratory symptoms¹⁸. Morcos et al conducted a small trial on vitamin D supplementation among children ages 1.5–13 years old and noted clinical and radiographic improvement in the supplementation group but did not demonstrate differences in vitamin D levels or weight gain at the end of therapy¹⁹. The most comprehensive trial was conducted recently by Mehta et al among 255 children from Tanzania 6 weeks to 5 years of age with active tuberculosis. The children were randomized to receive a daily multivitamin or placebo for 8 weeks after initiation of therapy. Overall, there was no difference in weight after 8 weeks, and there was also no effect in terms of CD4, CD8, and CD3 T-cell subsets^{20,21}.

MATERIALS AND METHODS

This study was conducted at department of Pulmonology, department of Biochemistry Ghulam Muhammad Mahar Medical College, Sukkur and department of Biochemistry, CMC Larkana covering the period from January, 2016 to May, 2019. The patients were included in present study after gave their consent for the analysis of TB and Malnutrition. All children were recruited from OPD of pulmonary diseases of GMMMC teaching hospital, Sukkur. All individual data, such as age, sex, socioeconomic surroundings, schooling Level, occupation, and history of any surgery or blood transfusion were collected. The TB has been diagnosed by using AFB Sputum smear

and by FNAC/biopsy in patient expected with extra pulmonary tuberculosis (EPTB). For screening of malnutrition, blood sample were collected and Total Protein, Albumin and A/G ratio were analyzed. Body Mass Index (BMI) was estimated by analyzing data from questioners..

RESULTS

Total 170 patients with Tuberculosis infection were recruited in present study, of the 170 patients 81 were males and 89 were females.. The most commonly affected age group was 3 - 8 years..

Table No.1: Tuberculosis detected in children (n = 170)

Male	89 (52.3%)
Female	81(47.7%)
Total TB positive	70

n = Total number of TB patient

Table No.2: Clinical presentation of the TB infected patients

Clinical presentation of the co-infected patients	
Symptoms	Percentage
Cough	90
Fever	78
Loss of appetite	76
Weight los	76
Dyspnea	44
Hemoptysis	14
Chest pain	10

Table No.3: Comparison of risk factor of Malnutrition in children with TB infection.

Risk factors of Malnutrition	Degree	Percentage%	p-value
BMI	High	13%	< 0.04
	Low	69%	< 0.01
Hb%	High	06%	< 0.05
	Low	79%	< 0.01
Total Protein	High	09%	< 0.02
	Low	71%	< 0.03
Albumin	High	11%	< 0.04
	Low	74%	< 0.04
A/G ratio	High	10%	< 0.04
	Low	71%	< 0.02

DISCUSSION

In present study, we observed that 13% children were infected with TB with low BMI and with low nutrition markers in Sindh, Pakistan which was significantly alarming. TB remains a significant source of morbidity and mortality among children in resource-limited settings. It is reported that of the 9 million new TB infections each year, 11% are in children¹². Other similar study in Bangladesh reported that malnutrition is also highly prevalent in children living in tuberculosis endemic countries and contributes to 2.0 million deaths in children fewer than 5 years of age. In

this study, we analyzed that 70% children were malnourished shown infected with TB^{12, 13}.

A similar study was conducted in India in 2000 shown low prevalence than presented HIV-TB co-infection study¹⁷. It had shown 10.91% prevalence which is lower than this study¹⁸. Another study of India from 1996 to 2001 shown the prevalence in Aligarh a states of India has 0.8% to 2.8% prevalence. In this study it was observed that in Sindh^{14, 15}, Pakistan there is a higher HIV-TB co-infection in Males than Females. HIV-TB co-Infection ratio has also reported in other part of the world¹⁶. Apart from for a few countries in Africa, the occurrence of co-infection has been reported to be elevated among males than females. But almost all other countries, there is title dissimilarity in the sexual category proportion¹⁷. In many studies that gave been conducted in different parts of Hindustan have indicated considerably elevated HIV-TB co-infection in Males than in Females patients¹⁸. The findings of the present study align with that pattern of India and of few countries in Africa. Moreover, in this present study, we observed that the age group which more frequently infected with HIV- TB co-infection is between 33-48 year in both males and females^{19, 20}. It is also align with other studies of world and in particularly to India. Almost all the patient was infected with HIV- TB co-infection were belonging to low socio-economic background^{21, 22}. The present study indicates that there is need to imperceptible change in society to improve the Health of people, particularly remote area of the countries. There are needs in public awareness and better treatment regimes^{23, 24}.

CONCLUSION

The prevalence of HIV-TB co-infection was 13.9%. Consequently, all TB patients should be assessed for HIV risk factors and counseled to undergo HIV testing. Males patients are more often infected with HIV-TB co-infection than females. Ages from 33 years to 48 years are more often infected with TB and also have co-infection with HIV. Results of this study are alarming and needs betterment in public awareness and treatment regimes..

Author's Contribution:

Concept & Design of Study:	Shafi MuhammaKhuwar
Drafting:	Arshad Hussain Laghari
Data Analysis:	Ghulam Sarwar Shaikh
Revisiting Critically:	Shafi Muhmmad Khuwar
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Surgical Management of Vesicovaginal Fistula, Single Center Experience at Urology Department Nishtar Medical University Hospital Multan

Mian Muhammad Asif Nawaz, Abdul Ghaffar, Umar Ghaffar and Zainab Javeed

ABSTRACT

Objective: To compare the efficacy of different approaches for repair of vesico-vagino fistula including transvaginal, transabdominal or the combined approach and to document the success rates and the complications of VVF repair.

Study Design: Prospective study.

Place and Duration of Study: The study was conducted at Urology Department Nishtar Medical University and Hospital Multan from October 2018 to April 2019 .

Materials and Methods: A total of 163 women diagnosed with vesico-vaginal fistula (VVF) on cystoscopy who met the inclusion criteria were selected. Transabdominal repair was performed in 111 patients when the fistula site could not be easily accessed per vagina, when VVF was above trigone or when the VVF was complex. Transvaginal repair was performed in 52 patients in cases of simple fistula. These patients were followed for 6 weeks at 2 week time interval. Rates of operative success, infection and recurrent fistula formation were compared. These outcomes were further stratified in respect to age of patient, size of fistula and type of fistula.

Results: Total 163 women having age range from 20 to 60 years with mean age of 38.18 ± 10.64 years. There were increased number of unsuccessful repair in transvaginal repair (17.31%) compared to transabdominal repair (4.5%) (p value 0.007). Stratification of outcomes with respect to age (Table IV) showed statistically significant increase in recurrent fistula formation in age groups 20-40 (p value 0.05) . Stratification with respect to size of fistula showed a significant decrease in infection rate with large fistulas compared to small and medium sized fistulas (p value 0.004). Stratification with respect to type of fistula showed no significant difference in infection rate, recurrent fistula formation or unsuccessful repair in simple or complicated type of fistulas.

Conclusion: This study concluded that the frequency of unsuccessful repair and recurrent fistula is more after vaginal repair compared to abdominal repair while infection rate was more after abdominal repair.

Key Words: Vesico-vaginal Fistula, Leakage of urine, trans-vaginal approach, trans-abdominal approach.

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INTRODUCTION

Vesico-vaginal fistula (VVF) is an abnormal communication between the bladder and the vagina that allows continuous involuntary urine leakage into the vaginal vault.¹ VVF is a condition having devastating consequences on the patient's physical and psychological health and continues to pose a significant challenge to the surgeon.

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Quick and accurate diagnosis followed by timely repair is essential to the successful management of these cases. A thorough understanding of the pathophysiology and anatomy of the fistula, potential factors that may compromise healing and experience in the fundamental principles of fistula repair are the vital tools towards proper management of the fistula.²

The etiology of VVF varies in different parts of the world. In the developing countries these result from obstetric complications, possibly due to inadequate medical care, early age of conception, vaginal lacerations from forceps rotations, cesarean sections hysterectomy and ruptured uterus while in developed countries, the main cause is iatrogenic injury during gynecologic surgery. Less frequent causes of VVF include various urological and gastrointestinal surgeries such as suburethral sling procedure, urethral and bladder neck surgery and surgery for pelvic carcinomas¹. Fistulas can be classified according to size and type as small (≤ 0.5 cm), medium (0.6 cm-2.4 cm),

large (≥ 2.5 cm), simple (small non-radiated, single) or complex (medium, large, radiated, multiple, recurrent) respectively.³

VVF repair can be approached transvaginally, transabdominally or in a combined approach if necessary. It can also be repaired laparoscopically or through robotic repair in limited cases.⁴ The transvaginal approach offers a lower complication rate and shorter postoperative recovery while transabdominal route is preferred when the fistula site cannot be visualized or easily accessed per vagina or when the VVF is complex.²

MATERIALS AND METHODS

A prospective analysis of 163 women was conducted after approval from ethical committee in the department of urology, Nishtar Medical University and Hospital Multan, Pakistan from 29th October 2018 to 27th April 2019. All the patients fulfilling inclusion criteria were enrolled from outpatient department (OPD) of Department of Urology, Nishtar Medical university and hospital Multan. The patients were explained about the objectives of this study and the fact that there is no risk involved to the patient while taking part in this study. Informed consent was taken from each patient.

Inclusion Criteria: Women diagnosed with vesico-vaginal fistula (VVF) on cystoscopy of either age.

Small (≤ 0.5 cm), Medium (0.6 cm-2.4 cm), Large (≥ 2.5 cm), fistula on cystoscopy.

Simple (small non-radiated, single) or complex (medium and large) fistula on cystoscopy.

Exclusion Criteria: Patients with the history of recurrence of fistula, multiple fistulae and radiation.

Patients with small bladder size, urethral destruction, circumferential involvement and severe vaginal scarring.

Patients having fistula at bladder neck and urethra and involving sphincter.

Patients who don't give consent of participation.

Preoperative Measures: Patients were admitted and complete history, detailed examination was done. Necessary laboratory investigations such as intravenous urogram and cystogram were obtained. Trans-vaginal or trans-abdominal approach were planned after diagnostic cystoscopy and EUA. Vesico-Vaginal fistulas were classified according to size as small (≤ 0.5 cm), medium (0.6 cm-2.4 cm), large (≥ 2.5 cm), and type such as, simple (single, small non-radiated) or complex (multiple, recurrent, medium, large, radiated).

Surgical Procedure: The trans-vaginal route was adopted in cases of simple infra-trigonal fistula having capacious vaginal cavity while VVF located at trigon or supra-trigonal area having less capacious vagina were approached by trans-abdominal route and also in cases of complex VVF.

Follow Up: These patients were followed for 6 weeks at 2 week time interval. All this data was noted on a predesigned form.

Statistical Analysis: Statistical analyses were performed using SPSS for Windows. Data was shown as mean \pm standard deviation (SD). T test were performed with a test level of $\alpha = 0.05$ the difference was considered to be statistically significant when the *P* value was less than 0.05.

RESULTS

Table No. 1: Percentage of patients according to Age distribution (n=163)

Age in (years)	No. of Patients	%age
20-30	44	26.99
31-40	59	36.20
41-50	33	20.25
51-60	27	16.56
Mean \pm SD	38.18 \pm 10.64	

Table No. 2: Outcome

Outcome	Frequency (%)	
	yes	No
Unsuccessful Repair	14 (8.59%)	149 (91.41%)
Infection	25 (15.34%)	138 (84.66%)
Recurrent Fistula formation	21 (12.88%)	142 (87.12%)

Table No. 3: Comparison of outcome between Abdominal versus Vaginal route.

Outcome		Abdominal (n=111)	Vaginal (n=52)	P-value
Unsuccessful Repair	Yes	05 (4.50%)	09 (17.31%)	0.007
	No	106 (95.50%)	43 (82.69%)	
Infection	Yes	21 (18.92%)	04 (7.69%)	0.064
	No	90 (81.08%)	48 (92.31%)	
Recurrent Fistula formation	Yes	13 (11.71%)	08 (15.38%)	0.514
	No	98 (88.29%)	44 (84.62%)	

Table No. 4: Stratification of Outcome with respect to age

Outcome		20-40 years (n=103)	41-60 years (n=60)	P-value
Unsuccessful Repair	Yes	11 (10.68%)	03 (5.0%)	0.212
	No	92 (89.32%)	57 (95.0%)	
Infection	Yes	17 (16.50%)	08 (13.33%)	0.588
	No	86 (83.49%)	52 (86.67%)	
Recurrent Fistula formation	Yes	19 (18.45%)	02 (3.33%)	0.005
	No	84 (81.55%)	58 (96.67%)	

Age range of the population of this study was between 20 to 60 years with mean age of 38.18 \pm 10.64 years. (Table I). Trans-abdominal repair was performed in 111 patients when the fistula site could not be easily accessed per vagina, when VVF was above trigon or

when the VVF was complex. Trans-vaginal repair was performed in 52 patients in cases of simple fistula. There were 47 patients with small (28.83%), 68 patients with medium (41.72%) and 48 patients with large.

Table No. 5: Stratification of Outcome with respect to size of fistula.

Outcome		Small (n=47)	Medium (n=68)	Large (n=48)	P-value
Unsuccessful Repair	Yes	04 (8.51%)	05 (7.35%)	05 (10.42%)	0.845
	No	43 (91.49%)	63 (92.65%)	43 (89.58%)	
Infection	Yes	09 (19.15%)	13 (19.12%)	03 (6.25%)	0.004
	No	38 (80.85%)	55 (80.88%)	45 (93.75%)	
Recurrent Fistula formation	Yes	04 (8.51%)	09 (13.24%)	08 (16.67%)	0.492
	No	43 (91.49%)	59 (86.76%)	40 (83.33%)	

Table No. 6: Stratification of Outcome with respect to Type of Fistula

Outcome		Simple (n=47)	Complicated (n=116)	P-value
Unsuccessful Repair	Yes	02 (4.26%)	12 (10.34%)	0.209
	No	45 (95.74%)	104(89.66%)	
Infection	Yes	10 (21.28%)	15 (12.93%)	0.180
	No	37 (78.72%)	101(87.07%)	
Recurrent Fistula formation	Yes	08 (17.02%)	13 (11.21%)	0.316
	No	39 (82.98%)	103(88.79%)	

DISCUSSION

We analysed a cohort of 163 women with Vesicovaginal fistula diagnosed on cystoscopy who met the inclusion criteria. Transabdominal repair was performed in 111 patients when the fistula site could not be easily accessed per vagina, when VVF was above trigone or when the VVF was complex. Transvaginal repair was performed in 52 patients in cases of simple fistula. Our study gives a comparative analysis on the procedures used for operating VVF including Transabdominal and transvaginal.

We found that there was a statistically significant increase in failure rate in transvaginal compared to transabdominal route to operate VVF. Infection rate despite having an increased rate in transabdominal was not statistically significant. Recurrence of fistula was greater in transvaginal method but again it was not statistically significant. Overall we preferred transabdominal as a superior procedure of choice to operate VVF in terms of success rate.

Our study went further to comment on various factors such as success rate, infection and recurrence when stratified in terms of age, size and type of fistula. We found statistically significant increase in recurrent fistula formation in age groups 20-40 compared with 41-60 age group. No significant difference was found in infection rate and unsuccessful repair when stratified by

age. We also found statistically significant decrease in infection rate with large fistulas compared to small and medium sized fistulas. No significant difference was observed in recurrent fistula formation or unsuccessful repair when stratified by size. Our study found no significant difference in infection, recurrent fistula formation or unsuccessful repair when stratified in terms of type of fistula ie simple or complicated type of fistulas.

Vesicovaginal fistula, (VVF), although reported in ancient Egyptian mummies of 2000 BC, is still a big problem in developing world. It is a devastating complication of obstetrics and gynecological surgery. Over 90% of fistulae in developing world are of obstetrical origin where as in the developed nations these are usually unfortunate complications of gynecological or other pelvic surgery. Abdominal hysterectomy remains the most common cause of VVF occurring in 1/800 hysterectomies. True incidence of VVF is not Known.⁵ Historically, the approach chosen by the surgeon has been dictated by the location of the fistula. The approaches include vaginal, abdominal, or combined abdominal and vaginal approaches. The abdominal approach has traditionally been used for supratrigonal fistulas, whereas the vaginal approach has been traditionally used for infratrigonal, bladder neck, and proximal urethral fistulas. Combined procedures are often reserved for complicated fistulas requiring the use of omentum or rectus muscle or for vesicovaginal fistulas with ureteral involvement. The advantages of transvaginal approaches include patient comfort and recovery time. The advantages of the abdominal approach include surgeon familiarity and the ability to perform simultaneous ureteral or bladder surgery. With the use of proper surgical technique and a well-vascularized buttress, even complex vesicovaginal fistulas can be repaired through a transvaginal approach.^{6,7}

Age of patients affected by VVF vary greatly between country to country and even in different regions of same country.^{8,9} Our study observed age range between 20 to 60 years with mean age of 38.18 ± 10.64 years. Majority of the patients 59 (36.20%) were between 31 to 40 years of age. Wall et al. found the leading cause of VVF to be obstetric trauma. They considered the age of the 'typical patient' to be 15.5 year⁸.

In another study from Ethiopia 40% of patients in the study cohort of 193 were teenagers, and 95.3% of the VVF resulted from obstetric trauma.¹⁰

In our study, we have done vaginal repair in 52 patients with simple fistula (small non-radiated, single), VVF located at trigone of bladder while transabdominal route was preferred in 111 patients when the fistula site could not be easily accessed per vagina, when VVF was above trigone or when the VVF was complex (medium and large). Unsuccessful repair was seen in 14 (8.59%), infection in 25 (15.34%) and recurrent fistula formation

in 21 (12.88%) patients. Different studies have reported different successful management rates. Rajamaheswari reported successful outcome for vaginal repair as 86.7% while 100% success rate for abdominal repair and recurrent fistula formation was observed in 12 % of these treated cases.¹¹ Kapoor R et al in his study on 52 VVF patients had a success rate of 94.2%. Thirty-two (61.5%) patients were managed by transvaginal route, of which 17 had supratrigonal and 15 trigonal fistulas. Twenty (38.5%) patients with complex fistulas were managed by abdominal route.

Another study from India reported 94.8 % success rate in vaginal repair while 100 % successful repair was achieved through abdominal repair.¹² Milicevic S et al¹³ has found successful primary repair of VVF in 75.00% of patients. The successfulness primary repairs with transvaginal and transabdominal approach with the use of omental flap was 100%, and with transvesical approach, it was 68.42%. Frajzyngier reported abdominal repair to be more successful (90% success rate) compared with that of vaginal repair (81% success rate).⁹ Gupta et al reported 91.7% success rate while among complication wound infection was 25%.¹ Some studies are also available at national level, in a study published from Islamabad reported 100 % success rate through transabdominal route while 80% success rate through transvaginal route.¹⁵ In a study conducted at Rawalpindi has reported overall 95 % success rate¹⁶, another study conducted at Lahore reported overall 87% success rate including 87% success rate through vaginal route while 88% success rate was reported through abdominal route.¹⁷ A study conducted at Jamshoro reported 93% overall successful rate.¹⁸ Many other studies have revealed higher success rates with abdominal approach. In our study, better results were obtained with transabdominal repair as compared to vaginal repair. On the other hand, there are surgeons who got excellent results with vaginal approach. The present study showed 83% success rate with transvaginal repair. Therefore, the success largely depends on a thorough evaluation followed by a prudent decision about the route of surgical repair. Success is also affected by many other factors, like general condition of the patient, size and site of the fistula, condition of the tissues, number of previous attempts at repair and operative facilities.

On the other hand, Atiq-ur-Rehman S et al¹⁹ has shown 91.67% success with transabdominal repair of VVF while 100% success with transvaginal repair.

In another series by Khawaja AR et al²⁰, majority of the patients (n=27) were repaired by trans abdominal route with a success in 26 patients (95.65%) and one failure. In literature, the success rate of repair by trans abdominal route is 94 - 98% and by trans vaginal 82%.²¹ It is concluded from our study that frequency of unsuccessful repair and recurrent fistula is more after

vaginal repair compared to abdominal repair while infection rate was more after abdominal repair.

Recurrence rate after VVF repair in our study is 12.88%²¹ and among these recurrence rate 11.71%¹³ in transabdominal repair but 15.38%⁸ in transvaginal repair with a p value 0.514. The result of our study are comparable to national and international studies: Ocrim LJ et al²², carried out a retrospective study which included 41 patients, out of whom 32 had a VVF and nine had a urethrovaginal fistula (UVF), the successfulness of the fistula closure was 92%, with 8% recurrence rate. These were managed by secondary and tertiary repair. Mubeen RM et al²³ showed successful surgical repair through transabdominal route in all 24 (100%) cases of VVF and in 4 (80%) out of 5 cases through trans-vaginal route with recurrence rate of 20 %. Sahito RA et al³⁷ wrote about the successfulness of the primary surgical repair with the abdominal approach in 30 patients with VVF in 86.67 % of cases with recurrence rate of 13.43%.

Infection was noticed in 25 case in our series with rate of 15.34%. Most of the studies have not highlighted the infection rates. Gupta et al reported 91.7% success rate while among complication wound infection was 25%.²⁴

CONCLUSION

VVFs are among the most distressing complications of gynecologic and obstetric procedures. As the best chance of a successful repair is at the first attempt so best decisions regarding technique and approach be adopted at the surgeons best satisfaction. We adopted the abdominal approach as a primary method of VVF repair with higher success rate as compared to vaginal route. Complications of adopted surgical procedure must be documented. Measures for prevention must include universal education, improvement in the status of women, and improved and accessible medical services.

Author's Contribution:

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Data Analysis:	Umar Ghaffar, and Zainab Javeed
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Frequency and Associated Risk Factors for Complications of Ventriculo Peritoneal Shunts in Children

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ABSTRACT

Objective: The objective of this study was to determine the frequency and associated risk factors for complications of Ventriculo-Peritoneal (VP) Shunts in children.

Study Design: Retrospective cross sectional study.

Place and Duration of Study: This study was carried out at the Department of Neurosurgery, Khalifa Gul Nawaz Teaching Hospital, Bannu from January 2013 to December 2017.

Materials and Methods: A total of 148 below 12 years children with hydrocephalus, who were operated for ventriculo-peritoneal shunts placement. Demographic findings, follow-up period, shunt type, etiology of hydrocephalus, and timing of complications were recorded. Descriptive statistics were computed. Complications of VP shunt were compared among age groups, genders, and causes of hydrocephalus, shunt types and timing of complications, using chi-square test. $P \leq 0.05$ was considered significant.

Results: The mean age was 5.3 ± 3.12 years. Most of children were below 3 years $n=108$ (73%). Males were the predominant gender, $n=102$ (68.9%). Most common complication of shunt was malfunction, $n=17$ (11.5%), followed by infection, $n=12$ (8.1%). Overall complication rate was 19.6%. Of total, 93.3% complications were found in less than 6 months. In younger age, the complications were more frequent statistically ($P < 0.001$). The timing of complications was different statistically ($P < 0.001$). The effect of VP shunt type, cause of hydrocephalus and gender on complications was not statistically significant ($P > 0.05$).

Conclusion: Infection and malfunction are the common complications of VP shunt placement, in children with hydrocephalus. Clinicians should be most vigilant especially in the first 6 month, to manage these complications promptly.

Key Words: Ventriculo-peritoneal shunt, hydrocephalus, infection, malfunction, children, Bannu.

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INTRODUCTION

The abnormal accumulation of cerebro-spinal fluid within the brain is called hydrocephalus, which can occur at any age. The pathology of hydrocephalus is complex, can be the outcome of a variety of in-birth, and acquired diseases affecting nervous system.¹

The morphologic characteristics of Hydrocephalus are effortlessly recognizable, but the complete understanding of patho-physiology is still lacking.

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The contemporary treatment options are limited, and invasive in nature. Some of the treatment options are cerebrospinal fluid diversion, through a catheter or endoscopic third ventriculo-stomy.² Due to large capacity of peritoneal cavity of fluid absorption, ventriculo-peritoneal (VP) shunt is the most frequently used. First and subsequent placement of peritoneal catheter can be performed easily.³

In clinical practice of medicine, there are a lot of failures of cerebrospinal fluid (CSF) shunt surgery.⁴ VP shunt has been associated with many abdominal complications like fibrous encapsulation of the peritoneal tip, distal tube's kinking or blocking⁵, slippage of shunt via the surgical wound, or movement of the shunt into the various compartments of abdominal cavity.⁶ Infection, paralytic ileus, CSF fistula, the abdominal tube causing perforation of bowel, inability of peritoneum to absorb the diverted CSF, peritoneal cyst or hydrocele formation, and spontaneous extrusion of the tube through the umbilicus⁷ and anus are other complications.⁸

The literature reported that the overall rate of shunt infection ranges from 3 to 15%.^{9, 10} and 90% of infections occur within the first 6 months.⁴ According to

McGirt *et al*¹⁰ in the first year after implanting the shunt, 45% of shunt failed due to infection, and after 2 years there was 6% failures. Failure due to obstruction of VP shunt with cells or tissue was more than 50% in the children.¹¹

Due to genetic, ethnic and environmental variations, the risk factors and frequency of complications of VP shunt in children with hydrocephalus, is different in various populations. So this study was to know the burden of this problem and consequently to provide local data in this perspective, which is helping clinicians in better care of children. So the objective of this study was to determine the frequency and associated risk factors for complications of ventriculo-peritoneal shunts in children.

MATERIALS AND METHODS

retrospective cross sectional The study was carried out from 1st January 2013 to 31st December 2017 at the Department of Neurosurgery, Khalifa Gul Nawaz Teaching Hospital, Bannu. Total 148 patients with hydrocephalus were operated for ventriculoperitoneal shunts. These patients were admitted through the outpatient department and through referral from pediatric medical units. Verbal informed consent was obtained from children's parent after explaining aim and details of the research. Following data was collected from the retrospective review of patient records: demographic findings, age at operation, follow-up period, shunt type, etiology of hydrocephalus, and timing of complication. The recognition of a bacteria from the CSF reservoir (above 50 leukocytes per mm³) along with positive blood culture when a subjective have any of the following features: fever, abdominal symptoms, neurologic symptoms, or shunt malfunction.¹² was defined as the partial or complete blockage of the shunt that lead to function it intermittently or not at all. Blockage may be from blood cells, tissue or bacterial accumulation. Malfunction was assessed through history, examination, plain radio-graphs and CT brain. The inclusion criteria were all patients with hydrocephalus operated in the Department of Neurosurgery, Khalifa Gul Nawaz Teaching Hospital, Bannu, either gender, and age from one month to 12 years. Patients with ventriculo-peritoneal shunts complications operated elsewhere admitted through outpatient department were excluded.

RESULTS

The mean age was 5.3 ± 3.12 years. Most of children were below 3 years, n=108(73%). Only n=17 (11.5%) were above 6 years. Males were the predominant gender, n=102(68.9%). Most common cause of hydrocephalus was congenital, n=83(56.1%), followed by post meningitis, n=45(30.4%), and least was posterior fossa space occupying lesion, n=20(13.5%). In n=97(65.5%) cases, Chhabra type shunt was placed, while in n=51(34.5%) cases, the Medtronic was

placed. Most common complication of shunt was malfunction, n=17(11.5%), followed by infection, n=12(8.1%). Overall complication rate was 19.6%.

Table No. 1: Characteristics of age group, gender, cause of hydrocephalus, type of shunt, type of complication in VP shunt and timing of complications

Variable		Frequ- ency	Percent	P- value
Age group	below 1 year	54	36.5	P<0.001
	1.1yr-3yrs	54	36.5	
	3.1yrs-6yrs	23	15.5	
	6.1yrs-12yrs	17	11.5	
	Total	148	100	
Gender	Male	102	68.9	P<0.001
	Female	46	31.1	
	Total	148	100	
Cause.of hydrocephalus	Congenital	83	56.1	P<0.001
	Post meningitis	45	30.4	
	Post fossa SOL	20	13.5	
	Total	148	100	
Type of shunt	Chhabra	97	65.5	P<0.001
	Medtronic	51	34.5	
	Total	148	100	
Type.of.compli cation in VP shunt	no complication	119	80.4	P<0.001
	Infection	12	8.1	
	Malfunction	17	11.5	
	Total	148	100	
Timing of complications	Nil	119	80.4	P<0.001
	within 1 week	7	4.7	
	1-4 weeks	6	4.1	
	5-12 weeks	9	6.1	
	13-24 weeks	5	3.4	
	More than 24 weeks	2	1.4	
	Total	148	100	

Of total, 93.3% complications were found in less than 6 months (upto 24 weeks). Only in 2 cases (1.4%), the complications in VP shunt had occurred after 6 months. All the difference for age group, gender, cause of hydrocephalus, type of shunt, type of complication in VP shunt and timing of complications were highly statistically significant. (Table 1)

In younger age, the complications were more frequent. Most of the complications were found in first year of life. These results were highly statistically significant (P<0.001). The type of complications in VP shunt was not statistically different among males and females (P=0.874). Most of the malfunction (blockage) of shunt was found within first week (29.4%). Most of the infection of VP shunt was in first week ((16.70%), and first month (16.70%). The timing of complications was different statistically (P<0.001). The effect of VP shunt type on complications was not statistically significant (P 0.682). Similarly, the cause of hydrocephalus was not statistically associated with complications (P=0.419). (Table 2)

Table No. 2: Comparison of VP shunt complications among age group, gender, cause of hydrocephalus, type of shunt, and timing of complications.

		Type of complication						P-value*
		Infection		Malfunction		no complication		
		N	%	n	%	n	%	
Age group	below 1 year	10	83.30	12	70.60	32	26.90	P<.001
	1.1yr-3yrs	1	8.30	2	11.80	51	42.90	
	3.1yrs-6yrs	1	8.30	2	11.80	20	16.80	
	6.1-12 years	0	0.00	1	5.90	16	13.40	
Gender	Male	9	75.00	12	70.60	81	68.10	.874
	Female	3	25.00	5	29.40	38	31.90	
Timing of complications	Nil	0	0.00	0	0.00	119	100.00	P<.001
	within one week	2	16.70	5	29.40	0	0.00	
	1-4 weeks	2	16.70	4	23.50	0	0.00	
	5-12 weeks	5	41.70	4	23.50	0	0.00	
	13-24 weeks	1	8.30	4	23.50	0	0.00	
	More than 24 weeks	2	16.70	0	0.00	0	0.00	
VP shunt type	Chhabra	7	58.30	10	58.80	80	67.20	.682
	Medtronic	5	41.70	7	41.20	39	32.80	
Cause of hydrocephalus	Congenital	6	50.00	6	35.30	71	59.70	.419
	Post meningitis	4	33.30	8	47.10	33	27.70	
	Post fossa SOL	2	16.70	3	17.60	15	12.60	

*chi-square test; $P \leq 0.05$ significant level; SOL, space occupying lesion

DISCUSSION

This study was done to find out the frequency of different complications and timing of Ventriculo-peritoneal shunt in children, so that we can overcome these problems in future.

Our results showed that overall complication rate was 19.6%. Of which, 93.3% complications were found in less than 6 months. Infection was found in 8.1% children. In younger age, the complications were more frequent ($P < 0.001$). Most of the complications were in the first 6 months. The timing of complications was different statistically ($P < 0.001$). The effect of VP shunt type, cause of hydrocephalus and gender on complications was not statistically significant ($P > 0.05$). Although CSF shunt placement contributed to the significant improvement in the managing outcome of hydrocephalus, the shunt has several complications, including infection, which is a major threat to pediatric patients¹³. The current study found that infection was found in 8.1% children. Lee *et al*¹² analyzed shunt infection rate and identify risk factors in a retrospective cohort study on 333 consecutive VP shunt cases in Korea. They reported that overall infection rate was 10.5%. Their results are near to our findings. In literature, the rate of infection after shunt implantation in children with hydrocephalus ranges from 3% to 20%.¹⁴⁻¹⁶

Our results revealed that the malfunction of VP shunt in children with hydrocephalus was in 11.5% cases. This was the most common complication. An Indian study on 137 children's clinical outcome of shunt surgeries reported that the most common complication of VP was blockage that causes it to function intermittently or not at all. They found the malfunction of VP shunt was in

10.94%.¹⁷ These results are in consistent with current study. The reasons for shunt obstruction may be the presence of higher concentration of protein and cellular contents in the cerebro-spinal fluid.

Our study showed that most of the complications were in the first 6 months ($P < 0.05$). This shows that success of shunt increased if survive in the first six months. Similar results were found in previous studies.^{17, 18} We used two types of VP shunts i.e Chhabra and Medtronic. We found no statistically difference in results. This shows that experience may be major reason responsible for success.

CONCLUSION

VP shunts placements are still associated with complications. Infection and malfunction are the common complications of VP shunt placement in children with hydrocephalus. Clinicians should be most vigilant especially in the first 6 month to manage these complications promptly..

Author's Contribution:

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Data Analysis:	Raza Muhammad Khan
Revisiting Critically:	Anwar Shah and Muhammad Ali Noman
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Comparison of Intraarticular Injection of Hyaluronic Acid and Steroids in Reducing Pain of Initial Stages of Knee Osteoarthritis

Effect of
Hyaluronic acid
and Steroids in
Injection knee
Osteoarthritis

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ABSTRACT

Objective: To compare the mean change in VAS score after intra-articular injection of Hyaluronic acid and Steroids in patients with initial stages of knee osteoarthritis.

Study Design: Randomized controlled trial study.

Place and Duration of Study: This study was conducted at the department of Orthopedics, BVH Bahawalpur from September 2017 to February 2018.

Materials and Methods: To compare the mean change in VAS score after intra-articular injection of Hyaluronic acid and Steroids in patients with initial stages of knee osteoarthritis

Results: The mean age in group A was 59.55 ± 7.60 years and group B 59.37 ± 8.26 years. Out of these 80 patients, 52 (65.0%) were females and 28 (35.0%) males with 1.85:1 female-male ratio. Mean pre-treatment VAS score in group A was 6.30 ± 1.38 while in group B was 5.95 ± 1.50 . Mean post-treatment VAS score in group A was 4.48 ± 1.26 while in group B was 1.60 ± 0.93 . Mean reduction in VAS score in group A was 1.82 ± 0.12 while in group B was 4.35 ± 0.57 .

Conclusion: We recommend hyaluronic acid in patients with initial stages of knee OA because significant reduction in mean VAS score (at 6 months) observed with intra-articular hyaluronic acid as compared to corticosteroid use.

Key Words: Knee osteoarthritis, hyaluronic acid, corticosteroid, intra-articular injection

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INTRODUCTION

Knee Osteoarthritis is a degenerative joint disease with gradually advancing softening and wearing of knee joint cartilage. It is characterized by following changes in subchondral bone like sclerosis, osteophytes and cyst formation along with synovitis and fibrosis of joint capsule¹. Pain, tenderness, stiffness and joint swelling are common symptoms in early stages, while deformity and loss of function occur in late stages. Although osteoarthritis (OA) can affect any synovial joint but osteoarthritis of knee is most cumbersome in terms of prevalence and disability^{2,3}. It is an age related disease⁴. It is most common cause of disability around the world and widespread musculoskeletal problem⁵.

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The estimated prevalence of symptomatic osteoarthritis of knee in the USA has been 12%. Severe pain results in functional impairment with limitation of daily life activities and poor quality of life of patients⁶.

It is divided into primary when no etiology found and secondary when there is definite etiology leading to disease. Risk factors are joint dysplasia, trauma, obesity, occupation and family history. On radiographic basis it can be divided into five stages, 0 to 4, with normal joint space to complete loss of joint space. Treatment options are, non-pharmacologic, pharmacologic and surgical. Non-pharmacologic are weight reduction, low impact exercise and physical therapy. Pharmacologic options are NSAIDs, intra-articular (IA) steroids and Hyaluronic acid (HA). Surgical options are joint debridement, realignment osteotomy, joint replacement and arthrodesis.

In one study conducted by Seth S. Leopold⁷ "Intra-articular injection of Steroids is compared with HA for initial stages of knee OA. Another study conducted by Adrian C. Jones⁸ also compared steroids with HA for initial stages of knee OA. As few studies have been done in Pakistan to compare the intraarticular injection of Steroids with Hyaluronic acids, so I have decided to carry-out study. If results of my study shows which recommended for use in Pakistan..

MATERIALS AND METHODS

This RCT conducted at department of Orthopedics BVH Bahawalpur from September 2017 to February 2018. Using non-probability consecutive sampling, 80 patients were enrolled with their consent including male and female, aged 40-70 years & Knee OA stage 1, 2 and 3 according to Kellgren and Lawrence classification. Patients with stage 4 Knee osteoarthritis, insufficiency of collateral ligaments, insufficiency of anterior and posterior cruciate ligaments, intraarticular injection within 3 months of registering into study, thrombocytopenia with platelet count less than $100 \times 10^9/\text{liter}$, radiographic findings of chondrocalcinosis, any systemic disease, cardiovascular, hematologic, tumor or anesthesia. immunosuppression were excluded from the study.

Two groups made as A and B, each containing 40 patients. Group A patients were injected depomedrol 80 mg intra-articularly using 22-G needle after local anesthetic. Patient may ask for another injection of steroid at any time during study period. Group B patients treated by Hyaluronic acid; three injections given at weekly interval. Year three Post graduate trainees performed the procedures. Following the injection patients were asked to take rest for 15 minutes before leaving and instructed to limit exercise for 24 hours and use only acetaminophen to relieve pain. Assessment of group A & B by VAS score was performed at 3 months and final outcome at 6 months. SPSS 21 used to analyze the data. Mean deviation and SD was calculated for age and mean reduction in pain score. Student 't' test used to evaluate the mean reduction in pain score in both groups and p-value ≤ 0.05 was regarded significant. For both groups stratification was performed regarding age, gender and stage of knee osteoarthritis to minimize the confounding effects.

RESULTS

Table No.1: Age distribution for both groups (n=80).

Age (years)	A (n=40)		B (n=40)		Total (n=80)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
40-50	09	22.50	12	30.0	23	28.75
51-60	12	30.0	10	25.0	23	28.75
61-70	19	47.50	18	45.0	34	42.50
Mean \pm SD	59.55 \pm 7.60		59.37 \pm 8.26		59.46 \pm 7.89	

Table No. 2: Mean pre & post therapy VAS score

VAS score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.30	1.38	5.95	1.50
Post-treatment (at 6 months)	4.48	1.26	1.60	0.93
Reduction in pain score	1.82	0.12	4.35	0.57

P-value <0.0001 which is statistically significant.

Table No. 3: Comparison of Mean reduction in VAS score in both groups for age 40-50 years.

VAS score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.40	1.42	5.83	1.53
Post-treatment (at 6 months)	4.80	1.03	1.75	0.87
Reduction in pain score	1.60	0.39	4.08	0.66

P-value <0.0001 which is statistically significant.

Table No. 4: Comparison of Mean reduction in VAS score in both groups for age 51-60 years.

VAS score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.28	1.32	6.40	1.43
Post-treatment (at 6 months)	4.43	1.34	1.40	0.97
Reduction in pain score	1.85	0.02	5.00	0.46

P-value <0.0001 which is statistically significant.

Table No. 5: Comparison of Mean reduction in VAS score in both groups for age 61-70 years.

VAS score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.25	1.48	5.78	1.56
Post-treatment (at 6 months)	4.31	1.35	1.61	0.98
Reduction in pain score	1.94	0.13	4.17	0.58

Table No. 6: Comparison of Mean reduction in VAS score in both groups for Male gender.

VAS score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.19	1.36	5.92	1.53
Post-treatment (at 6 months)	4.41	1.12	1.60	0.96
Reduction in pain score	1.78	0.24	4.32	0.57

P-value <0.0001 which is statistically significant.

Table No. 7: Comparison of Mean reduction in VAS score in both groups for Female gender.

VAS Score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.54	1.45	6.0	1.51
Post-treatment (at 6 months)	4.62	1.56	1.60	0.91
Reduction in pain score	1.92	0.11	4.40	0.60

P-value <0.0001 which is statistically significant.

Table No. 8: Comparison of Mean reduction in VAS score in both groups for Stage 1.

VAS score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.53	1.50	5.94	1.39
Post-treatment (at 6 months)	4.59	1.37	1.63	1.02
Reduction in pain score	1.94	0.13	4.31	0.37

P-value <0.0001 which is statistically significant.

Table No. 9: Comparison of Mean reduction in VAS score in both groups for Stage 2.

VAS score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.21	1.31	5.78	1.63
Post-treatment (at 6 months)	4.57	1.22	1.50	0.94
Reduction in pain score	1.64	0.09	4.28	0.69

Table No. 10: Comparison of Mean reduction in VAS score in both groups for Stage 3.

VAS score	A (n=40)		B (n=40)	
	Mean	Standard Deviation	Mean	Standard Deviation
Pre-treatment (baseline)	6.00	1.32	6.20	1.62
Post-treatment (at 6 months)	4.11	1.17	1.70	0.82
Reduction in pain score	1.89	0.15	4.50	0.80

P-value <0.0001 which is statistically significant.

DISCUSSION

Osteoarthritis (OA) is, no doubt, one of the most common types of chronic arthritis, with radiographic evidence of medial compartment and patellofemoral part of knee joint involved in greater than 50% of population over 65 years of age.⁹ Around, 18% women and 10% males have symptomatic Osteoarthritis. It is a degenerative joint disease with gradually advancing softening and wearing of knee joint cartilage characterized by mobility impairment and joint pain. Currently there is no definitive cure and treatment goals are symptomatic relief, improvement in function and joint mobility thus optimizing quality of patient's life.¹⁰ Non-pharmacological as well as pharmacological methods are used to manage OA of the hip and/ or knee (and other sites). Patients having advanced osteoarthritis and unresponsive to medicines are offered joint replacement surgery.^{9,10}

Analgesics, NSAIDs, IA steroids injection and IA hyaluronan injections are main drugs to control pain of knee osteoarthritis. Recently disease modifying drugs have been introduced to slow up degenerative process

in the cartilage along with pain relief for examples chondroitin sulfate, glucosamine sulfate and hyaluronan.¹¹ IA injections of HA have been found beneficial in the management through improving synovial fluid viscosity, lubrication of joint, inhibiting proteoglycan degradation, optimizing hyaluronan production, and expressing anti-inflammatory and analgesic effects.^{12,13} IA corticosteroid injections inhibit inflammatory cytokines and appeared relatively safe for treatment of OA in the past decade.¹⁴ However, symptom free interval is considerably low than the suggested interval between the doses of IA corticosteroids.¹⁵ The effects of Corticosteroids and placebos, Hyaluronan and other placebos have been studied in various systematic reviews but CS and HA effects comparing studies are very few. So, this randomized controlled study has compared mean change in VAS score after intra-articular Steroids and Hyaluronic acid injection to treat initial stages of osteoarthritis knee.

Primary osteoarthritis is often asymptomatic and commonly affects the elderly group with radiographic evidence in approximately 80-90% of individuals older than 65 years.¹⁶ Symptoms Typically after the age of 50 years early symptoms appear. The prevalence rises dramatically after 50 years because joint cartilage tensile strength decreases with age associated changes in proteoglycans & collagen and reduced supply of nutrients to cartilage.¹⁶ The age ranged 30-70 years in our study while mean was 59.46 ± 7.89 years. The mean age in group A was 59.55 ± 7.60 years and in group B was 59.37 ± 8.26 years. 34 (42.50%) patients constituting main bulk were found between 61-70 years.

The predominance ratio of female gender to male (1.85:1) in our study coincides with results of many previous studies.^{17,18,19,20} Similarly erosive osteoarthritis more common in females with a ratio 12:1 (female-to-male).¹⁶

In a meta-analysis done by Wang F et al²¹, high quality trials with 583 participants reflected equal effectiveness for CS and HA following one month. VAS mean difference was 1.66 (95% CI; -0.90, 4.23). However, 03 months later, the mean difference was -12.58 (95% CI; -17.76, -7.40), while 06 months later, the difference was -9.01 (95% CI; -12.62, -5.40), preferring HA. Hence in comparison with CS, HA possessed greater relative effect. In our study, mean pre-treatment VAS score in group A was 6.30 ± 1.38 while in group B was 5.95 ± 1.50 . Mean post-treatment VAS score was 4.48 ± 1.26 in group A while in group B was 1.60 ± 0.93 . Mean reduction in VAS score was 1.82 ± 0.12 in group A while in group B was 4.35 ± 0.57 . So statistically significant difference exist between the two groups ($p < 0.0001$). Jones AC et al²⁰ in his study has shown the mean VAS at the start and end of study in Hyaluronic acid and steroids groups respectively as 53.2 ± 5.6 and

55.3 \pm 5.3, 28.2 \pm 7.2 and 48.6 \pm 9.6 with the mean reduction of 6.7 \pm 4.3 and 2.5 \pm 1.6 respectively. Other studies²²⁻²³, consisting 116 CS treated and 129 patients with HA (n=245), expressed reduce VAS score (mean 1.66 mm) with CS in comparison with the HA group following one month but statistically the difference was not significant (P=0.20; I2=48%; 95% CI, -0.90, 4.23). Three studies^{24,25,26}, involving 165 HA treated and 155 patients treated with CS (n=320), favoring efficacy of HA with significant reduction in VAS score (mean of 12.58 mm, range 7.40 - 17.76) following 03 months when compared with steroid group (95% CI; P<0.00001; I2=42%). A conclusion of five studies^{20,22-25} after six months of treatment with 217 HA and 194 patients of CS injection (n=411) showed results favoring HA intraarticular knee injection therapy with significant reduction in VAS score (mean 9.01 mm, range 5.40 to 12.62), in comparison with CS group (P<0.00001; I2=47%, 95% CI).

Narayanan SS et al²⁷ in his study concluded that a regime of three intraarticular injection of hyaluronic acid administered in three consecutive weeks has a significant effect on functional outcome and reduction of osteoarthritic knee pain for at least six months. Gydek A et al²⁸ has shown VAS pain score at rest and during walking before treatment with hyaluronic acid as 3.4 \pm 2.2 and 5.0 \pm 2.1 respectively. After treatment the VAS pain score at rest and during walking decreased to 1.5 \pm 1.5 and to 2.2 \pm 1.7 respectively.

Results of many studies are expressing short term functional improvement and symptomatic relief with intraarticular corticosteroids in osteoarthritis of Hip and Knee. Ravaud et al²⁹ RCT study of 6 months concluded that corticosteroids injection into joint improved symptomatic outcome for initial four weeks and gradually effect decreased over 12 weeks. A quality review consisting of 1973 patients (knee osteoarthritis) in 28 RCTs expressed improvement in pain for 1-34 weeks without improvement in function with intraarticular steroids. Nine trials assessed HA and hylan derivatives vs IA steroids. HA products showed similar outcome along with more durable benefit over 5-13 weeks after injection.³⁰

Stretching over 6.7 years, Petrella et al³¹ recent study with 537 patients having osteoarthritis of knee given weekly three hyaluronic acid (500-730 kD) injections intraarticularly. The same cycle repeated if patient desired so. There was 27 \pm 7 weeks interval between the two courses. The outcome assessed at 6 months follow up. Some long term benefit of hyaluronic acid also noted. Overall this study concluded reduction in mean VAS score with IA hyaluronic acid vs IA steroid in Knee osteoarthritis patients.

CONCLUSION

This study concluded that there is significant reduction in mean VAS score (at 6 months) with hyaluronic acid

compared to IA injection of corticosteroid in patients with initial stages of knee OA. So, we recommend that intra-articular hyaluronic acid injection should be used routinely in the management of knee OA for reducing pain as well as morbidity of these particular patients..

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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Coagulation Activation Markers and Anemia in Patients Presenting with Chronic Kidneys Disease

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ABSTRACT

Objective: To study coagulation activation markers and anemia in chronic kidney Disease patients.

Study Design: Comparative / cross sectional study.

Place and Duration of Study: The study was conducted at the Pathology Department of Hayatabad Medical Complex Peshawar (HMC) from Feb 2017 to May 2018.

Materials and Methods: In this study total of 100 patients of chronic kidney disease (CKD) were included and 50 individuals were taken as a control group. All patients of CKD were evaluated for anemia and hemostatic marker, i.e D-dimer, PT and APTT.

Results: A total of 95 (95%) of the patients were anemic. Mean Hemoglobin (Hb) level was 9.625 ± 1.253 g/dl. Significantly low as compared with the control group. In 75% of CKD patients, D-dimer levels were elevated. Mean D-dimer level was in the range of 500-1000ng/ μ l, significantly elevated as compared to control group. 3 out of 100 CKD patients showed prolonged PT and 4 out of CKD patients showed prolonged APTT. Mean PT and APTT were 11.52 ± 1.562 seconds and 28.562 ± 1.562 respectively. 5 out of 100 CKD patients showed thrombocytopenia. Mean platelets counts were $150.562 \pm 10.562 \times 1/\mu$ l. Similarly 6 out of 100 CKD patients showed prolonged BT mean BT as 12.562 ± 1.265 minutes.

Conclusion: The study concluded that chronic kidney disease patients are significantly associated with anemia and hemostatic abnormality. Therefore proper attention should be given to these patients, as anemia and coagulation abnormality may lead to severe complications and increase morbidity and mortality from the disease. These patients should be properly managed regarding anemia and hemostatic abnormality, to improve their life style. Further work up and assessment is necessary in this regard to prevent any thromboembolic phenomenon.

Key Words: Chronic kidney disease, Anemia, Coagulation profile, D-dimer.

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INTRODUCTION

The US National Kidney Foundation's kidney dialysis outcomes quality initiative guidelines defines chronic kidney disease as kidney damage or estimated glomerular filtration rate of $<60\text{ml/min/1.73m}^2$ for more than 3 months.¹

Both hematological and hemostatic abnormalities occur

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in chronic kidney disease. The major cause of anemia in CKD is lack of erythropoietin synthesis in diseased kidneys which is usually of normochromic normocytic.² predispose the patients to bleeding.³

Hemolysis, Iron deficiency, Folate and B12 deficiency are also contributing factor to anemia in CKD. Renal anemia is one of the most complication of chronic kidney disease and majority of the patients present with anemia.⁴ CKD patients presenting with anemia has high risk of cardiovascular disease.⁵

Chronic kidney disease patients are also associated with coagulation disorder leading to thrombotic complications and this is the most common cause of death.⁶

The coagulation disturbance includes platelets dysfunction, vascular endothelium abnormality, fibrinolytic system and Von Willebrand factor (VWF) abnormality. VWF is secreted by endothelial cells and megakaryocytes and increases level of VWF is a sign of endothelial injury and risk of thrombotic events.⁷ Fibrinogen, FVII and FVIII are important coagulation factors in coagulation system activation and these markers have been shown to associated with increased thrombotic events.⁸ Increased levels of pro coagulant complex, D dimer, fibrinogen VWF, and protein C

increase level of thrombotic embolism and heart failure.⁹ D dimer is plasmin mediated photolytic degradation of fibrin clot, and its elevated levels shows thromboembolic phenomena in a patient presenting clot.¹⁰

The aim of the study is to evaluate the anemia and hemostatic markers in chronic kidney disease patients. As prothrombin time (PT), activated partial thromboplastin time (APTT), Bleeding time (BT) and D dimer levels immediate and early management of anemia improved patient life style and reduce further morbidity and mortality regulating from anemia and thrombotic complication in these patients.

MATERIALS AND METHODS

The study was conducted in the pathology department of Hayatabad Medical Complex Peshawar and medical department of the same hospital from February 2017 to February May 2018.

A total of 100 patients of chronic kidney disease were in the study and 50 individuals were taken as a control healthy individuals. Patients were both males and females patients Septicemia, DVT (deep venous thrombosis), Malignancy, pregnancy, chronic disorders like SLE and Rheumatoid arthritis were excluded from the study.

Blood samples of 5ml were collected from each patients of chronic disease in a tube containing sodium citrate. The citrated tube were centrifuged to separate plasma for determination of D-dimer, PT and APTT.

Similarly sample of 2ml were also collected in EDTA tube for determination of hemoglobin level to indicate anemia. Hb levels were determined by hematology Analyzer cell dyn Ruby USA for the patients of chronic kidney disease. D-dimer levels were also performed on sample of all chronic disease patients, D-dimer is a fragments cross-linked fibrin clot, which has degraded plasmin. Its level increases in any condition where clot formation and its subsequent fibrinolysis occurs. So its elevated level indicate a hypercoagulable state and thromboembolic events in anywhere in the body system.

Minalex D-dimer is a latex agglutination test and give us semi quantitative results its procedure include take 20µl of plasma and 20µl of D-dimer and observe for agglutination with 180 seconds agglutination indicates positive value more than 250ng/µl. Then for further quantitation serial dilution of sample is done in which we dilute 100µl plasma in 100µl of normal saline in a plane tube and then 100µl is taken and put in another tube containing 100µl of normal saline this make a serial dilution for 1:2, 1:4, and 1:8 respectively which further elaborate the result of D-dimer as 250-500ng/ml, 500-100ng/ml and 100-200ng/ml. The same procedure for undiluted i-e 20µl of D-dimer mixed with 20µl of sample. Raised level of D-dimer indicates thromboembolic events in the body and give immediate

information to the clinicians to go further supportive investigation to localize thrombosis.

PT and APTT were performed CP 3000 coagulation analyzer. These investigations indicate the activity of both extrinsic and intrinsic pathway.

All data were subjected to statistical analysis by sums chi square and T test level of significance set at $p < 0.0022$ bleeding time were also performed on patients of chronic kidney disease. According to standard procedure normal bleeding time was denoted 7-9 minutes.

RESULTS

In total males and females all these patients of CKD were subjected to Hb level and hemostatic parameters

Table No.1: Frequency of anemia and abnormal hemostatic markers in chronic kidney disease (CKD)

S. No.	Anemia and Hemostatic parameters in CKD	Percentage
1	Anemia	90%
2	D-dimer	75%
3	PT	3%
4	APTT	4%
5		5%
6	Bleeding time	6%

Table No 2. Mean value of anemia and hemostatic parameter in chronic kidney disease. (CKD)

S No	Anemia and hemostatic parameters	Mean of control group
1	Anemia	9.625±1.253g/dl
2	D-dimer	40% 500-1000ng 35% 100-7000ng
3	PT	16.52±1.562 seconds
4	APTT	43.562±1.562
5	Platelet	120.5654±10.562 ×10 ³ /µl
6	BT	12.562±1.265 minutes

that is D-dimer, PT and APTT. In our study 90% of patients were anemic. Hb level was 9.625±1.253gm/dl significantly lower as compared to control group D-dimer levels were $p < 0.0023$ also studied 75% of the patients of CKD showed elevated D-dimer levels, 15 out of 100 had D-dimer level at the range of 250-500mg/ml. 40 out of 100 patients had D-dimer level at the range 500-100ns/ml and 30 out of 100 patients had D-dimer levels at the range of 100-200ng/ml. D-dimer was significantly elevated as compared to control group $p < .00326$. Similarly PT and APTT were also performed

on all these patients 3 out of 100 showed prolong PT and 4 out of 100 showed prolong APTT. Mean PT and APTT were 15.5 ± 1.562 second and 43.562 ± 1.562 respectively. Similarly 5 out of 100 patients showed thrombocytopenia mean platelet counts was $120.5654 \pm 10.562 \times 10^3/\mu\text{l}$ significantly lower as compare to control group $p < .00325$. Bleeding time were also assessed in chronic kidney disease patients 6 out of 100 showed prolonged bleeding time. Mean bleeding time was 12.5 ± 19.26 seconds. Which were significantly higher as compared to control group p value $p < .00326$.

DISCUSSION

Chronic kidney disease is a condition associated with permanent loss of glomerular rate, which in turn leads to the development of uremia. High blood urea creatinine levels and accumulation of waste products effect and every system of the body, Anemia and coagulopathy is one of these effects.¹⁰

In the present study 85 out of 100 chronic kidney disease patients had anemia. Mean Hb level was $9.5 \pm 0.52 \text{ gm/dl}$ significantly lower as compared to control group mean Hb in control group were $13.5 \pm 1.256 \text{ gm/dl}$.¹¹

A similar study has been conducted by Mimura et al that majority of patients with CKD and associated with anemia.¹² Study of Juillerat JL et al. also show similar observation to study that anemia is common complication in CKD patients.¹³ Go, As et. al also reported in their study that anemia is common in CKD patients.¹⁴ The exact mechanism for anemia in multifactorial, numerous studies suggest anemia in CKD is mainly due to erythropoietin deficiencies.^{15, 16} Other factors that contribute to anemia is circulating uremic induce inhibitor of erythropoiesis shortened red cell survival, metabolic and mechanical factor IV deficiencies disorders iron hemostasis and hepcidine excess all contribute anemia in CKD.^{17, 18}

The national kidney foundation kidney disease outcomes quality initiative (NKF-KDOQI) guidelines 2000 recommended Hb targets should be generally maintained in the range of 11-12gm/dl.¹⁹ The 2007 KDOQI guide lines indicate target Hb levels should not exceed 13g/dl as high Hb level exceeding 13.5g/dl is associated with composite events like death and stroke.²⁰

In the presenting study hemostatic markers that is D-dimer, platelets counts, Bleeding time, PT and APTT were also studied. In our study D-dimer levels were elevated in 75% of chronic kidney disease patients. A similar study has been conducted by Mohammed Sadiq et al. that chronic kidney disease is associated with elevated D-dimer levels, in another study Miozzari M et al. also reported that elevated D-dimer level reported in chronic kidney disease patients.^{21, 22}

Similarly 6 out of 100 patients of CKD showed prolong bleeding time. Mean bleeding time was 12.56 ± 1.265 minutes. Different authors conducted with prolong study that chronic kidney disease is associated with prolong Bleeding time shows similar correlation to our study.^{23, 24}

5 out of 100 chronic kidney disease showed thrombocytopenia mean platelets count was $120.565 \pm 10.562 \times 10^3/\mu\text{l}$. while rest of the patients have normal platelets count as compared to control group. Similarly 4 out of 100 chronic kidney disease had prolong prothrombin time and 3 out of 100 patient had prolong APTT. Mean PT value of prolong PT and APTT were 16.5 ± 1.562 seconds 43.562 ± 1.562 seconds respectively as compared to control groups. A lot of studies conducted and reported that chronic kidney disease is associated with thrombocytopenia and prolong PT and APTT similar correlations had been reported Mohapatara et al.²⁵ Herman and Guffer also reported in their study that chronic kidney disease is associated with thrombocytopenia and prolong PT.^{26, 27} Patients with chronic disease associated with coagulation abnormality and thromboembolic phenomenon is common findings among patients with chronic kidney disease.²⁸ VWF levels increase in CKD patients and has pro coagulants effect and risk for thrombotic events.²⁹ Fibrinogen, FVII and FVIII, D-dimer level also increases and associated with prevalence of thromboembolic complication.³⁰

CONCLUSION

The study concluded that chronic kidney disease is associated with severe anemia and coagulation abnormalities as evidenced by low HB level and elevated D-dimer levels. Abnormal hemostasis and anemia both increase the risk for hospitalization and thrombotic events, which in turn leads to increase mortality and morbidity. Therefore the physician should strictly watch patients of CKD to maintain Hb level of such patients to a level to improve their life style and also take measure to reduce thrombotic complications in such patients which will further reduce the mortality and morbidity resulting from CKD.

Author's Contribution:

Concept & Design of Study:	Shahtaj Khan
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Vitamin D Deficiency in Patients with First Episode of Acute Coronary Syndrome

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Mehfooz Ali

ABSTRACT

Objective: To determine the frequency of Vitamin D deficiency in acute coronary syndrome patients.

Study Design: Cross Sectional Study.

Place and Duration of Study: This study was conducted at the Department of Cardiology ward or Coronary care unit (CCU) at Liaquat National Hospital and Medical College, Karachi from October 2018 and April 2019.

Materials and Methods: This single center, non probability consecutive, cross sectional study was conducted from 6th October 2018 and 5th April 2019. A total of 159 patients presented first time with acute coronary syndrome were incorporated in this research. A thorough examination and detailed history of all the systems, especially examination of cardiovascular system and abdomen was done. 5 cc bloods was taken from the prominent peripheral vein and collected. Blood sample was shifted to the laboratory within 30 minutes from the time of withdrawn for the measurement of 25 Hydroxyvitamin D level. Pre-designed proforma was used to collect and document data.

Results: There were 109(68.55%) male and 50(31.45%) female. Frequency of deficiency of vitamin D in patients with first episode of acute coronary syndrome (ACS) was observed in 74.21% (118/159).

Conclusion: There were 109(68.55%) male and 50(31.45%) female. Frequency of deficiency of vitamin D in patients with first episode of acute coronary syndrome (ACS) was observed in 74.21% (118/159).

Key Words: Acute coronary syndrome, cardiovascular disease, Vitamin D deficiency

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INTRODUCTION

Around the world, cardiovascular disease (CVD) is the most highlighted reason for mortality, causing more than 17 million deaths per year ^[1]. Coronary Heart Disease (CHD) is one of the most common causes of preventable death and ranks second and third in male and female over 15 years of age respectively in terms of disease burden as judged by Disability-Adjusted Life Years lost ^[2]. There is a remarkable rise in CHD burden in low-income and middle-income countries.^[3]

Countries of south Asia i.e. Pakistan, India, Bangladesh, Nepal, Sri Lanka are counted to have one fourth of the world's population. It also contribute in the greatest proportion of load of cardiovascular disease in the comparison of any other region around the globe³.

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Coronary artery disease, leading to acute coronary syndrome (ACS), accounts for about half of the total deaths total around the world associated with cardiovascular disease (CVD) ^[4]. Suspected acute coronary syndrome (ACS) is indicated from the data of developed countries, it is often taken as chest pain, which is counted to be the common diagnosis on being admitted into the Emergency Departments (ED) ^[5]. Patients' identification who were at increased risk of death or re-hospitalization within the duration of a year of being admitted to the emergency department (ED) having acute coronary syndrome (ACS) (i.e. ST elevation myocardial infarction's diagnosis, non-ST elevation myocardial infarction, or unstable angina (UA), by which ongoing therapy could be helped to be guided ^[6].

Timely Identification and management of modifiable risk factors reduces the morbidity and mortality ^[7].

An association of vitamin D and cardiovascular disease has been supported by epidemiological research through the body of evidence ^[8]. It has been reported for vitamin D deficiency to be associated with considerable increases in the occurrence of factors related to cardiovascular risk i.e. hyperlipidaemia, myocardial infarction, stroke and hypertension, chronic kidney disease and diabetes of type 1 and type 2 as well ^[9]. Deficiency of vitamin D is health issue around the globe with the commonness of 70%-100% in population generally ^[10].

Aim of my study is to determine the frequency of Vitamin D deficiency in acute coronary syndrome patients. As above mentioned studies show variation in result. Results of my study will provide current magnitude of Vitamin D deficiency in patients with acute coronary syndrome. After completion of this study, exact magnitude of Vitamin D Deficiency in patients with ACS was gained and recommendations was made for screening of vitamin D in all patients presenting with ACS. So that strategies could be device to prevent morbidities and mortalities by treating vitamin D deficiency at an earlier stage in patients with ACS.

MATERIALS AND METHODS

This single center, non probability consecutive, cross sectional study was conducted from 6th October 2018 and 5th April. Study population in the inclusion criteria was either gender with age of >25 years and <70 years, who were presented first time with acute coronary syndrome, admitted in the cardiology ward or coronary care unit (CCU) at Liaquat National Hospital and Medical College, Karachi. A detailed history and thorough examination of all the systems, especially examination of cardiovascular system and abdomen was done in the ward or CCU before sending the levels of vitamin D to exclude the presence of co-morbid diseases. Patients meeting the inclusion criteria was enrolled in the study. The purpose and procedure of the study was explained and an informed consent was taken from the patients included in this study before sending sample for vitamin D levels. 5 cc blood was taken from the prominent peripheral vein and collected in the red top bottle. Blood sample was shifted to the laboratory within 30 minutes from the time of withdrawn for the measurement of 25 Hydroxy vitamin D level. Report was collected within due time. Pre-designed proforma was used to collect and document data.

Statistical analysis: A statistical package for social science (SPSS-22) was used to analyze data. Frequency and percentage was computed for gender, Occupation, Unstable Angina, Non STEMI, STEMI, sun exposure time at least 30 minutes daily (Yes/No) and Vitamin D Deficiency. Mean and standard deviation was estimated for age, BMI and vitamin D level. Stratification was done to control effect modifies like age, sex, BMI, sun exposure time, occupation, Unstable Angina, Non STEMI, STEMI to observed an outcome. Post stratification chi-square test was applied. $p \leq 0.05$ was considered significant.

RESULTS

A total of 159 patients presented first time with acute coronary syndrome were included in this study. Most of the patients were above 40 years of age as shown in figure 1. The average age, weight, height, BMI and vitamin D level is presented in table 1.

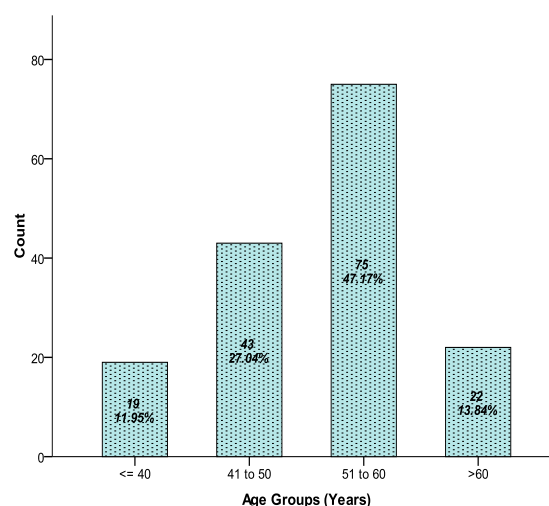


Figure No.1: Age Distribution Of The Patients N=159

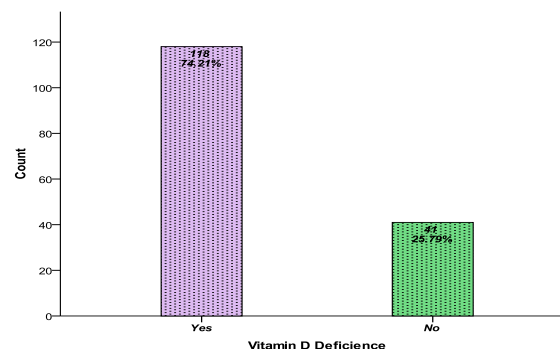


Figure No.2: Frequency Of Vitamin D Deficiency in Patients With First Episode Of Acute Coronary Syndrome N=159

Table No. 1: Descriptive statistics of the patients n=159

Statistics		Age (Years)	Weight (kg)	Height (cm)	BMI (kg/m ²)	Vitamin D3 Level
Mean		51.19	154.21	67.62	28.36	21.63
Std. Deviation		9.16	5.54	12.50	4.68	9.953
95% Confidence Interval for Mean	Lower Bound	49.76	153.34	65.67	27.63	20.07
	Upper Bound	52.63	155.08	69.58	29.10	23.19
Median		53.00	152.4	68	28.30	17.
Inter quartile Range		10	9	15	6.21	8

There were 109(68.55%) male and 50(31.45%) female (Table-2). There are different type of occupation like doctor, bankers, teacher, data analyst, computer engineer, engineers, retired govt. job and other so we convert variable into categories employees and not employee. It was observed that 71.07% of the patients were employed as shown in Table-2. Smoking habit was observed in 52(32.7%) cases (Table-2).

Table No. 2: Frequency Distribution Of Gender, Occupation, Smoking, Hypertension, Diabetes Mellitus, Sun Exposure Time, Unstable Angina, ST Elevation Myocardial Infarction, Non ST Elevation Myocardial Infarction) (n=159)

Gender	Frequency (n=159)	Percentage (%)	
Male	109	68.55%	
Female	50	31.45%	
Total	159	100%	
Occupation			
Employee	113	71.07%	
Non-employee	46	28.93%	
Total	159	100%	
Other factors	Yes	No	Total
Smoking	52(32.70%)	107(87.30%)	159(100%)
Hypertension	49(30.82%)	110(69.18%)	159(100%)
Diabetes mellitus	80(50.31%)	79(49.69%)	159(100%)
Sun exposure time at least 30 minutes daily	23(14.47%)	136(85.53%)	159(100%)
Unstable angina	87(54.72%)	72(45.28%)	159(100%)
ST elevation myocardial infarction	34(21.38%)	125(78.62%)	159(100%)
Non ST elevation myocardial infarction	38(23.90%)	121(76.10%)	159(100%)

Table No. 3: Frequency Of Vitamin D Deficiency In Patients With First Episode Of Acute Coronary Syndrome Stratified By Age, Gender, Bmi, Occupation and Sun Exposure Time

Variables	Vitamin D Deficiency		Total	P-Value
	Yes	No		
Age Groups (Years)				0.15
≤ 40 Years	11(57.9%)	8(42.1%)	19	
41 to 50 Years	34(79.1%)	9(20.9%)	43	
51 to 60 Years	59(78.7%)	16(21.3%)	75	
>60 Years	14(63.6%)	8(36.4%)	22	
Gender				0.12
Male	77(70.6%)	32(29.4%)	109	
Female	41(82%)	9(18%)	50	
Body mass Index				0.45
≤25 kg/m ²	39(72.2%)	15(27.8%)	54	
25 to 30 kg/m ²	41(70.7%)	17(29.3%)	58	
>30 kg/m ²	38(80.9%)	9(19.1%)	47	
Occupation				0.09
Employee	88(77.9%)	25(22.1%)	113	
Not Employee	30(65.2%)	16(34.8%)	46	
Sun Exposure time at least 30 min daily				0.0005
Yes	1(4.3%)	22(95.7%)	23	
No	117(86%)	19(14%)	136	

Chi-square test applied for each variables

Hypertension and diabetic mellitus was observed in 69.18% and 49.69% cases as shown in Table-2. Regarding acute coronary syndrome unstable angina was observed in 54.72% patients, non-ST elevated myocardial infarction 23.9% and ST elevated

myocardial infarction 21.38% cases as shown in table-2. There were 23(14.47%) patients who had sun exposure time at least 30 minutes daily as shown in Table-2. Frequency of vitamin D deficiency in patients with first episode of acute coronary syndrome was observed in 74.21% (118/159) patients as shown in figure-2. Rate of vitamin D deficiency was not significant with respect to age groups, gender, BMI, occupation while it was significantly high in those patients who had no exposure to sun at least 30 minutes daily (p=0.0005) as shown in Table 3.

Table No. 4: Frequency Of Vitamin D Deficiency In Patients With First Episode Of Acute Coronary Syndrome Stratified By Other Factors

Variables	Vitamin D Deficiency		Total	P-Value
	Yes	No		
Smoker	37(71.2%)	15(28.8%)	52	0.53
Hypertension	77(70%)	33(30%)	110	0.069
Diabetic Mellitus	68(86.1%)	11(13.9%)	79	0.001
Acute Coronary Syndrome				
Unstable Angina	59(67.8%)	28(32.2%)	87	0.043
Non-SETMI	29(76.3%)	9(23.7%)	38	0.730
STEMI	30(88.2%)	4(11.8%)	34	0.035

Chi-square test applied for each variables

Similarly rate of vitamin D deficiency was also significantly high in diabetic patients and those patients who had unstable angina and STEMI as shown in Table 4.

DISCUSSION

Deficiency of vitamin D is quite commonly occurring around the globe [11]. 25-hydroxyvitamin D's (25-OH D) low level, vitamin D's main circulating storage form, is present in 1/3 to 1/2 of healthy middle-aged to elderly adults.[12] The cross-sectional association of lower vitamin D level and plasma renin activity has been reported by the clinical studies [13], blood pressure (BP),[14] coronary artery calcification (CAC),[15] and commonly occurring cardiovascular disease.[16] Furthermore, increased rates hypertension and coronary heart disease (CHD) has been reported by ecological investigations with the cumulative distance from the equator, IT has been indicated by the phenomenon which has been endorsed that greater commonness of deficiency of vitamin D is found in the regions which are less exposure to sunlight[17].

Acute coronary syndrome (ACS) was presented in 159 patients for the first time and those patients were involved in this investigation. Patients were of the age of above 40 years mostly (41%). The commonness of acute coronary syndrome (ACS) has been reported to be increased with age in both males and females. The lifetime risk of developing CHD in the persons with the age of 40 years was computed to be 49% in males and it was 32% in females. The people with the age of 70

years, the lifetime risk was computed to be 35% in males and 24% in females ^[18]. 68.55% of the total respondents were males in the study and rest of 31.45% were females.

Cigarette smoking is the only most changing risk factor responsible for cardiovascular mortality and morbidity. It has been estimated that 30% of all deaths because of coronary heart can be due to cigarette smoking ^[19]. The influence of smoking of cigarette as coronary heart disease's (CHD) risk factor was shown in the first Euroaspire research, a registration and management survey of the main cardiovascular risk factors in comparatively young people (with the age of less than 70 years) hospital survivors of an acute coronary event (ACE) or first coronary interference which was found in 4800 patients of heart, greater than 85% patients having the age of less than 50 years were reported to be the past or present cigarette smokers. ^[20] In our study smoking habit was observed in 32.7% cases of acute coronary syndrome.

In our study it was observed that 71.07% of the patients were employed which is establishing the association of work stress and CAS in the context of underlying behavioural and biological mechanisms, and indicating the specificity of this relationship in the populations of working age. An essential case-control study (INTERHEART) comprised of 11,119 patients with a first myocardial infarction (MI) and with 13,648 age and gender-matched controls in the countries equal to 52; it was indicated by research that 'permanent' stress at work was in correlation with the magnitude of more than twice the odds of myocardial infarction (MI) in the comparison of those people who were facing no stress at work ^[21]. In this research, frequency of deficiency of vitamin D in patients having first episode of acute coronary syndrome (ACS) was seen in 74.21 percent of patients. In the same way, high deficiency of vitamin D was confirmed in patients (98%) having coronary syndrome by Luis et al in 2013^[22]. It was stated by Satish K, et al in 2014,^[23] that from the patients enrolled in the study, 67.5% of them were having the deficiency of 25-hydroxyl-vitamin D, and 16% of them were insufficient, 83.5% of them were with unusually low 25-vitamin D level. In the same way, it was reported by Mahdavi K et al ^[24] that 72% of patients with acute coronary syndrome to had serum 25-hydroxyvitamin D level of 20 ng/ml or less. In another investigation, 92% of the patients were having suboptimal levels of 25(OH) D, the percentage of severely deficient was 22.2% and it was reported that optimal 25(OH)D levels significantly lowered all cause and mortality related to cardiovascular disease in patients having metabolic syndrome ^[25].

CONCLUSION

Results indicated the substantial relationship of deficiency of Vitamin D in patients having acute

coronary syndrome (ACS). Increasing evidence is there that vitamin D deficiency may be an essential and previously neglected factor in cardiovascular disease's pathogenesis. Deficiency of vitamin D is associated with a broad spectrum of cardiovascular disease and the related risk factors. Moreover, it is related with greater mortality and morbidity. A role may be played by the supplementation of vitamin D in the reduction of cardiovascular disease's morbidity and mortality..

Author's Contribution:

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

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To Assess the Beneficial Effects of Rosuvastatin Before Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome

Imran Khan Sandeelo¹, Faisal Ahmed¹, Nouman Kakepoto¹, Mehfooz Ali Shah¹,
Chander Parkash¹ and Hamid Ali²

ABSTRACT

Objective: To assess the frequency of major adverse cardiovascular events in patients who receive high dose Rosuvastatin before PCI.

Study Design: Case series study.

Place and Duration of Study: This study was conducted at the department of cardiology, Liaquat National Hospital & Medical College, Karachi from March 2018 to April 2019.

Materials and Methods: During the period of study total number of ACS patients for percutaneous coronary intervention at Liaquat national hospital in the department of cardiology in which 271 patients were admitted and samples of 153 patients were taken by Non probability consecutive sampling.

Results: The frequency of periprocedural myocardial injury/non fatal MI in patients who receive high dose Rosuvastatin before percutaneous coronary intervention is 6.5%, ECG changes after procedure that is development of pathological Q-wave found in 1.3% and sudden death in 0.7%.

Conclusion: The use of single high loading dose of rosuvastatin is not only helpful to reduce periprocedural myocardial injury but also decreases other major adverse cardiac events such as development of pathological Q-wave, non fatal myocardial infarction but no effect on prevention of sudden death.

Key Words: Statin, angioplasty, percutaneous transluminal

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INTRODUCTION

The main cause of acute coronary syndrome¹⁻⁴ is reduced flow of blood in coronary arteries in such a way that a part of cardiac muscle is incapable of functioning properly or it dies. Chest pain is the main symptom of ACS which can be radiated to jaw or left arm, that is associated with sweating and nausea. ACS consists of unstable Angina (USA), & non ST elevation myocardial infarction (NSTEMI) & ST elevation myocardial infarction (STEMI)⁵

As the living standards of people have changed in recent times with the change in diet the probability of ACS has augmented which can be really dangerous for

health of human,^{6,7} relying on imperfect statistics the price for hospitalization in United states of America for coronary artery atherosclerosis has touched 10 billion to 40 billion dollars, and more than one million patients with ACS are admitted in hospital annually⁸.

Investigators assessed efficacy of statins in diminishing PMI and major adverse cardiovascular events (MACE) in patients with ACS who are planned to undergo PCI previously.⁹ Although some trials supported statin pretreatment¹⁰, others demonstrated that it does not provide clinical benefits in terms of PMI⁹. Therefore our study aimed to assess the effect of single high dose of rosuvastatin in patients with ACS before (PCI) in our population..

MATERIALS AND METHODS

This single center, non probability consecutive, case series study was conducted from May 2018 to April 2019. Study population in the inclusion criteria was either gender with 30 to 70 years of age, who were diagnosed cases of acute coronary syndrome attending department of Cardiology at Liaquat National Hospital Karachi. The patients who are eligible and are fulfilling the criteria of inclusion were advised and given permission from the ethical committee of Liaquat

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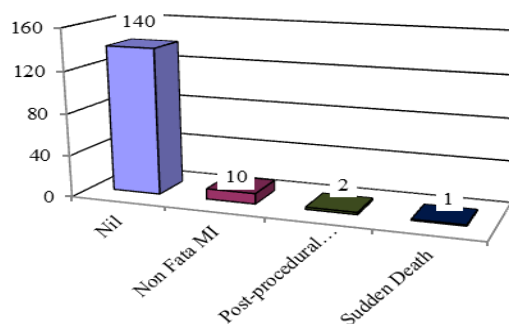
National Hospital and a written informed consent was taken from all the patients by principal investigator. Baseline Electrocardiogram was performed by trained electrocardiogram technician and blood sample for Trop I, CKMB level were taken from peripheral venipuncture done by expert nurses in the presence of investigator. Tablet rosuvastatin 40mg was given orally. All patients were taken to catheterization lab, Percutaneous coronary intervention was performed by expert interventional cardiologist having experience more than 5 years, after procedure patients were shifted to monitoring set up (coronary care unit). After 6 hours of procedure Trop I, CKMB & CRP were reassessed to compare with baseline level, 3 fold increase in Trop-I and CKMB level from baseline was considered as Periprocedural myocardial injury and Patients were monitored for major adverse cardiac events i.e. cardiac death and non fatal myocardial infarction during hospital stay. After 24 hrs electrocardiogram was performed to assess the changes with baseline electrocardiogram. Development of pathological Q-wave was considered as non fatal myocardial infarction. All the data was recorded on a pre designed Performa. Confounding variables were controlled by strictly following the inclusion and exclusion criteria.

RESULTS

Between July 2018 and Jan 2019 the total number of patients gone through the procedure (PCI) in cardiology department were 271 out of these 153 patients were included in our study.

Of all 153 patients base line Trop-I & CKMB were documented on proforma. Out of which 13 patients (8.5%) found to have major adverse cardiovascular events, in which 12 patients showed increase in base line Trop-I, CKMB levels and two with ECG changes after the procedure from these two, one was with isolated ECG changes and other was associated with increase in trop-I and CKMB levels.

Results were calculated of 13 patients with positive findings; results showed frequency distribution of male gender was 98 (64.1%) (Table # 2) with mean age of 58.79 ± 8.30 years shown in (Table # 1), with mean base line trop-I was 5.54 ± 5.74 ng/ml and CKMB levels 457.25 ± 229.92 IU/L and 6 hours post procedure mean trop I level 7.66 ± 6.75 ng/ml and CKMB 708.14 ± 339.907 IU/L (Table # 1). Frequency distribution of diagnosis is given in (Table # 2). Frequency distribution of 3 fold increase in baseline trop-I and CKMB is shown in (Table # 2). Frequency Distribution of major Adverse Cardiac events is Post-procedural pathological Q wave (2/153 patients) 1.3%, non fatal MI 6.5% (10/153 patients) and sudden death 0.7% (1/153 patients) in (graph # 1). Frequency and association of major adverse cardiac events is discussed according to age, base line trop-I in (Table #3 & 4) respectively in trop I is present according to age in (Table # 5).



Graph No.1: Frequency of Major Adverse Cardiac events.

Table No. 1: Descriptive Statistics

	Mean	SD
Age (Years)	58.79	8.30
Base line Trop-I	5.54	5.74
Base line CKMB	457.25	229.92
6 Hours post-procedural TropI	7.66	6.75
6 Hours post-procedural CKMB	708.14	339.907

Table No. 2: Frequency Distribution of Diagnosis, 3 Fold increase in Baseline TropI, 3 Fold increase in Baseline CKMB

Gender	Frequency (n)	Percentage (%)
Male	98	64.1
Female	55	35.9
TOTAL	153	100
Diagnosis		
Un Satable Angina	17	11.1
NSTEMI	126	82.4
STEMI	10	6.5
TOTAL	153	100
3 Fold increase in Baseline TropI		
Yes	12	7.8
No	141	92.2
TOTAL	153	100
3 Fold increase in Baseline CKMB		
Yes	12	7.8
No	141	92.2
TOTAL	153	100

Table No.3: Frequency and Association of MACE According to Age

		≤45 Years	>45 Years	P-value
Postprocedural pathological Q wave	n	1	1	0.160
	%	8.3%	0.7%	
Non Fata MI	n	1	9	
	%	8.3%	6.4%	
Sudden Death	n	0	1	
	%	0.0%	0.7%	
Nil	n	10	130	
	%	83.3%	92.2%	
TOTAL		12	141	153

Results showed that there is no significant association between MACE and Age.

Table No. 4: Frequency and Association of MACE According to Baseline TropI Level

		≤5.5	>5.5	P-value
Postprocedural pathological Q wave	N	2	0	0.047*
	%	2.0%	0.0%	
Non Fata MI	N	10	0	
	%	10.2%	0.0%	
Sudden Death	N	1	0	
	%	1.0%	0.0%	
Nil	N	85	55	
	%	86.7%	100.0%	
TOTAL		98	55	153

Results showed that there is significant association between MACE and base line trop i level.

Table No. 5: Frequency and Association of 3 Fold increase in TROPI According to Age Group

		≤45 Years	>45 Years	P-value
Yes	N	4	8	0.097
	%	16.7%	6.2%	
No	N	20	121	
	%	83.3%	93.8%	
TOTAL		24	129	153

Results showed that there is no significant association between 3 Fold increase in TROPI and Age.

DISCUSSION

Statins expressively minimize cardiovascular events in different patients who are having cardiovascular illness and patients who have probability of having cardiovascular illness¹¹

PCI is an important part of management of ischemic cardiac illness. Joined with proof based pharmacological strategies, the practice of PCI in suitable patients diminish illness and death across the world.¹²

Risk of adverse cardiac events is reduced by high dose statins in patients suffering from ACS, inflammatory markers were reduced with high dose statins within 24 hours directly after PCI which proposes that anti-inflammatory consequence of statins can be a way that reduces periprocedural events. Statin treatment improved clinical results in patients going through PCI.¹³

Recent meta-analyses indicated that high-dose pretreatment with statins reduces PMI in patients with ACS¹⁴ In Ye et al¹⁸ meta-analysis, it was found that compared with the conventional dose of rosuvastatin, the loading dose of rosuvastatin could significantly reduce the level of inflammatory marker (hs-CRP) after PCI, including at 24 hours, 48 hours and four weeks, suggesting that the loading dose of rosuvastatin could decrease the inflammatory index and reduce the incidence of postoperative infection, which is beneficial to the prognosis of patients after PCI. In addition, the levels of LDL-C and cTnT of the high-dose group were significantly lower than the conventional dose group.

When routinely measured, biomarker release after PCI is common, occurring in 5% to 30% of cases: most of these are minor releases. Large elevations in biomarker release (e.g., CK-MB release 5 to 8 ULN) are independently associated with mortality.¹⁵ In our data two with ECG changes after the procedure from these two one was with isolated ECG changes and other was associated with increase in trop-I and CKMB levels that is (1/10 in 153 patients) 10%.

Cay et al¹⁶ performed a trial, and 299 patients were randomized to a rosuvastatin-treatment (n = 153) group and 146 patients were placed in to a no-treatment group. A forty mg loading dose of rosuvastatin was administered 24 h before PCI, and the CK-MB and cTnI levels were measured before and at 12 h after PCI. The incidence of CK-MB and cTnI elevation in the rosuvastatin group was significantly lower compared with the control group and Cay indicated that high loading dose of rosuvastatin (40 mg/day) could effectively reduce the incidence of peri-procedural myocardial necrosis and infarction. In 2011, a 12-month follow-up trial was also performed by Yun et al¹⁷. In our study we analysed that the frequency of periprocedural myocardial injury in patients who receive high dose Rosuvastatin before PCI is 6.5% with mean age of patients underwent the procedure with adverse outcome was 58.79 ± 8.3 years, with male predominance 64% as compare to Ye et al¹⁸ study, 445 patients with ACS who underwent PCI were randomly assigned to receive no statin treatment before PCI (control group, n = 220) or to receive 40mg rosuvastatin loading before PCI (rosuvastatin group, n = 225), and cardiac death, non-fatal MI, non-fatal stroke and any ischemia-driven revascularization were assessed after 12 months. During the follow-up, major adverse cardiac events occurred in 20.5% of patients in the control group and 9.8% of patients in the rosuvastatin group (p = 0.002), and the incidence of death and non-fatal MI was significantly higher in the control group compared with loading dose of atorvastatin (p = 0.021).

The fundamental mechanisms of initial defensive action are not taken due to effects of lowering cholesterol levels ,since all trials involved in examination used a temporary pre-ailment having high dose statin, that could not imposed sufficient impact on the level of cholesterol. Different studies showed that initial lipid-independent role of statin, that is Pleiotropic effect and comprising antithrombotics influence,¹⁹

Previously described pleiotropic properties of statins might play role to diminish myocardial necrosis because of technical microembolization in locating of PCI, specifically patients suffering from ACS and high provocative status, in which there is multipart communication between thrombosis and disturbance in functioning /activation, irritation, may originate an

applicable advantage from initial high amount of statin treatment an aggressive strategy²⁰

In our country cardiovascular interventional procedures are increasing day by day so the high incidence of major cardiac events is expected and can be prevented by use of preprocedural statin, as the frequency of MACE with cardiovascular intervention in at risk patients is around 12.6% which can be reduced to 7.4% with high dose statin pretreatment,²¹ while our study shows the occurrence of major cardiovascular events with ECG changes after procedure that is development of pathological Q-wave found in 1.3% along with 6.5% Non fatal Myocardial Infarct and sudden death in 0.7%. In Pan et al study high-dose RSV preloading before PCI lead to a 58 % reduction in MACE and a 60 % reduction in PMI.²²

CONCLUSION

In conclusion, the use of high loading dose of rosuvastatin is not only helpful to reduce PMI but also decreases other major adverse cardiac events such as development of pathological Q-wave, non fatal myocardial infarction and no effect on prevention of sudden death. So it decreases mortality in patients going through coronary interventions with ACS. As it decreases the frequency of complications during PCI so it comes out with multiple benefits, with an ability to recover with speed after the procedure in short time spent in hospital to minimize the expenses..

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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Left Ventricular Diastolic Dysfunction in Patients of Type-II Diabetes Mellitus: A Cross Sectional Study

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Nayyer uz Zaman⁵ and Zahid Irfan Marwat⁶

ABSTRACT

Objective: To determine the frequency of left ventricular diastolic dysfunction in patients with type II diabetes mellitus.

Study Design: Cross sectional study.

Place and Duration of Study: This study was conducted at the Department of Medicine, KTH Peshawar for six months from February to July 2018.

Materials and Methods: A total of 171 type-II diabetic patients were observed. After informed written consent, inclusion and exclusion criteria, all patients were subjected to detailed history, clinical examination and measurement of Body Mass Index in term of kg/m² using standard weight machine and measuring tape. Following this, they were subjected to standard M Mode echocardiography to measure Left Ventricular Diastolic Function.

Results: Total 171 (100%) patient, 72(42%) male and 99(58%) females with a mean age of 52±7.25 years, mean duration of type-II DM 14±4.372 years, mean BMI 27±3.11 were enrolled in the study. Total 72(42%) patients were diagnosed with LVDD. It was more prevalent among female 41 (24%) than males 31(18.1). None of P-value showed significant result.

Conclusion: Study concludes that the frequency of left ventricular diastolic dysfunction is quite high in female type-II diabetes mellitus. Longer the duration of Diabetes and greater the BMI, more prevalent LVDD is in Type-II DM.

Key Words: Frequency, Left ventricular diastolic dysfunction, Type II diabetes mellitus, Body mass index.

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INTRODUCTION

Diabetes mellitus (DM) is an important health issue worldwide. Over the past two decades, the prevalence of diabetes has increased drastically from 30 to 177 million.¹ If continued than, by 2030, 360 million people

will be declared diabetic. Worldwide, It is the fifth leading cause of death and causes about 3 million deaths per year¹. Prevalence of diabetes in the urban areas of Pakistan is 6% in males and 3.5% in females, whereas in the rural areas the estimated prevalence in males is 6.9% and in 3.5% in females². In a survey by WHO, it was shown that in 1995 Pakistan was 8th on the list of top ten countries with a high prevalence of diabetes and there were 4.3 million people with DM. However, it is estimated that in the year 2025, Pakistan will be 4th on the list with 14.5 million people with this disease³.

Type II DM has reached epidemic proportions worldwide⁴⁻⁶. It is a known risk factor for cardiovascular disease (CVD), especially, ischemic heart disease (IHD) and chronic heart failure (CHF)⁵. However, even in the absence of IHD or hypertension, abnormalities in heart structure and function develop in type II diabetic patients. These malformations are called diabetic cardiomyopathy; which basic pathophysiologic mechanisms still remain poorly known⁷. Patil VC et al proposed that changes in the cardiac structure such as fat droplet deposition, myocardial hypertrophy and fibrosis are consequences of diabetic cardiomyopathy. Some early changes in cardiac function like loss of contractile function, also manifest as abnormal diastolic function⁸.

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Even high prevalence and more severe left ventricular diastolic dysfunction (LVDD) is seen in patients with diabetes and having autonomic neuropathy as reported in one study 33% of LVDD in patients having diabetes with autonomic neuropathy and without autonomic neuropathy⁹. The prevalence of diastolic dysfunction in type 2 DM were 40% and 32% respectively.¹⁰

The present study is designed to determine the frequency of LVDD in patients with type II DM. No such study has been done in our local population so far. This study will be very useful in generating future research strategies and developing recommendations for routine management of type II DM patients with LVDD.

MATERIALS AND METHODS

This cross-sectional study was conducted in outpatient department of Medicine, Khyber Teaching Hospital for duration of six months after approval was obtained from research and ethics board of the institute. All patients of either gender presenting with type II DM with at least 5 years' duration, age above 30 years to 60 years were included. Previously diagnosed patients of LVDD, past history of coronary artery disease, valvular heart diseases, atrial fibrillation and symptomatic patients of peripheral arterial diseases were excluded. A total sample size of 171, keeping 32% proportion of LVDD among in patients with diabetes, 95% confidence level and 7% margin of error was calculated by WHO calculator of sample size. The purpose and benefits of the study were explained to obtain informed written consent. All patients underwent detailed history, clinical examination and measurement of BMI in term of kg/m² using standard weight machine and measuring tape. Following this, they were subjected to standard M-Mode echocardiography to measure LVD function. The procedures were done by an experienced cardiologist who had minimum of five years of experience.

The data was recorded in a pre-designed proforma. Strictly exclusion criteria had followed to control confounders and bias in the study results. Data were analyzed using SPSS version 19. Quantitative variables like age, duration of diabetes, BMI, were described in terms of means±standard deviation. Categorical data like gender and LVDD were described in terms of frequency and percentages. LVDD was stratified among age, gender, BMI and duration of diabetes to control effect modification. Post-stratification was done through chi-square test keeping P value less than or equal 0.05 was significant. All results were presented as tables.

RESULTS

Total 171 (100%) patient, 72(42%) male and 99(58%) females with a mean age of 52±7.25 years, mean duration of type-II DM 14±4.372 years, mean BMI

27±3.11 were enrolled in the study. Total 72(42%) patients were diagnosed with LVDD. (Table 1)

LVDD was found more prevalent among female 41 (24%) than males 31(18.1). The age group of 51-60 years had more cases of LVDD i.e. 34(19.9%). Greater the BMI 45(26.3) and longer the duration of type II DM 30 (17.5%), more patients are suffering from LVDD. However, none of P-value appeared significant. (Table 2)

Table No.1: Frequency and percentage for age, gender, duration of diabetes, BMI and LV diastolic Dysfunction. (n=171)

Variable		Frequency	Percentage
Age	30-40 years	26	15.2%
	41-50 years	64	37.4%
	51-60 years	81	47.4%
Duration of diabetes	5-10 years	33	19.3%
	11-15 years	65	38.0%
	16-20 years	73	42.7%
BMI	22-25	65	37.4
	26-30	107	62.6
LV diastolic dysfunction	Yes	72	42.1
	No	99	57.9
	Total	171	100%

Table No.2: Stratification of left ventricular diastolic dysfunction with respect to gender, age, duration of diabetes and BMI. (n=171)

Variable		LVDD			P-value
		YES(%)	No(%)	Total(%)	
Gender	Male	31(18.1)	41(24.0)	72(42.1)	0.830
	Female	41(24.0)	58(33.9)	99(57.9)	
Age	30-40 years	11(6.4)	15(8.8)	26(15.2)	
	41-50 years	27(15.8)	37(21.6)	64(37.4)	
	51-60 years	34(19.9)	47(27.5)	81(47.4)	
Duration of diabetes	5-10	15(8.8)	18(10.5)	33(19.3)	0.909
	11-15	27(15.8)	38(22.2)	65(38.0)	
	16-20	30(17.5)	43(25.1)	73(42.7)	
BMI	22-25	27(15.8)	37(21.6)	64(37.4)	0.987
	26-30	45(26.3)	62(36.3)	107(62.6)	
	Total	72(42.1)	99(57.9)	171(100)	

DISCUSSION

Among type-II DM, 42% of patients had LVDD which is quite high prevalence. Similar results were observed by Hameedullah et al in which even high prevalence and more severe LVDD was seen.⁹ Furthermore, Kazik A et al reported 40% of LVDD in type 2 diabetes.¹⁰ Likewise results were observed by Virendra C et al in which out of the total 127 subjects, 69 (54.33%) from the case group had diastolic dysfunction and 11% amongst 100 in the control group population showed the diastolic dysfunction (P < 0.001). Patients with a longer duration of DM (of 11 to 15 years) had a higher prevalence of diastolic dysfunction (P < 0.02). Diastolic

dysfunction was present in majority of the subjects with autonomic neuropathy and retinopathy.¹¹ Soldatos et al in their case-control study of 55 individuals with type -II DM found that Diastolic dysfunction, present in a significant proportion of population with Type-II DM.¹² Van Heerebeek et al in their study of 36 types -2 DM patients stated that the cardiomyocyte resting tension is more important when left ventricular ejection fraction is normal. Excessive diastolic left ventricular stiffness is an important contributor to heart failure in subjects with DM.¹³ Diabetes is presumed to increase stiffness through myocardial deposition of collagen and advanced glycation end products.

Masugata et al in their case-control study of 77 normotensive patients found that, the cardiac diastolic dysfunction without LV systolic dysfunction in patients with well-controlled type 2 DM is related neither to hypertension nor LV hypertrophy, but rather to aging and the duration of type 2 DM.¹⁴ Annonu et al¹⁵ in their found that duration of diabetes mellitus of 11 to 15 years had more prevalence of diastolic dysfunction as compared to the 6 -10 years group ($P < 0.02$).

From AM et al in their study of 484 subjects between 1996 to 2007 years ensued that duration of diabetes ≥ 4 years was independently associated with LVDD.¹⁶

Sohail et al. stated that LVDD is much more prevalent in patients with type-2 diabetes mellitus and LV diastolic dysfunction is an early marker of diabetic cardiomyopathy. He found 30.76% of patients with type-2 DM had diastolic dysfunction.¹⁷ Exiara et al found a high relation of increasing age with LVDD in normotensive, asymptomatic and well-controlled DM type 2 patients.¹⁸ A total of 63.2% patients had LVDD in their study compared to our prevalence of 54.33%. Bonito et al stated that, an impairment of LV diastolic function occurs early in the natural history of type-2 DM, and is related to clinical evidence of microangiopathic complications.¹⁹ From Am et al. in another study found that, 411 (23%) patients had diastolic dysfunction and diabetic patients with diastolic dysfunction had a significantly higher mortality rate compared with those without diastolic dysfunction.²⁰

Poulsen et al in their prospective observational study of 305 patients with type 2 DM found that abnormal LV filling is closely associated with abnormal myocardial perfusion on myocardial perfusion scintigraphy.²¹

Takeda et al in their population of 544 consecutive Japanese DM patients with ejection fraction $\geq 50\%$, found that diastolic dysfunction plays a crucial role in the induction of HF with normal systolic function in DM patients, regardless of the severity of DM and renal dysfunction.²²

Poanta et al in their study of 58 subjects found that cardiac autonomic neuropathy was associated with LVDD in patients with type-II DM, but without clinical manifestation of the heart disease.²³ Similarly Poirier et

al stated that diastolic dysfunction and cardiac autonomic neuropathy are associated in patients with otherwise uncomplicated well-controlled type-II DM.²⁴ Hameedullah et al in their study population of 60 patients with type-II DM found that there was strong correlation between HbA1c level and diastolic indices.²⁵ Diastolic dysfunctions were more frequent in poorly controlled diabetic patients, and its severity is correlated with glycemic control. Schannwell CM et al in their study population of 87 subjects concluded that even young subjects with diabetes mellitus suffer from diastolic dysfunction, while systolic ventricular function is normal.²⁶ From the above discussion and comparison with study, we found a high prevalence of LVDD in subjects with type-II DM, and it was correlated with age, duration of diabetes, various obesity indices.

CONCLUSION

Our study concludes that the frequency of left ventricular diastolic dysfunction is quite high in female type-II diabetes mellitus. Longer the duration of diabetes and greater the BMI, more prevalent LVDD in Type-II DM. Researchers need to conduct some longitudinal studies and find out the association of LVDD with type-II DM, duration, BMI and gender. Furthermore, there is need of improved management plans for type-II DM patients with LVDD..

Author's Contribution:

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Factors Associated With Increased Prevalence of Diabetic Foot Ulcer and its Poor Outcome

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ABSTRACT

Objective: To determine factors associated with increased prevalence of Diabetic Foot Ulcer and its poor outcome in our set up

Study Design: Observational / prospective study

Place and Duration of Study: This study was conducted at Bahawalpur Victoria Hospital, Bahawalpur from December 2015 to February 2016.

Materials and Methods: One hundred and one patients above the age of 18 years presenting with DFU were enrolled. Detailed history was taken regarding patient's education, type and duration of diabetes, smoking and comorbidities like hypertension and ischemic heart disease(IHD). We evaluated ulcer for duration, site, pain and depth of wound.

Results: Majority of patients were male(69.3%), had type 2 Diabetes(95%) and were uneducated(82.17%). Mean age was 59 ± 10.43 years and mean duration of diabetes was 10.38 ± 7.9 years. 32.6% patients had Hypertension, 23.7% had IHD and 24.7% were smokers. 85.1% had sensory neuropathy and 41.58% had retinopathy. PAD(18.8%) and nephropathy(7.9%) were relatively uncommon. Patients were divided into three groups based on outcome: healed(2.97%), unhealed(63.36%) and amputation(33.66%) group. Mean duration of presentation was 24 ± 10.39 days in healed, 72.61 ± 179.49 days in unhealed and 49.82 ± 41.75 in amputation group. Wagner classification showed that 0% in healed, 70.31% in unhealed and 94.11% ulcers in amputation group were of grade 3 or above. Sensory neuropathy (94.11%) and smoking(29.41%) were more common and mean HbA1c(8.05 ± 1.55) was highest in amputees.

Conclusion: DFU is common in old, uneducated males with long duration of Diabetes. Hypertension, IHD, neuropathy, retinopathy and smoking were common in DFU patients. PAD and nephropathy were uncommon. We observed high amputation and low healing rates. Sensory neuropathy, wagner grade (p values < 0.05), poor glycemic control and smoking (p values $> .05$) were associated with poor outcome. Earlier presentation and aggressive treatment according ulcer grade can improve outcome of this disabling morbidity.

Key Words: Factors, Prevalence, Diabetic Foot Ulcer, Outcome.

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INTRODUCTION

The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and will be 4.4% in 2030.¹ The prevalence of diabetes in Pakistan is very high. According to Diabetes Prevalence Survey of Pakistan prevalence of type 2 diabetes is 16.98%.²

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as macrovascular. Diabetic foot ulcer (DFU) is a common and serious complication of diabetes and most common cause of lower extremity amputation.³ It is attributable to both microvascular complication like neuropathy and macrovascular complication like peripheral arterial disease(PAD). Infection is a most common precipitating factor.

Large number of patients with DFU present in surgical departments for dressing and debridement and in medical departments for glycaemic control. Treatment of DFU is a challenge for clinicians.

Many studies have been done all over the world to find out risk factors of DFU. The purpose of this study was to find out the factors associated with increased prevalence of DFU and its poor outcome in our setup. Identification of these predictors and poor prognostic factors will have an important role to prevent this potentially disabling morbidity. Morbidity and mortality of diabetes is mostly because of its complications which can be microvascular as well.

MATERIALS AND METHODS

This study was conducted in BV Hospital Bahawalpur from December 2015 to February 2016. One hundred and one patients above the age of 18 years presenting with DFU were enrolled. Detailed history was taken regarding patient's education, type and duration of diabetes, smoking and comorbidities like hypertension and ischemic heart disease(IHD). We evaluated ulcer for duration, site, pain and depth of wound. Wagner classification was used to grade ulcer. Detailed CNS examination was done to see evidence of sensory, motor and autonomic neuropathy and retinopathy. Palpation of peripheral pulses and doppler flow study was done for PAD. Routine investigations done included complete blood and urine examination, fasting and random blood glucose, glycated haemoglobin (HbA1c) and renal parameters.

Patients were classified into three groups to identify the factors associated with poor outcome: first group included patients with healed ulcer, second group of patients with unhealed ulcer but without need for

amputation and third group with a minor or major amputation.

Statistical Package for Social Sciences(SPSS) version 20 was used for statistical analysis of data. Descriptive analysis was applied to calculate frequency and percentage for qualitative variables. Mean and standard deviation was calculated for quantitative variables. Chi square test was used to analyse variables in three groups. P value of <0.05 was considered significant.

RESULTS

Out of 101 patients, 70(69.3%) were males. Mean age was 59.04 ± 10.432 (22-82) years, 96(95%) had type 2 Diabetes and 83(82.17%) patients were uneducated. Mean duration of DM was 10.38 ± 7.9 (0.03-30) years. Thirty three patients(32.67%) had hypertension, 24 (23.76%) had IHD, 25(24.7%) were smokers. Eighty six(85.1%) had sensory, 27(26.73%) had motor and 7(6.93%) had autonomic neuropathy, 19(18.81%) had PAD, 42(41.58%) had retinopathy and 8(7.9%) had nephropathy.

Table 1: Demographic, clinical and biochemical Characteristics of DFU patients

	Healed ulcer	Discharged with unhealed ulcer	Amputation	Total	P value
Number(%)	3(2.97)	64(63.36)	34(33.66)	101	
Gender Male	1(33.33)	45(70.31)	23(67.64)	70(69.3)	0.33
Female	2(66.66)	19(29.68)	11(32.35)	31(30.7)	
Age(years) (mean \pm SD)	57-60 58.5 \pm 2.12	22-77 (57.41 \pm 10.68)	38-82 (62.515 \pm 10.222)	22-82 (59.05 \pm 10.43)	0.00
Education					0.00
Uneducated	02(66.66)	54(84.37)	27(79.41)	83(82.17)	
Under-matric	00(0)	03(4.68)	01(2.94)	04(03.96)	
Matric	00(0)	04(6.25)	02(5.88)	06(05.94)	
Undergraduate	00(0)	00(0)	02(5.88)	02(01.98)	
Graduate	00(0)	03(4.68)	02(5.88)	05(04.95)	
Post graduate	01(33.33)	00(0)	00(0)	01(00.99)	
Duration of diabetes(years)	5-20 (13.33 \pm 7.63)	03-30 (10.28 \pm 7.53)	0.16-28 (10.58 \pm 10.36)	0.03-30 (10.38 \pm 7.9)	0.97
Type of Diabetes					
Type 1	00(0)	05(4.95)	00(0)	05(04.95)	0.23
Type 2	03(100)	59(92.18)	34(100)	96(95.04)	
Hypertension	03(100)	18(28.12)	12(35.29)	33(32.67)	0.04
Smoking	00(0)	15(23.437)	10(29.411)	25(24.75)	0.51
-IHD	00(0)	13(20.31)	11(32.35)	24(23.76)	0.33
-PAD	00(0)	13(20.31)	06(17.64)	19(18.81)	0.57
-Neuropathy					
Sensory	02(66.66)	52(81.25)	32(94.11)	86(85.14)	0.03
Motor	01(33.33)	14(21.87)	12(35.29)	27(26.73)	0.34
Autonomic	0(0)	03(04.68)	04(11.76)	07(06.93)	0.33
-Retinopathy	01(33.33)	24(37.50)	17(51.51)	42(41.58)	0.96
-Nephropathy	00(0)	05(7.81)	03(9.09)	08(7.9)	0.54
Serum/Creatinine(mg/dl)	0.1 - 0.6 (0.35 \pm 0.25)	0.1-6.8 (1.29 \pm 1.05)	0.7-4.2 (1.246 \pm 0.82)	0.10-6.80 (1.30 \pm 1.05)	0.24
-FBS(mg/dl)	121-324 (122.5 \pm 101.5)	69-400 (174.1 \pm 83.26)	75-280 (153 \pm 58.55)	69-400 168.53 \pm 76.79	0.051
-RBS(mg/dl)	118-220 202 \pm 54.04	94-564 (255.45 \pm 102.716)	117-408 (226.75 \pm 83.79)	94-564 248.98 \pm 102.25	1.00
-HbA1c(%)	5.9-8.6 (7.16 \pm 1.35)	6.0-9.0 (7.23 \pm .81)	6.0-14.0 (8.05 \pm 1.55)	6.0-14.0 (7.63 \pm 1.23)	0.221

Table No.2: Clinical characteristics of DFU

	Healed N=3	Unhealed N=64	Amputation N=34	Total N=101	P value
Duration of DFU(days)	12-30 (24±10.39)	2-1095 (72.61±179.49)	7-180 (49.82±41.75)	2-1095 (63.86±142.82)	0.56
Pain	01(33.33)	08(12.50)	0(0)	09(8.9)	0.04
Site					
Fore foot	01(33.33)	22(34.37)	19(55.88)	42(41.58)	0.11
Mid foot	01(33.33)	27(42.18)	06(17.64)	34(33.66)	
Hind foot	00(0)	09(14.06)	03(08.82)	12(11.88)	
Whole foot	01(33.33)	06(09.37)	06(17.64)	13(12.87)	
Number					
Single	03(100)	52(81.25)	23(67.64)	78(77.22)	0.32
Multiple	00(0)	12(18.75)	11(32.35)	23(22.77)	
Wagner Grade					
1	01(33.33)	00(0)	00(0)	01(0.99)	0.00
2	02(66.66)	19(29.68)	02(05.88)	23(22.77)	
3	00(0)	45(70.31)	28 (82.35)	73(72.27)	
4	00(0)	00(0)	01(02.94)	01(0.99)	
5	00(0)	00(0)	03(08.82)	03(2.97)	

Regarding ulcer characteristics, mean duration of ulcer at the time of presentation was 63.86 ± 142.82 (2-1095) days. Nine (8.9%) patients had painful ulcer, 8 (7.9%) had past history of DFU, 78 (77.22%) had single ulcer, 1 (0.99%) had wagner grade 1, 23 (22.77%) had grade 2, 73 (72.27%) had grade 3, 1 (0.99%) had grade 4 and 3 (2.97%) had grade 5 ulcer. Fasting blood glucose was $69-400 \text{ mg/dl}$ (mean: 168.53 ± 76.79), Random blood glucose $94-564 \text{ mg/dl}$ (mean: 248.98 ± 102.25), Glycated Hemoglobin (HbA1c) $6-14\%$ (7.63 ± 1.23) and serum creatinine was $0.10-6.80 \text{ mg/dl}$ (mean: 1.30 ± 1.05).

Three (2.97%) patients had healed ulcers at the time of discharge, 64 (63.36%) were discharged on treatment with unhealed ulcer and 34 (33.66%) patients needed amputation.

Table 1 shows demographic, clinical and biochemical characteristics of patients of three groups.

Table 2 shows clinical characteristics DFU of three groups.

DISCUSSION

Global prevalence of DFU is 6.3%.⁴ Diabetes, due to its high prevalence and serious complications, is one of the most important diseases in the world and has always attracted attention of researchers. DFU is one of its dreadful complications as it can sometimes need a major amputation to save life. So it is very important that its risk factors should be identified and treated well in time to save a limb.

In our study we found that majority of patients were males (69.3%) and their mean age was 59 ± 10.43 years comparable with the study of Rodrigues with 62.8% males and mean age of 63.4 ± 14.1 years.⁵ Ahmad also found mean age of 58.09 ± 11 years and male patients were 80.1%.⁶ Old age is associated with increased risk of micro and macrovascular complications and slower immune response to infection. Males are more prone to trauma due to their occupational activities. Unlike our studies, Khan found that 58.7% patients of DFU were females.⁷

We found that 82% of our patients were uneducated. Yekta reported that 57.4% patients were uneducated.⁸ Mariam in Ethiopia observed 49.1% and Yazdanpanah in Iran found 36.6% of DFU patients were uneducated.^{9,10} So education level of our patients was much lower as compared to other studies. Uneducated people are not aware of foot care essential for diabetic patients. They often walk bare foot and are prone to foot ulcer.

Mean duration of diabetes in our patients was 10.38 ± 7.9 years. Musa and Al Rubeaan reported mean durations of 8.5 ± 3.7 and 20.53 ± 7.96 years respectively indicating that DFU was more common in patients with long duration of diabetes.^{11,12}

We found hypertension in 32.76% patients. Comparable with our results, Al-Maskari found hypertension in 34.9% cases.¹³ But other studies like that by Yekta and Al-Rubeaan reported that hypertension was more common in DFU (46.8 and 56.7% respectively).^{8,12} In our study history of IHD was observed in 23.7% cases. Yesil found IHD in 31.3% cases¹⁴ and Rodrigues in 54.4% cases.⁵ This indicates that hypertension and IHD are associated with increased prevalence of DFU.

We observed smoking in 24.75% patients. Wang found that 50% of DFU patients were smokers.¹⁵ Smoking is a risk factor for PAD and it also worsens sensory neuropathy.¹⁶

We found sensory neuropathy in 85.1% cases. Yesil and Wang reported neuropathy in 84.1% and 54.64% cases respectively.^{14,15} Loss of sensation and foot deformities predispose foot to trauma and ulceration.

Retinopathy was observed in 41.58% cases. Yekta and Yesil reported retinopathy in 38.2% and 63.2% cases respectively.^{8,14} This showed that DFU was associated with microvascular complications of diabetes. All patients with DFU should be referred for ophthalmological examination.

We found that nephropathy (7.9%) was not common among our patients. Ali also found nephropathy in 7% patients.¹⁷ Impaired renal function deceptively leads to better glycemic control and risk of ulcer reduces. But

contrary to our studies Yesil reported nephropathy in 52.6% patients with DFU.¹⁴

PAD(18.81%) was less common in our study. Yesil observed limb ischemia in 55.9% cases and Khan in 62.8% cases.^{14,7} This shows that PAD was more common in other studies.

To determine factors associated with poor outcome, we classified our patients into three groups: healed(2.97%), unhealed(63.36%) and amputation(3.66%) groups. Wang reported healing in 83.6%, non-healing ulcer in 10.21%, and amputation in 6.19% patients.¹⁵ Yesil observed healed ulcer in 48.7%, unhealed ulcer in 14.1% and amputation in 37.1% cases.¹⁴ Healing rate was higher in these studies due to longer follow up and better quality of treatment. Many other studies have been conducted all over the world showing high amputation rates in DFU.^{18,19,20} But Bondor in Romania found amputation in only 3.6% cases of DFU.³ This proves that better management and patient education can reduce high amputation rates in DFU in other parts of the world also.

Mean duration of DFU at the time of presentation was 24 ± 10.39 days in healed, 72.61 ± 179.41 days in unhealed and 49.82 ± 41.75 days in amputation group (p value was 0.56). Wang reported mean duration of 5.67 ± 3.03 weeks in healed, 34.20 ± 12.08 weeks in unhealed and 15.08 ± 11.79 weeks in amputees.¹⁵ Both studies showed that longest duration of presentation was not associated with worst outcome. But Jiang reported that longer duration of presentation is a poor prognostic feature for DFU.¹⁹

All types of neuropathy, sensory (94.11, 81.25 and 66.66%), motor (35.29, 21.87 and 33.33%) and autonomic (11.76, 4.68 and 0%) were more common in amputation group than in unhealed and healed ulcer groups respectively. This means that neuropathy is an important risk factor for DFU as well as amputation. This is statistically significant as p value is 0.03 for sensory neuropathy. Wang also found that neuropathy is more common in patients who had amputation.¹⁵ Boyko also found that neuropathy influences diabetic foot ulcer outcome.²¹ Painless neuropathic ulcers remain unnoticed for a long time and present late. But unlike our observation, Yesil found highest percentage of neuropathy in healed(89.6%) followed by unhealed(82.7%) and amputation(77.5%) groups.¹⁴

We found that nephropathy was 0% in healed, 7.81% in unhealed and 9.09% in amputation group. So nephropathy although uncommon in our study, was more frequent in amputees. But this observation was not statistically significant (p value 0.54). Ali found that nephropathy was not frequent in amputees(3.30% versus 3.77%).¹⁷ Yesil found nephropathy in 52.9% in healed, 50.6% in unhealed and 53.1% in amputation group.¹⁴ Wang reported that nephropathy is associated with increased risk of amputation.¹⁵

We observed retinopathy in 33.33% cases in healed, 37.50% in unhealed and 51.51% in amputation group (p value 0.96). Yesil reported that retinopathy was more common in his patients(62.1, 64.2 and 64.3% in healed,

unhealed and amputation groups respectively).¹⁴ Yekta found that retinopathy was associated with poor outcome. (68.8% in amputation and 19.4% in non-amputation groups).⁸ Visual impairment can seriously affect outcome of DFU.

We found PAD in 0% in healed, 20.31% in unhealed and 17.64% cases in amputation group (p value 0.57). But Yesil found that limb ischemia was more common in patients with amputation (36.1% healed, 59.3% unhealed and 80.8% in amputation group).¹⁴ Xu B also found that PAD is more common in amputation as compared to non amputation group (68.11% versus 25.04%).²² Similar to our observation Musa in Saudi Arabia also found that ischemic ulcer is less common in amputation group.¹¹ So we conclude that PAD is a less common predictor for amputation in Pakistan and some other countries like Saudi Arabia.

In our study HbA1c was highest in amputees (8.05 ± 1.55). This indicated that poor glycemic control increases risk of amputation but this was not statistically significant (p value is 0.22). Al-Rubeaan also found high HbA1c in patients who underwent amputation.¹² But Ali did not find association between poor glycemic control and amputation.¹⁷ Musa unusually found low HbA1c in amputation group considering coexistent renal impairment as underlying cause.¹¹

We found smoking in 29.4% patients who underwent amputation as compared 23.4% who did not. This revealed that smoking increases risk of amputation but p value was 0.51. Yesil found smoking almost equally in amputation(45.5%) and unhealed groups(45.7%) while in healed group it was less common(36.1%).¹⁴ Sayiner also observed that smoking increases risk of amputation in DFU.¹⁸

Our study showed that Wagner grade was significantly high in amputation group (grade 3- 82.35%) as compared to unhealed (grade 3-70.31%) and cured (grade 3- 0%) groups. It was found to be statistically significant (p value 0.00). Yesil observed that 53.1% patients who underwent amputation had grade 4 ulcer.¹⁴ Wang and Jiang also observed that amputation was associated with higher wagner grade.^{15,19} This supports that wound state according to wagner grade is a predictor for amputation.

CONCLUSION

We found that DFU is more common in old, uneducated males with long duration of Diabetes. Hypertension, IHD, neuropathy, retinopathy and smoking were associated with increased prevalence of DFU. We observed very high amputation and low healing rates which is an alarming situation. Sensory neuropathy, wagner grade (with p values <0.05), poor glycemic control and smoking (p values >0.05), and were associated with poor outcome. PAD and nephropathy were relatively less common in our patients. All these co-morbidities should be managed aggressively along with patient education programmes

about foot care for prevention of DFU. Early referral to a tertiary care hospital for aggressive wound care and adequate glycemic control will prevent amputation. More prospective studies are needed to confirm our findings with larger sample size and longer follow up.

Author's Contribution:

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Rate of Pin Tract Infection Among Children With Supra Condylar Fracture of Humerus; Buried Versus Percutaneous K-Wires

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ABSTRACT

Objective: The comparison of pin tract infection rate between buried K-wire fixation and subcutaneous K-wire fixation in supra condylar fracture of humerus in children.

Study Design: Prospective study.

Place and Duration of Study: This study was conducted at the Department of Orthopedic Unit Sir Ganga Ram Hospital Lahore from January 2019 to June 2019.

Materials and Methods: Children up to 14 years of age admitted to orthopedic unit of study institution during study period having supra condylar fracture of humerus (Gartland type-3) not more than 3 days old were included in this study. These cases were divided into two groups Group-A & Group-B. Open or closed reduction of fracture using K-wires were done in all cases but wires were buried in cases of group-A and wires were kept percutaneous in group-B. Rate of pin tract infection was seen in both groups on follow-up and compared with each other. All data was recorded on a predesigned performa and analyzed on statistical software SPSS (version 20) and Microsoft office (version 2017).

Results: There were total 169 cases in our study divided into two groups group-A (N=79) and group-B (N=90). Mean age of patients was 6.5 years. Out of 79 cases with buried k-wires 1.3% cases developed pin tract infection and out of 90 cases with percutaneous k-wires 6.6% cases developed pin tract infection having statistically significant difference with p-value <0.005. Other complications related to surgical wound were also observed such as hypersensitivity of scar tissue seen in 1 case, ulnar nerve palsy in 3 cases, loosening of k-wires in 3 cases, retrograde migration of wires in 1 cases, tendinitis in 2 cases and osteomyelitis was reported in one case. Mean time of hospital stay after operation was 3±1 days. Mean time of union was 4.5 weeks (3-7 weeks).

Conclusion: Our study concluded that among patients with fixation of supra condylar fracture humerus with percutaneous exposed kirschner wires (k-wires) rate of pin tract infection was much higher than buried k-wires and second surgery may be needed to remove infected wires that is a burden on the patient and doctor as well with increased morbidity. Among patients with buried k-wires second surgery is must to remove it after fracture healing but pin tract infection rate is much low.

Key Words: Supra condylar fracture of humerus, Kirschner wires, pin tract infection, ulnar nerve palsy

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INTRODUCTION

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Supra condylar fracture of humerus is a most common fracture among children. Displaced supra condylar fracture of humerus is fixed with k-wires either by closed reduction or open reduction. But closed reduction method is more suitable.¹ There are many complications associated with this technique but most common is pin tract infection, that is treated by appropriate antibiotics after culture and sensitivity and removal of pins. If this infection is not treated early then it can lead to osteomyelitis, septic arthritis, early fusion of physis and flexor sheath infection. Commonly Gartland classification is used for supra condylar fracture of humerus. In Gartland type 1 and 2 closed reduction and immobilization by cast is used commonly and in type-3 fractures suitable technique is open or closed reduction with percutaneous or buried k-wire fixation.² Rate of pin tract infection is increased

when kirschner wires are left in situ for prolong period of time. There are many methods to prevent this infection such as pin site cleaning daily, release of tethered skin, coating pins with antiseptics and application of topical antibiotics as a prophylaxis. According to a study daily cleaning of pins enhances fear among children and their parents as well so cleaning after 2 days or weekly is also effective having same outcomes.³ Some studies have been done previously on safety of semi sterile technique of percutaneous pinning in supra condylar fracture of humerus but that showed high rate of pin tract infection so semi sterile technique is not suitable.⁴ Supra condylar fracture of humerus accounts 65% of all elbow fractures in children.⁵ In type-3 displaced fractures closed reduction is much difficult to achieve due to thin bone present between coronoid and olecranon fossae and stripping of periosteal layer as well as hyper flexion at elbow to maintain reduction can lead to compartment syndrome and neurovascular compromise. In our study rate of pin tract infection has been determined in percutaneous versus buried k-wire fixation in supra condylar fracture of humerus and both open and closed techniques were used according to surgeon priority..

MATERIALS AND METHODS

This study was conducted in orthopedic unit of Sir Gangaram Hospital Lahore. It is a cohort study of prospective type. It is an experimental study. Study was started in January 2019 and completed after six months in June 2019. All children up to the age of 14 years having closed supra condylar fracture of humerus Gartland type-3 not more than 3 days old were included in this study. These cases were admitted in the ward for open or closed reduction and fixation with kirschner-wires. History was taken related to mode of injury and time duration, demographic data like name, age, gender and residential address were noted on a proper designed performa. All cases were divided into two groups group-A & B. In group-A K-wire fixation of fracture was done and wire ends were buried in the skin while in group-B wires were kept percutaneously. Reduction of fracture was done by either closed or open techniques. K-wires were inserted either two crossed k-wires (one from medial and other from lateral side) or two lateral k wires. Ends of k-wires were bent to prevent migration of wire. After fixation splint was applied to the patient and they were given same type of antibiotic regimen for 7-10 days duration. They were examined for any complication particularly pin tract infection on follow-ups after 15 days, 4 weeks and then 6 weeks. Patients above the age of 14 years, having open fracture or older fracture were not included in this study. Patients giving history of any manipulation from quacks before admitting to the hospital with compromised skin conditions on examination were not included in this study as well. In which patients pin tract infection was

found on follow-ups, pus for culture and sensitivity was sent, conservative management was given for 10 days and if not treated then patient admitted for k-wire removal and then managed for pin tract infection accordingly. Pin tract infection was diagnosed on the basis of Modified Openheim classification. Patients having grade-2 score were diagnosed for having pin tract infection. All data was collected on a performa and analyzed using SPSS-20 and Microsoft office-2017. Chi square test was applied on the data. P-value less than 0.05 were considered statistically significant. Results were expressed in the form of tables and graphs..

RESULTS

Total 169 cases were studied including 98(58%) male and 71(42%) female children. In 79(46.7%) cases of group-A after k-wire fixation of fracture wires were buried in the skin and pin tract infection was reported in 1(1.3%) cases while in 90(53.3%) cases of group-B wires were kept percutaneously and pin tract infection was reported in 6(6.6%) cases. Overall rate of pin tract infection in 169 study cases was 4.14%.

Table No.1: Modified Openheim classification¹⁶

Grades	Clinical findings
1	Slight discharge and redness around pin
2	Redness and tenderness in soft tissue with or without discharge of pus
3	As in grade-2 but failure to improve with antibiotics
4	Severe soft tissue involvement affecting more than one pin
5	As in grade-4 with bone involved visible on x-ray
6	Sequestrum formed in the bone with sinus formation

Table No.2: Treatment outcome in both groups (N=169)

	Percutaneous k-wires (n=90)	Buried k-wires (n=79)	p-value
Number of cases with infected wires	6 (6.6%)	1 (1.3%)	0.005
Open reduction	18 (22.8%)	21 (23.3%)	0.01
Closed reduction	61 (77.2%)	69 (76.7%)	0.05
Wires removed early due to infection	2 (2.2%)	1 (1.3%)	

Table No.3: Complications related to k-wires

complications	Number of patients (N=169)	%
Excessive granulation	2	1.18
Scar hypersensitivity	1	0.6
Wire loosening	3	1.8
Retrograde migration of wire	1	0.6
Revision of procedure	1	0.6
Penetrating tendinitis	2	1.18
osteomyelitis	1	0.6
Ulnar nerve palsy	3	1.8%

Mean time of fracture union was 4.5 weeks (3-7 weeks). Out of 79 cases of group-A, open reduction was done in 18(22.8%) cases while closed reduction was done in 61(77.2%) cases. In group-B, out of 90 cases open reduction was done in 21(23.3%) and closed reduction was done in 69(76.7%) cases. Modified Openheim classification was used to diagnose pintract infection among cases in study group. Hence patients having at least grade-2 infection were diagnosed as having pin tract infection. Out of 90 cases of percutaneous k-wires, 6(6.6%) wires were infected, open reduction and k-wire fixation was done in 18(22.8%) cases while closed reduction and k-wire fixation was done in 61(77.2%) cases and due to infection early removal of wires done in 2(2.2%) cases. Out of 79 cases with buried k-wires only one case got pin tract infection, open reduction of fracture was done in 21(23.3%) and closed reduction was done in 69(76.7%) cases, early removal of wires done in only one case.

DISCUSSION

In pediatric fracture kirschner wires are most commonly used for internal fixation. Two k-wires are passed through fracture either crossed k-wires or two lateral k-wires can be used. Studies have proved that two lateral wires are as good as two cross wires.⁶ In this study we compared rate of pintract infection among buried and percutaneous k-wires. Data recorded regarding various complications after operation. Previously conducted study on 490 cases reported pin tract infection in 4.3% cases, superficial infection was present in 3.1% and deep infection like osteomyelitis and septic arthritis was found in 1.2% cases. In our study rate of pin tract infection was higher (22.2%) as compared to this study but rate of deep infection was much lower (0.6%).⁷

In percutaneous pinning microbes enter into the wound through pin site openings and create infection. A study described very simple method of using rubber stopper on percutaneous ends of pin to prevent pin tract infection. It is very simple and inexpensive way of infection prevention with excellent results.⁸

A study conducted in united state concluded that preoperative use of antibiotics reduces rate of infection which was just 2.4% according to their study. Preoperative one dose of antibiotics is more effective than using post operative multiple doses. This rate is much lower as their health system is more developed than our system and highly developed operation theaters as well.⁹

There are two techniques fracture reduction, open reduction with incision or closed reduction without giving large incision. Both techniques reduce fracture successfully but there is cosmetic disadvantage in open technique and wound healing takes time followed by

formation of a scar tissue. While in closed method no scar tissue is formed.¹⁰

Most of the supra condylar fractures occur between 5-10 years of age and 98% are extension type. According to a study conducted in India most of the fractures were found in male children (59.5%) and mostly on left side (57.14%). Most common mode of injury was trauma while playing (42.8%). They used crossed k-wire fixation via medial approach and on follow up after 3 months, 6 months and one year range of motion on elbow was satisfactory in most of the cases.¹¹

Previously a study conducted in Pakistan in M.M. Medical College reported that there is no significant difference in outcomes in cross k-wire fixation or two lateral k-wires fixation but there was found some risk of iatrogenic ulnar nerve injury in medio-lateral cross k wire fixation but it was just neuropraxia which recovered after mean time of 3-months.¹²

According to another study conducted in Turkey on open supra condylar fractures of humerus gustilo type-1 and 2 in children and management by k-wires fixation reported that out of 26 study cases 23 showed excellent outcome and in other 3 cases successful outcome found. Pin tract infection rate was just 3%. These results were excellent in open fractures.¹³

Kwak-Lee et al described that two lateral pin insertion and one medial pin insertion has better outcome than just two lateral pins insertion. According to a study conducted by Shahid Hussain et al cross k wires fixation was done through lateral approach and it showed satisfactory results in 90% cases with good range of motion according to Flynn's criteria within 6 weeks after pins removal.^{14,15}

In our study crossed k-wire fixation was done in most of the cases and in other two lateral wires were passed. Open and closed both techniques were used and in mostly cases pins ends were buried while in others they left percutaneously. Main objective of this study was to determine rate of pin tract infection in percutaneous vs buried k-wires.

CONCLUSION

In this study it has been evident that in percutaneous kirschner-wire fixation of supra condylar fracture of humerus rate of pin tract infection is high as compared to those in which k-wires are buried beneath the skin and its ends are not exposed. In buried k-wires there is low rate of infection and hence no need of early removal and low chances of fracture displacement due to infection. There is one disadvantage of buried k-wires and that is burden on the patient of second surgery for removal of k-wires that is done under general anesthesia in children that is financial as well as emotional burden on the patient and parents of children and also burden on the doctor for preparing the patient for second surgery.

Author's Contribution:

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Pattern of Presentation of Gall Bladder Carcinoma and its Surgical Management in South East Punjab.

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ABSTRACT

Objective: The objective of this study was to determine the pattern of presentation of Gall Bladder Carcinoma and Surgical Management in South Punjab.

Study Design: Prospective study.

Place and Duration of Study: This study was conducted Surgical Department of District Headquarters & Teaching Hospital, D.G. Khan Medical College, Dera Ghazi Khan from July, 2018 to July 2019.

Materials and Methods: Total of 25 patients of Carcinoma of Gall Bladder were treated within period of one year. There were 4 males and 21 females with male to female ratio 1:5. Ages of patients ranges from 38 to 72 years with max. incidence in 5th decade. Presenting features were pain in right hypochondrium in 88%, nausea & vomiting in 60%, weight loss in 40%, Jaundice in 28%, mass in right hypochondrium in 20%, pruritis in 20%, fever in 12%, anorexia in 12% and ascites in 4% of cases. The investigations done in these patients were USG abdomen, CT abdomen and other basic investigations.

Results: All the patients were operated and divided into three groups. (i) Nevin staging system I & II. (ii) Nevin III Patients with stage IV & V. Simple cholecystectomy was done in 10 patients of group I. extended cholecystectomy was done in two patients of group II. Laparotomy and biopsy of mass with palliative surgery and bile drainage in 13 patients of group III. Adenocarcinoma was diagnosed in 88% (22 patients) and squamous cell carcinoma in 8% (2 patients) was diagnosed on histopathological study.

Conclusion: The study concludes that gallstones are most important factor causing the carcinoma. So malignancy should be suspected in any long standing cases of cholelithiasis. So early cholecystectomy should be recommended in gall stone cases.

Key Words: gall stone, carcinoma of gall bladder, cholecystectomy.

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INTRODUCTION

Although the gall bladder cancer is not a commonest malignancy yet it is the most commonest tumor of biliary tract and fifth most common malignancy of alimentary tract in USA¹. seen even in young patients of 25 years of age. It is found in 2% of gall bladder operations and in about 80% instances, gall stones are found. It is common in females with male to female ratio 1:4. Its incidence increases with age but in our

Country.² it has been The clinical presentation of all bladder carcinomadiffers depending on the stage of the disease. Common presentations are³ pain in 66%, wt loss in 59%, jaundice in 51% and right upper quadrant mass in 40% patients. Mostly the tumor is discovered preoperatively by biopsy report or at advanced stage.

The tumor spreads by variety of routes⁴ including lymphatic, vascular, direct extension and intra peritoneal seedling.

The treatment of gall bladder cancer is surgery, though the opinions vary to the exact operative procedure which should be done. It is potentially curable in early stages but unluckily the diagnosis is very difficult in early stages. Surgical treatment varies from simple cholecystectomy, extended cholecystectomy, palliative surgery to radical surgery which comprises hepatic wedge resection, extended right hepatectomy, pancreaticoduodenectomy with local and paraortic lymphadenectomy. Burger and malt⁵ (1999) states that there are no surgical benefits following extensive resections.

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MATERIALS AND METHODS

This study was conducted on 25 patients in Teaching Hospital D.G.Khan Medical College, Dera Ghazi Khan from July-2018 to July-2019. The study covers the South Punjab and adjoining areas of Balochistan, Sindh and KPK.

The following protocol with proper history and clinical evaluation was done. History comprises of age, sex, weight, occupation, pain, jaundice, mass in abdomen, nausea, vomiting, anorexia, weight loss with fever, if present. History of pruritis and colour of urine and colour of stool was also noted in patients with jaundice. Family history of jaundice, gall stones and malignancy was also noted. General and special physical examination includes lymphadenopathy, jaundice, mass, visceromegaly and ascites.

The investigations were CBC, ESR, Platelets count, complete urine examination, RPM, S/E, Stool examination, LFT's, PT, APTT, X-ray Chest, ultrasound abdomen and CT abdomen was done. All patients were operated, patients were staged according to "NEVIN" staging system of carcinoma of gall bladder in stage I, II, III, IV and V, and the patients were divided into three groups on basis of operative findings and stage of disease;

- Group I (Stage I & II)
- Group II (Stage III)
- Group III (Stage IV & V).

Group I comprises of 10 patients and simple cholecystectomy was done. Group II comprises of 2 patients underwent cholecystectomy + 3 – 5cm wedge resection of surrounding hepatic parenchyma plus lymph node clearance.

13 patients of Group III were operated, as just only biopsy of mass and 2 nodes in most of these patients. Simple bile drainage was done in 2 cases and has extensive involvement of CBD. The tissue was saved and sent for histopathological evaluation..

RESULTS

During one year, 25 patients of CA gall bladder were studied 22 patients (88%) were admitted through outdoor, 2 patients were referred from medical ward with history of pain in abdomen. Only one (8%) came through casualty department with severe billiary colic. These 25 patients were selected for study and were operated.

Among these 25 patients, there were 21 (84%) females and 4 (16%) males with female to male ratio of 5:1 ranged from 38-73. There were 9 (36%) patients in age group 41-50 years and 10 (40%) patients in age group 51-60 years. Four patients (16%) were above 60 years of age where only one (4%) patient was above 70 year. Thus maximum incidence was seen in 5th decade of life. None of the patient was seen in second or third decade of life. In male patients, the youngest was 38 years of

age. The oldest one was of 73 years. In female patients the youngest one was 40 years of age while oldest female was 68 year of age. All the 21 female patients were married. All these females were housewives. One female worked in office. Among the male patients 2 were labourers while remaining 2 were gazetted Govt. Officers. Thus out of 25 patients only 5 belonged to middle class, while the other belonged to poor status. In 3 males (13.63%) and 19 females (86.36%) complained of pain in right hypochondrium. Many of the patients also complained of associated flatulence and dyspepsia but pain was the most distressing symptom.

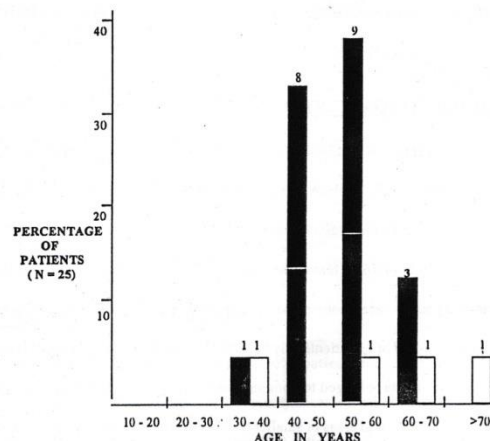


FIGURE NO. 1
AGE & SEX DISTRIBUTION (DECADE WISE) IN
PATIENTS
WITH CARCINOMA GALL BLADDER

■ FEMALE
□ MALE

Figure-1: Age Sex Distribution Decade wise in Patients

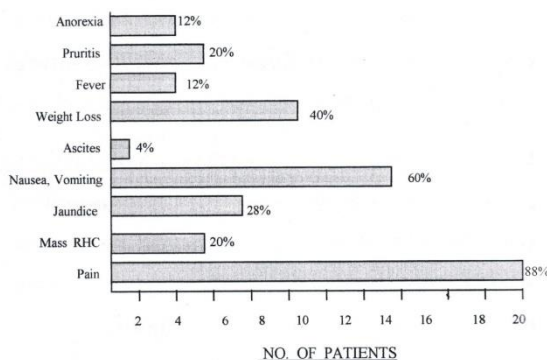


FIG. No. 2
PREVALENCE OF VARIOUS CLINICAL FEATURES IN PATIENT
WITH CARCINOMA GALL BLADDER

Figure-2: Prevalence of Various Clinical Features in Patients with Carcinoma Gall Bladder

In 2 (50%) patients of 4 male patients and in 13 (61.90%) of 21 female patients complained of nausea and vomiting was present. Over all 60% patients

presented with complain of nausea / vomiting. 4 male patients and 6 females patients have the history of weight loss.

Jaundice was present in 2 (50%) of 4 male patients and 5 (23-80%) of 21 female patients. Thus 7 out of 25 patients were jaundiced in this study. 3 (14.28) of 21 female patients and 2 (50%) of 4 male patients presented with mass right hypochondrium, history of pruritis was positive in 5 (20%) patients among which 3 were females 2 were males. Ascites was observed only in one male patient who had advanced disease with peritoneal metastasis.

Thus pain in right hypochondrium was the most common symptom observed in this study. It was present in 22 (88%) out of 25 cases. Next common symptom was nausea & vomiting, observed in 15 (60%) patients, 10 (40%) patients and history of weight loss whereas 7 (28%) patients presented with Jaundice, 5 (20%) patients presented with mass in right hypochondrium. Pruritis was observed in 5 (20%) cases fever in 3 (12%) and ascites was present in one (4%) patient.

Table No. 1: Laboratory investigations.

Findings of Investigations	No. of Patients	%age
Decreased Haemoglobin	13	52%
Increased total leukocyte count	15	60%
Increased ESR	15	60%
Increased serum bilirubin	07	28%
Increased serum alkaline phosphatase	07	28%
Increased SGOT and SGPT	07	28%

Table No. 2 : Nevin's staging of carcinoma Gall Bladder

Stage of the disease	No. of patients	%age
Stage I	03	12%
Stage II	07	28%
Stage III	02	08%
Stage IV	04	16%
Stage V	09	36%

DISCUSSION

Carcinoma of GB is commonest malignancy of biliary tract⁶, ranks 5th in frequency among digestive tract cancers.⁷ it is asymptomatic in its early course, therefore most patients present with advanced disease.

When gallstones are present for prolonged period time, they bring metaplastic and dysplastic changes in mucosa that leads to development of CA gallbladder.

Incidence of carcinoma in our set-up is due to gallstones, presence of chronic typhoid carrier state, early age marriages, use of contraceptives and increased exposure to environmental and industrial pollutants especially of rubber and textile industries⁹.

Similarly in a study carried out in young age group involvement in cases of carcinoma of gallbladder has been reported. Our results correlate well with other local Pakistani literature but figures are less than western literature indicating an earlier age involvement in our set-up.

Carcinoma of gallbladder with other biliary tract diseases is more common in females¹¹ in our study there were 21 females and 4 males, male to female ratio is 1:5.

Other studies from Taiei, France and United Kingdom¹² have showed a male female ratio of 1:4 where as study from USA showed a ratio of 1:3.

Pain in right hypochondrium was present in 88% Jaundice in 28% of our cases while others reported 30% - 45%¹³.

Mass right hypochondrium was present in 20% of our cases while other have reported 15-40-60%.

A pre-operative diagnosis of carcinoma of gall bladder is difficult as there is no remarkable difference in clinical and biochemical findings between benign and malignant gall bladder disease. In our study the carcinoma of gall bladder was incidental finding in 12% of patients on histological examination. While in 10% pre-operative diagnosis was possible with the help of ultrasonography. However in this case the disease was advance in stage IV and VI.

CT scan has been used to detect carcinoma gall bladder. "Thrsenal and colleagues"¹⁴ showed that 19% carcinoma gall bladder could be diagnosed with CT scan. In my study CT scan was done in 1 patient who could afford and 100% helpful in diagnosis.

The ultrasonography is the best method of investigation¹⁵. Because it is cheapest, easily available and noninvasive diagnostic modality.

The treatment which was done in our study was simple cholecystectomy, extended cholecystectomy, biliary drainage, and biopsy in advanced stages. Radical surgery was not attempted in any patient. International literature¹⁶ also favours the fact that extensive surgical resections are not associated with improved survival.

Adeno-carcinoma is the commonest type of carcinoma of gall bladder followed by squamous cell carcinoma and undifferentiated tumours..

CONCLUSION

Carcinoma of gall bladder is commonest malignancy specially in "wanner and nevin" case in the long standing gall stones so early cholecystectomy should be preferred. Ultrasonography is the useful diagnostic test especially with modern machines, the carcinoma of gall bladder can be diagnosed.

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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Examine the Importance of Amniotic Fluid Index (AFI) on Perinatal Outcome in Low Risk Term Pregnancy

Naila Ehsan Chauhan, Maryam Shoaib, Rohana Salam, Sakina Naeem,
Samia Saifullah and Zubia Bugti

ABSTRACT

Objective: Examine the clinical importance of low amniotic fluid index (AFI) on perinatal outcome in low risk pregnancy at term.

Study Design: Prospective study

Place and Duration of Study: This study was conducted at the Department of Obstetrics & Gynaecology, Sandeman Provincial Hospital Quetta from July 2018 to June 2019.

Materials and Methods: One hundred and twenty patients were included. They were categorized into two groups; Group A females having low amniotic fluid index ≤ 5 cm with term pregnancy admitted in labour room for delivery and Group B females with AFI > 5 cm were selected as a control. Demographic details were recorded after written consent. Outcomes were examined such as NST measure, mode of delivery, Apgar score at 5 minutes, need to NICU, low birth weight, meconium aspiration and respiratory distress.

Results: No significant difference observed between cases and controls regarding age of mother, non-stress test (NST) (reactive 81.67% vs 76.67%) and C-section delivery [30% vs 25%] ($P > 0.05$). Significant difference was observed regarding Apgar score at 5 minutes < 7 between both Groups (33.33% vs 8.33%) [$P < 0.05$]. There was also a significant difference observed regarding need for admission to neonatal intensive care unit (8.33% vs 1.67), low birth weight (8.33% vs 1.67%) and meconium aspiration (11.67% vs 3.33%) between both groups ($P < 0.05$). No perinatal death was recorded between cases and controls.

Conclusion: We found no significant difference regarding NST and mode of delivery among both groups. However, patients with low AFI had a high rate of neonatal complications as compared to patients with standard AFI > 5 cm.

Key Words: Amniotic fluid index (AFI), Low risk pregnancy, Perinatal outcomes

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INTRODUCTION

Amniotic fluid index (AFI) is described as a semi quantitative ultrasound estimate used to indicate quantity of amniotic fluid.¹ As per indications by ultrasound examination, there is an increased risk of intra-partum fetal compromise in pregnant females with oligohydramnios.²⁻⁵ High rate of pregnancy complications, neonatal morbidity and mortality is directly associated with oligohydramnios. Amniotic fluid index will be helpful to detect high risk cases, requiring increasing need of antepartum surveillance.⁶

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Females diagnosed with oligohydramnios have adverse perinatal outcomes such as low birth weight, fetal distress, neonatal mortality and high rate of morbidity. It is also associated with increased rate of C-section deliveries.^{7,8} However, AFI is not a qualitative predictor of unfavorable outcomes and even the presence of any adverse outcome such as isolated term is still under questioned and not proving the AFI as a good predictor of perinatal and maternal outcomes.^{9,10} The accurate pathophysiologic mechanism of oligohydramnios has not been identified, but during uterine contractions umbilical cord risk is one likely explanation. The present study was conducted aimed to examine the importance of amniotic fluid as a predictor of perinatal outcome in low risk term pregnancy..

MATERIALS AND METHODS

This prospective study was conducted at Department of Obstetrics & Gynaecology, Sandeman Provincial Hospital Quetta from 1st July 2018 to 30th June 2019. One hundred and twenty pregnant females were equally divided into two groups i.e. Group A (amniotic fluid index of ≤ 5 cm with low risk pregnancy at term) and

Group B (amniotic fluid index of ≥ 5 cm and ≤ 20 cm). Females with singleton, non anomalous pregnancy with intact membrane and term pregnancy were included. Females with previously perinatal loss, previous caesarean section, recurrent missed abortions, post term pregnancy, intrauterine growth restriction (IUGR) evidence, medical disorder which has effect on fetomaternal results e.g. hypertension, diabetes as well as cardiac disease were excluded. Non-stress test was done at the time of admission. Both group A and group B matched for parity, age, non anomalous conceptus, gestational age and intact membranes. The outcome measures were mode of delivery, meconium presence, NST measures, at five minutes Apgar score, neonatal unit admission and perinatal mortality. All the data was analyzed by SPSS 21. Student t' test was used to compare the findings. P-value <0.05 was set as significant..

RESULTS

From all the study patients, 25 (41.67%) patients Group A and 23 (38.33%) Group B (controls) were ages between 20 to 30 years, 27 (45%) Group A and 28 (46.67%) Group B patients were ages 31 to 40 years, 8 (13.33%) in Group A and 9 (15%) patients in Group B were ages 41 to 50 years. ($P>0.05$) found regarding age of mother between both groups (Table 1).

According to the non-stress test (NST), we found no significant difference ($P>0.05$) between cases and control (Table 2). According to the mode of delivery we found $P>0.05$ found between both groups (Table 3). Twenty (33.33%) patients in Group A had ≤ 7 Apgar score at five minutes and in Group B 5 (8.33%) patients had Apgar score >7 at five minutes and found significant difference among both groups [$P<0.05$] (Table 4).

Table No.1: Frequency of age in both groups

Age (years)	Group A	Group B
20 – 30	25 (41.67%)	23 (38.33%)
31- 40	27 (45%)	28 (46.67%)
40 – 50	8 (13.33%)	9 (15%)

P value ≥ 0.05

Table No.2: NST finding between both groups

NST	Group A	Group B
Reactive	49 (81.67%)	46 (76.67%)
Non reactive	2 (18.33%)	14 (23.33%)

P value ≥ 0.05

Group A had 5 (8.33%) and Group B had 1 (1.67%) neonates need admission to NICU. Meconium aspiration was found in 7 (11.67%) in Group A and 2 (3.33%) in Group B. Respiratory distress found in 3 (5%) neonates in Group A and 1 (1.67%) in Group B. In Group A 5 (8.33%) neonates had low birth weight while in Group B only 1 (1.67%) neonate had low birth

weight. There was no neonatal mortality observed between both groups (Table 5)

Table No.3: Mode of delivery

Type of Delivery	Group A	Group B
Vaginal (Normal)	38 (63.33%)	40 (66.67%)
C-Section	18 (30%)	15 (25%)
Vaginal (Instrumental)	4 (6.67%)	5 (8.33%)

P value ≥ 0.05

Table No.4: APGAR score at five minutes

Score	Group A	Group B
≤ 7	20 (33.33%)	5 (8.33%)
≥ 7	40 (66.67)	55 (91.67)

P value <0.05

Table 5: Neonatal outcomes between both groups

Neonatal outcome	Group A	Group B
No complication	40 (66.67%)	55 (91.67%)
NICU Admission	5 (8.33%)	1 (1.67%)
Meconium aspiration	7 (11.67%)	2 (3.33%)
Respiratory Distress	3 (5%)	1 (1.67%)
Low birth weight	5 (8.33%)	1 (1.67%)
Mortality	-	-

P value <0.05 .

DISCUSSION

In high risk pregnancies decreased amniotic fluid carries increased risk of intra-partum complications.¹¹ Conflicted views regarding perinatal outcome are expressed in different studies therefore the picture in low risk pregnancies is still not clear.^{12,13}

In our study there was a significant difference observed regarding need for admission to NICU, low birth weight and meconium aspiration between both groups p-value <0.05 . No perinatal death was recorded between cases and controls. These results were comparable to other studies in is usually result of cord compression in labour. They are most often seen during normal labour and in patients with low amniotic fluid index. Variable deceleration in female with low amniotic fluid index was observed in this study which is not statistically significant. In our study 25 (41.67%) patients in Group A and 23 (38.33%) in Group B (controls) were between 20 to 30 years of age, 27 (45%) and 28 (46.67%) patients were 31 to 40 years in Group A and Group B respectively, 8 (13.33%) in Group A and 9 (15%) patients in Group B were 41 to 50 years. Many studies showed similarity to our study in which the majority of patients were between 25 to 40 years.^{14,15}

Variable deceleration identified on CTG group p-value >0.05 . These results were different to the study by Bachhav et al¹⁶ in which they reported significant difference between cases and controls regarding NST p

value <0.05 . We found no significant difference between both groups p-value >0.05 regarding mode of delivery. These results were comparable to some other studies.^{17,18} We also observed that 20 (33.33%) neonates born in Group A had ≤ 7 Apgar score at five minutes and in Group B 5 (8.33%) neonates had Apgar score >7 at five minutes P-value <0.05 . Bachhav et al¹⁶ showed similarity to our study results regarding Apgar score at five minute.

In the present study all the patients had received non-stress test NST at the time of admission and we found there was no significant difference between the study group and control which there was a significant difference observed in patients having low amniotic fluid than the patients with AFI >5 cm.^{19,20} Some of the studies showed difference to our study results regarding neonatal complications in which no significant difference was observed between cases and controls.²¹⁻²³.

CONCLUSION

We concluded from this study that there was no significant difference observed regarding NST and mode of delivery among cases and controls. However, patients with low amniotic fluid index had a high rate of neonatal complications such as admission to NICU, low birth weight, meconium aspiration and respiratory distress as compared to patients with AFI index >5 cm..

Author's Contribution:

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Data Analysis:	Sakina Naeem, Samia Saifullah and Zubia Bugti
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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 Post-operative Drain Insertion versus No Drain after Total Thyroidectomy

Muhammad Akram Dogar, Adeel Riaz and Ammarah Afzal

ABSTRACT

Objective: To compare insertion of post-operative drain versus no drain in patients undergoing total thyroidectomy in terms of operative time, hospital stay and frequency of post-operative complications.

Study Design: Randomized controlled trial.

Place and Duration of Study: This study was conducted at the Department of General Surgery, Central Park Teaching Hospital, Lahore from 1st July 2016 to 30th June 2017.

Materials and Methods: Sixty two patients of benign multinodular goiter were included in the study. Patients were randomly divided into two equal groups of 31 patients each by lottery method. In Group A, a redovac suction drain was inserted after total thyroidectomy while Group B post-operative drain was not placed. Mean operative time, hospital stay and postoperative complications between the two groups were compared.

Results: The mean operation time was 73.16 ± 10.15 minutes in Group A while it was 61.23 ± 8.61 minutes in Group B ($p=0.000$). The mean hospital stay was 2.42 ± 0.50 days in Group A while it was 1.44 ± 0.53 days in Group B ($p=0.000$). The mean pain score in Group A was 4.77 ± 0.99 while in Group B it was 3.23 ± 1.12 ($p=0.000$). The difference in complications (hematoma, seroma and surgical site infection) was non-significant ($p=0.641$).

Conclusion: Total thyroidectomy for benign multinodular goiter without post-operative drains had a less operative time, lesser hospital stay and was associated with less post-operative pain as compared to patients with postoperative drain insertion. The complication rate between the two groups was comparable.

Key Words: Thyroidectomy, Operative time, Drain, Complications, Hematoma, Seroma.

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INTRODUCTION

The earliest description of thyroid surgery for goiter dates back to year 952 AD by Albucasis. Roger Frugardii of Salerno school of surgery performed the first thyroidectomy and described the procedure in his book *Practica Chirurgiae*. Thyroid surgery was revolutionized by Theodore Kocher who standardized the procedure to reduce the mortality rate to 1% in the late 19th century for which he received a Nobel Prize in 1909.¹ Safety of performing thyroid surgery got a major boost with the introduction of hemostatic devices like Harmonic scalpel and LigaSure and it is the commonest endocrine surgical procedure performed in the world nowadays.² Due to its location in close proximity to the major blood vessels in the neck, surgery of thyroid gland requires strict control of

hemostasis to avoid postoperative complications especially hematoma formation.³

The more conservative options of thyroid surgery like near-total and sub-total thyroidectomy are associated with increased incidence of recurrence. The redo surgery predisposes the patients to high rate of complications and most of the patients undergoing conservative procedures still require thyroxine supplementation.⁴ Total thyroidectomy is therefore considered as the procedure of choice in patients presenting with both benign conditions like Graves' disease and multinodular goiter and also for most of the cases of thyroid carcinoma.^{5,6} Post-operative drain insertion is a routine practice in most of the hospitals across the country. Drains are inserted to reduce the tissue dead space and are used as prophylaxis against the development of hematoma which is a major dreaded complication following thyroid surgery.⁷

More recently the routine insertion of postoperative drains has been questioned by head and neck surgeons from across the world with the argument that drains did not prevent complications rather the ensuring meticulous hemostasis after surgery was all that mattered.⁸ The advocates against the use of drains argue that the incidence of post-operative bleeding and hematoma following thyroid surgery is only 0.1-1.1%.⁹ In addition, Insertion of drain not only increases post-operative pain and discomfort but it also prolongs the

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hospital stay significantly thereby increasing the costs and it has also been reported to increase the incidence of surgical site infections.¹⁰

The aims of our study was to compare post-operative insertion of drain versus no drain in patients undergoing total thyroidectomy in terms of operative time, hospital stay and frequency of post-operative complications. The rationale of this study being the scarcity of data available in the national literature with only one study comparing total thyroidectomy with drain versus no drain.^{11,12} Earlier studies have also yielded conflicting results regarding comparison of two groups. The findings of my study will help adopt the better evidence based technique with less post-operative pain, shorter hospital stay and less post-operative complications which are beneficial outcomes in the management of these patients.

MATERIALS AND METHODS

This randomized controlled trial was conducted in the Department of General Surgery, Central Park Teaching Hospital, Lahore from 1st July 2016 to 30th June 2017 on patients who underwent total thyroidectomy on elective operation list for benign multinodular goiter. The inclusion criteria comprised of diagnosed cases of multinodular goiter belonging to both genders, having age between 20 to 65 years, ASA class I, II and III, and a normal thyroid profile (euthyroid). Patients with the diagnosis of thyroid cancers, ASA class IV and V, previous history of neck surgery including thyroid surgery, deranged coagulation profile and comorbid illnesses like ischemic heart disease, hypertension and diabetes mellitus were excluded from the study. A total of 62 patients were included and they were divided in two groups. Each group comprised 31 patients. Patients were grouped randomly by using the lottery method into two equal groups consisting of 31 patients each. All the patients who were diagnosed as cases of benign multinodular goiter by detailed history, thorough clinical examination, ultrasound neck, FNAC of thyroid and laboratory investigations including thyroid function tests and had normal thyroid function tests (Euthyroid) were included in the study. We performed total thyroidectomy by the standard conventional vascular ligature technique in all patients. The team was headed by a professor/ associate professor assisted by post graduate residents.

In Group A patients, a Redivac suction drain of size 14/16 F was placed after total thyroidectomy beneath the deep cervical fascia after the removal of whole of thyroid tissue and hemostasis. Drain output was measured in the post-operative period after every 12 hours. Suction would be maintained and confirmed by charging the drains. Drains were removed if the drain output did not increase in a 12 hour period after first post-operative day. While in group B patients, post-operative redivacdrain was not placed. The operative

time of all patients was documented in minutes from the start of the surgery till the application of last skin suture. All the patients were followed after surgery for post-operative pain according to the VAS (Visual Analogue Score). The VAS was determined by first teaching the patients about the score and was then documented as expressed by the patients. The documentation of pain score was done after 24 hours of surgery. The hospital stay was calculated from the time of completion of surgery till discharge from the hospital in days. Post-operatively patients were also followed for the development of hematoma, seroma and surgical site infections on the 1st, 7th and 14th post-operative days. The final assessment and recording of post-operative complications was made on the 14th post-operative. The data was analyzed using SPSS-20..

RESULTS

The mean age of patients included in the study was 43.05 ± 8.61 years. In Group A (drain group), the mean age of patients was 41.97 ± 8.30 years (range 31-58 years) while in Group B (no drain group), the mean age of patients was 44.13 ± 8.91 years (range 32-60 years), the difference being statistically non-significant ($p=0.327$). Out of the total 62 patients included in the study, 48 patients (77.4%) were females and 14 patients (22.6%) were males with male to female ratio of the 1:3.43. The gender distribution amongst the two groups is shown in Figure 1. There was no statistical difference between the two groups in terms of gender ($p=0.544$).

The overall mean operative time of the study was 67.19 ± 11.10 minutes. The mean operation time was 73.16 ± 10.15 minutes (range 54-94 minutes) in Group A while it was 61.23 ± 8.61 minutes (range 46-82 minutes) in Group B. The difference in the mean operative time between the two groups was found to be statistically significant ($p=0.000$). The overall mean duration of hospital stay of the study sample was 1.93 ± 0.71 days. The mean hospital stay was 2.42 ± 0.50 days (range 1.5-3.5 days) in Group A while the mean hospital stay was 1.44 ± 0.53 days (range 1.0-3.0 days) in Group B. The difference in the mean hospital stay between the two groups was also found to be statistically significant ($p=0.000$). Post-operative pain score was documented as per the VAS after 24 hours of surgery. The mean pain score in Group A was 4.77 ± 0.99 while in Group B it was 3.23 ± 1.12 . The difference between the groups was statistically significant ($p=0.000$). Complications were observed in 5 patients (8.06%) out of a total of 62 patients. Three patients (9.68%) belonged to Group A while 2 patients (6.45%) were from Group B. The difference in overall complications between the two groups was statistically non-significant ($p=0.641$). There was 1 patient (3.23%) in Group B, a 59 years old female who developed hematoma who was re-explored while there was no case of hematoma formation in Group A, the difference between the groups being

statistically non-significant ($p=0.313$). Two patients (6.45%) in Group A and 1 patient (3.23%) in Group B presented on the follow-up visit with seroma formation which were managed conservatively.

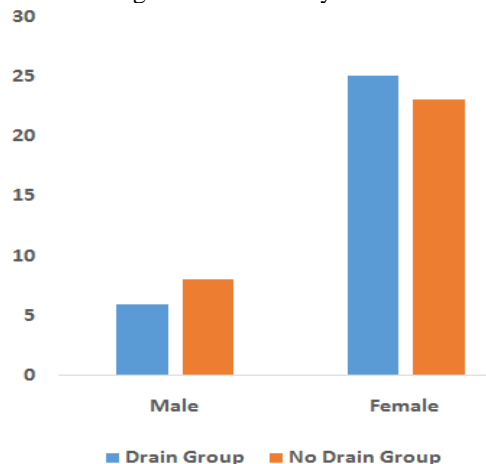


Figure No.1: Distribution of patients according to gender

Table No.1: Results of the study

Variable	Group A (n=31)	Group B (n=31)	p value
Age (years)	41.97±8.30	44.13±8.91	0.327
Gender (Male :Female)	6 (19.35%): 25 (80.65%)	8 (25.81%): 23 (74.19%)	0.544
Operation time (minutes)	73.16±10.15	61.23±8.61	0.000
Hospital stay (days)	2.42±0.50	1.44±0.53	0.000
Pain Score (VAS)	4.77±0.99	3.23±1.12	0.000
Complications	3 (9.63%)	2 (6.45%)	0.641
Hematoma	0 (0%)	1 (3.23%)	0.313
Seroma	2 (6.45%)	1 (3.23%)	0.554
Surgical site infection	1 (3.23%)	0 (0%)	0.313

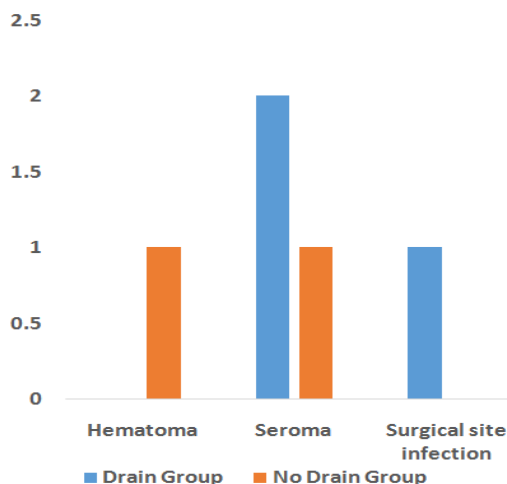


Figure No. 2: Distribution of complications between the two groups

The difference between the two groups was statistically non-significant ($p=0.554$). As regards surgical site infection, 1 patient (3.23%) in Group A developed surgical site infection which was managed by

intravenous antibiotics. There was no case of surgical site infection in Group B. The difference between the groups in terms of surgical site infection was also statistically non-significant ($p=0.313$) [Table 1]. The complications between the two groups are shown in figure 2.

DISCUSSION

Thyroidectomy is one of the most common endocrine surgery procedures performed worldwide. A search of local literature only yielded one study on drain versus no drain in patients undergoing thyroidectomy conducted by Nawaz et al.¹¹ The mean age of patients in our study was 43.05 ± 8.61 years. The mean age was reported to be 37.94 ± 8.96 years in a study by Ahmed et al.³, while Nawaz et al.¹¹ reported a mean age of 42 ± 4.24 years. Similarly Mohialdeen et al.¹³ reported a mean age of 43 ± 8.9 years in 2016 from Iraq. Our study showed a preponderance for female gender with 77.4% patients. Similarly Abaszadeh et al.¹⁴ and Mohialdeen et al.¹³ reported the frequency of female patients to be 79.4% and 75% in their studies respectively. A much higher percentage of 94.3% female patients was reported by Ahmed et al.³

The difference in the operative time between the drain and no drain groups was found to be significant ($p=0.000$). Abaszadeh et al.¹⁴ reported that the operative time in the no drain group was 131.94 ± 38.85 minutes versus 147.22 ± 39.31 minutes in the drain group, which was statistically significant ($p=0.009$). On the contrary a study by Chalya et al.¹⁵ reported that the mean operative time was 105.5 ± 38.4 minutes in drain group versus 102.1 ± 36.3 minutes in without drain group with a non-significant difference ($p=0.756$). Another study by Deveci et al.¹⁶ reported an operative time of 86.45 ± 18.93 minutes in no drain group versus 88.80 ± 21.33 minutes in drain groups with the difference being statistically non-significant ($p=0.19$).

The difference in the hospital stay between the groups was also found to be statistically significant in our study ($p=0.000$). A study by Kalemra-Ssenyondo et al.¹² reported that the mean hospital stay was significantly higher in the drain group 2.41 ± 0.89 days versus 1.71 ± 0.76 days in without drain group ($p=0.0008$). Nawaz et al.¹¹ also reported that the mean duration of hospital stay was 3.63 ± 0.707 days in the drain group vs 1.19 ± 2.145 days in no drain group respectively which was statistically significant ($p<0.05$). Chalya et al.¹⁵ also reported that the mean hospital stay was 4.6 ± 1.2 days in no drain group versus 7.4 ± 2.6 days in the drain group, the difference being statistically significant ($p=0.002$).

Patients in our study reported a significantly higher pain score in the drain group after 24 hours of surgery ($p=0.000$). Similarly Nawaz et al.¹¹ reported a significantly higher pain score of 6.09 ± 0.7 in drain group versus a score of 4.12 ± 0.42 in no drain group

after 24 hours. Deveci et al¹⁶ also reported that the mean pain score after 24 hours was significantly higher in the drain group (3.09 ± 0.77) versus the without drain group (2.08 ± 0.74) with a p value of 0.001. Muthaa et al¹⁷ also reported that the mean pain score was significantly lower in the without drain group (1.4 ± 0.8) versus drain group (4.7 ± 2.0) after 24 hours respectively ($p=0.001$).

Our study did not find any statistical difference in the overall as well as individual complications including hematoma and seroma formation or the development of surgical site infections between the two groups ($p>0.05$). Because of its rich blood supply and vital location in the neck, hematoma can become a life threatening emergency.¹⁸ Drain insertion is mainly done to avoid this complication. Similar to our results a study by Kalemera-Ssenyondo et al¹² reported that the frequency of hematoma formation was 2.94% versus 0% ($p=0.31$), seroma formation was 8.82% versus 5.88% ($p=0.64$) and wound infection was 0% versus 0% ($p=1.00$) in the drain versus no drain groups respectively.

Chalya et al¹⁵ reported that the frequency of complications in the drain group was 15.6% versus 13.3% in without drain group. The difference being statistically non-significant ($p=0.218$). Nawaz et al¹¹ also reported that the frequency of hematoma formation was 0% versus 1.47% ($p>0.05$), seroma formation was 1.7% versus 4.41% ($p>0.05$) and wound infection was 1.47% versus 0% ($p>0.05$) in the drain versus no drain groups respectively which were comparable results to our study. A meta-analysis by Tian et al¹⁰ published in 2017 also reported that there was no statistically significant difference between the drain and no drain groups in terms of hematoma and seroma formation. However there was a significantly higher chance of developing surgical site infections in the drain group as compared to no drain group ($p=0.012$).

With the introduction of newer hemostatic devices like ligature small jaw and focus harmonic scalpel, the safety of thyroid surgery has increased and total thyroidectomy has become the standard procedure of choice in all the major centers in the world.^{19,20} Keeping in view the results of our study and those compared above, total thyroidectomy can be performed without the insertion of post-operative drains. In this present era in which the practice of evidence based surgery has been emphasized from time to time, local evidence based guidelines need to be formulated. The limitation of our study was the small sample size of 62 patients. We recommend drain less thyroidectomy for reducing hospital stay, and post-operative pain. We also recommend further research on this topic with bigger sample size for assessment of better technique in terms of postoperative drain insertion or vice versa in the local population.

CONCLUSION

Total thyroidectomy for benign multinodular goiter without the insertion of post-operative drains had a less operative time, lesser hospital stay duration and was associated with less post-operative pain as compared to patients with postoperative drain insertion. The complication rate between the two groups was comparable. Meticulous dissection coupled with effective hemostasis was the determinant of preventing post-operative complications. Thus we recommend that post-operative drain insertion is not routinely required in total thyroidectomy.

Author's Contribution:

Concept & Design of Study:	Muhammad Akram Dogar
Drafting:	Adeel Riaz
Data Analysis:	Ammarah Afzal
Revisiting Critically:	Muhammad Akram Dogar, Adeel Riaz
Final Approval of version:	Muhammad Akram Dogar

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

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Comparison of Limberg Flap with Karydakis Repair in Pilonidal Sinus Disease

Adeel Riaz, Ammarah Afzal and Muhammad Akram Dogar

ABSTRACT

Objective: To compare Limberg flap with Karydakis repair in pilonidal sinus disease in terms of operative time and post-operative complications.

Study Design: Randomized controlled trial.

Place and Duration of Study: This study was conducted at the Department of General Surgery, Central Park Teaching Hospital, Lahore from July 2016 to June 2017.

Materials and Methods: A total of 204 patients who underwent surgery for pilonidal sinus disease were included. Patients were randomly divided into two equal groups of n patients each by lottery method. Patients in Group L underwent surgery via the Limberg flap technique while patients in Group K were managed by the Karydakis repair technique. Both groups were then compared in terms of mean operative time, VAS pain score, postoperative complications and recurrence rates.

Results: The mean operation time was 50.59 ± 9.1 minutes in Group L versus 41.04 ± 8.63 minutes in Group K, which was statistically significant ($p < 0.001$). The mean VAS pain score was 2.51 ± 1.16 in Group L versus 3.19 ± 1.45 in Group K, which was also statistically significant ($p < 0.001$). The difference in frequency of overall complications ($p = 0.391$) and the recurrence rate ($p = 0.268$) was statistically non-significant.

Conclusion: Karydakis repair is the better technique in terms of having lesser operation time and lesser frequency of wound dehiscence while Limberg flap technique is associated with lesser post-operative pain.

Key Words: Pilonidal sinus, Operation time, Recurrence, Limberg flap, Karydakis repair, Complications

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INTRODUCTION

The earliest description of pilonidal sinus dates back to the year 1833 when Herbert Mayo described the disease.¹ The term "pilonidal" was conceived in 1880 from two Latin words "pilus" which means hair and "nidus" which means nest by Hodges.² The disease got recognition as the "Jeep bottom or simply jeep disease" in the Second World War for its high prevalence among the soldiers especially drivers. Some 79000 soldiers were operated for the disease at that time.^{3,4} The commonest site involved in the boy is the natal cleft while the disease can also effect the web spaces of fingers, abdomen, neck, scalp and axilla.⁵ Pilonidal sinus has been reported to affect between 26-700 patients per 100000 population with the peak sufferers being young patients between 15-24 years of age. The disease was reported to affect 8.8% of Turkish

military personnel.^{2,6} A number of surgical procedures have been advocated by surgeons across the globe. They include minimally invasive techniques like sinusectomy or video-assisted endoscopic ablation procedure (EPSiT); wound excision and laying open; and closure techniques like Karydakis repair, Limberg flap, VYZ plasty, oval flap technique and Bascom cleft lift procedures amongst others.⁷⁻⁹

The lack of consensus on one technique highlights the lack of a gold standard procedure with studies reporting variable outcomes. An ideal procedure should completely cure the disease with minimum complications and should have minimal or no recurrence.² Limberg flap and Karydakis repair are two of the most widely performed procedures for pilonidal sinus disease. Both techniques consist of closure of natal cleft away from midline to avoid trapping of hair.^{10,11}

MATERIALS AND METHODS

This randomized controlled trial was carried out at Department of Surgery, Central Park Teaching Hospital Lahore from 1st July 2016 to 30th June 2017. Two hundred and four patients presenting with pilonidal sinus disease were included. They were divided in two groups; Limberg flap and Karydakis repair groups respectively. All the patients included in the study were operated on elective list. Inclusion criteria included patients of either gender presenting

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with sacrococcygeal pilonidal sinus; with age ranging from 15 to 60 years, and having ASA grade I to III. All those patients who presented with a concurrent abscess; recurrent pilonidal sinus; concurrent perianal pathology like fistula in ano; ASA grade IV and V; diabetes mellitus and compromised immune status were excluded from the study sample. The details of surgery were explained to the patients and both the group of patients were operated by the same surgical team. All the operations were carried out in Jack knife position under spinal anesthesia. The operative site was shaved before surgery and a dose of 1.2 grams of Augmentin (Amoxicillin and clavulunite) as prophylactic antibiotic was administered before anesthesia. Methylene blue dye was injected to delineate all the tracks of the pilonidal sinus. Patients in Group L were operated by the Limberg flap technique while Group K patients underwent surgery by the Karydakakis repair technique. In the Limberg flap group, a rhombus shaped area including the pilonidal sinus tract was excised up till the pre-sacral fascia. A rhombus shaped tension free fasciocutaneous flap was then placed to cover the defect as shown in Figure 1. While in the Karydakakis repair group, an elliptical D shaped incision was given and extended down till pre-sacral fascia to excise the pilonidal sinus tract. A double layered closure was then done with the suture line lying away from midline as shown in Figure 2. The operative time was recorded in both groups from the time of skin incision till the application of last stitch at the end of surgery. Both group of patients had a redivac suction drain placed which was removed if the drain output remained less than 20 mL in 24 hours.

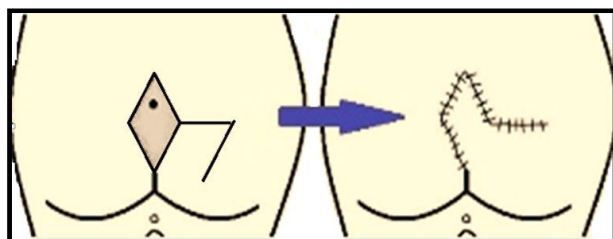


Figure 1: Limberg flap

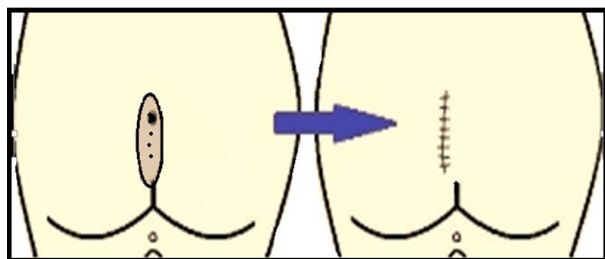


Figure 2: Karydakakis Repair

Postoperative complications that were assessed in both groups included postoperative pain according to the visual analogue scale; development of hematoma, seroma or surgical site infection and dehiscence. Pain score was determined on the 28th postoperative day for

comparison between the two groups. Patients were examined on the follow-up visits weekly in the first month and monthly thereafter. Any complications found on examination including wound dehiscence, hematoma formation, seromaformation, and surgical site infection were documented and adequately managed as required. Patients were also followed for development of recurrence within 3-6 months of surgery. The data was analyzed using through SPSS-25.

RESULTS

The overall mean age of patients included in our study was 27.21 ± 8.24 years. The mean age of patients in Group L was 28.06 ± 8.71 years while in Group K, the mean age of patients was 26.36 ± 7.69 years ($p=0.142$). The study comprised predominantly of male patients with the male to female ratio being 1:0.23. The distribution of patients according to gender is depicted in Table 1. The difference between the two groups was not significant ($p=0.281$).

The mean operation time was 45.81 ± 10.06 minutes. In Limberg flap, the mean operation time was 50.59 ± 9.1 minutes with a range 30-66 minutes while in karydakakis repair, the mean operation time was 41.04 ± 8.63 minutes with a range 26-62 minutes. The difference between the groups was found to be significant ($p<0.001$). The pain and discomfort was determined by the mean visual analogue score on the 28th postoperative day for comparison between the groups. The mean VAS pain score was 2.51 ± 1.16 the Limberg flap group versus a score of 3.19 ± 1.45 in the Karydakakis repair group, the difference between the groups being statistically significant ($p<0.001$). As regards the overall complications, 24 patients (23.53%) in Limberg flap, and 19 patients (18.63%) in karydakakis repair developed complications. The difference between the two groups was statistically non-significant ($p=0.391$). The frequency of different complications is shown in Table 2.

Table No. 1: Frequency of genders in both groups (n=204)

Gender	Limber Flap		Karydakakis Repair	
	No.	%	No.	%
Male	86	84.3	80	78.4
Female	16	15.7	22	21.6

Table 2: Distribution of complications (n=204)

Complication	Limber Flap		Karydakakis Repair	
	No.	%	No.	%
Wound dehiscence	16	15.9	6	5.9
Hematoma	8	7.8	3	2.9
Seroma	6	5.9	4	3.9
SSI	3	2.9	8	7.9
None	69	67.5	81	79.4

The most common complication observed in the study sample was wound dehiscence which was found in 15 patients (14.7%) in Limberg flap and 6 patients (5.9%) in Karydakakis repair, the difference being statistically

significant ($p=0.038$). The comparison of individual complications has been expressed in Table 3.

Table No.3: Summary of results

Variable	Limberg Flap	Karydakís Repair	p value
Overall complications	24 (23.53%)	19 (18.63%)	0.391
Wound Dehiscence	15 (14.71%)	6 (5.88%)	0.038
Hematoma	6 (5.88%)	3 (2.94%)	0.306
Seroma	3 (2.94%)	4 (3.92%)	0.701
Surgical site infection	9 (8.82%)	7 (6.86%)	0.602
Recurrence	9 (8.82%)	5 (4.90%)	0.268

DISCUSSION

Sacroccocygeal pilonidal sinus is a common disease of young adults with the disease having predilection for military personnel, and drivers. A number of surgical procedures have been practiced across the globe with variable success rates. The disease is notorious for recurrences and procedure related complications. It affects the individual's productivity by causing a loss of work days and also increases the financial burden. Very few studies have compared Limberg flap with Karydakís repair in the Pakistani population.

In our study the overall mean age of patients was 27.21 ± 8.24 years. A study by Bostanoglu et al¹² reported the a comparable mean age of patients to be 27.3 ± 9.1 years for Limberg group and 26.2 ± 6.5 years for Karydakís group. Another national study on pilonidal sinus by Jabbar et al¹³ reported the mean age of patients 27.40 ± 5.90 years for Limberg flap group. Similarly Abdelraheem et al¹⁴ reported a mean age of 27.4 ± 6.2 years, while Bali et al¹⁵ reported a mean age of 25 and 23.5 years for the two groups respectively. Ahmed et al¹⁶ also reported a slightly higher mean age of 32.2 ± 9.8 years for Limberg flap and 33.6 ± 9.7 years for Karydakís repair groups respectively. Male patients comprised of 81.37% patients in our study. Bostanoglu et al¹² and Bessa et al¹⁷ reported a higher frequency of males with 95.49% and 93.33% patients respectively.

We found a statistically significant lesser operative time with the Karydakís repair technique as compared to Limberg flap technique ($p<0.001$). Similarly Bali et al¹⁵ reported that the mean operative time was 48 minutes for Karydakís repair versus 54 minutes for Limberg flap with the difference being statistically significant ($p=0.001$). Bessa et al¹⁷ also reported that the mean operative time for Karydakís technique was 33 minutes versus 52 minutes for Limberg flap which was statistically significant ($p<0.001$). Ates et al¹¹ also reported similar findings with a significantly less operative time of 42.32 ± 8.64 minutes with Karydakís repair versus 50.14 ± 6.96 minutes for Limberg flap group ($p=0.001$). On the contrary a study by Tokac et al⁶ in 2015 reported that the mean operative time was 42.9 ± 6.2 minutes for Karydakís repair versus 44.5 ± 6.6 minutes for Limberg flap with a non-significant difference ($p>0.05$). Arslan et al¹⁸ also reported an operative time of 51.1 ± 6.8 minutes for Limberg flap

and 50.9 ± 7.3 minutes for Karydakís repair with the difference being non-significant ($p>0.05$).

Coming over to the complications, patients reported a higher pain score after 4 weeks of surgery in the Limberg flap group as compared to Karydakís repair group ($p<0.01$). Similarly Ates et al¹¹ reported a VAS pain score of 3.23 ± 1.14 in Limberg flap group versus a VAS score of 2.22 ± 1.01 in the Karydakís repair group on the 30th postoperative day with a statistically significant difference ($p=0.001$). On the contrary, Bali et al¹⁵ reported that the mean pain score of 2 was significantly lower in the Limberg flap group versus a score of 4 in the Karydakís repair group ($p<0.001$).

There was no difference in the overall complications between the two groups. We only found a statistically significant difference in the frequency of wound dehiscence between the two groups which was also the commonest complication as well ($p=0.038$). No difference was found in terms of frequency of hematoma formation, seroma formation and surgical site infection between the two groups ($p>0.05$).

Comparable results were reported in a study by Bessa et al¹⁷ reported complications were observed in 23.3% patients in Karydakís repair group versus 40% patients in Limberg flap group. The difference was statistically non-significant ($p=0.08$). None of the patients reported full thickness wound disruption or dehiscence in Karydakís group versus 15% patients in Limberg group which was statistically significant ($p=0.003$). The difference between the two groups in terms of wound infection ($p>0.99$) and fluid collection or seroma formation ($p=0.24$) was also comparable to our study. Tokac et al⁶ also reported that wound infection was noticed in 6.6% in Limberg flap group versus 6.5% Karydakís repair group, the difference being statistically non-significant ($p>0.05$).

Another multicenter randomized controlled trial by Can et al also reported an overall complication rate of 12.9% in Limberg flap group versus 10.3% in Karydakís repair group with a statistically non-significant difference ($p=0.467$). The frequency of wound infection was 3.9% in Limberg flap group versus 4.4% in Karydakís repair group. Similarly the frequency of wound dehiscence was 2.6% in Limberg flap group versus 2.9% in Karydakís repair group. Lastly the frequency of seroma formation was 2.6% in Limberg flap group versus 1.5% in Karydakís repair group respectively.¹⁹ Another study by El Hadidi et al from Egypt also reported non-significant difference between the two groups in terms of complications ($p=0.44$).²⁰

Contrary to our results, a study by Bali et al¹⁵ reported that the frequency of hematoma formation was 21.6% in Limberg flap versus 8.82% in Karydakís repair with a statistically significant difference ($p=0.004$). Similarly 23.53% patients developed wound infection in Karydakís group versus 10.8% in Limberg flap which was also statistically significant ($p=0.001$). Lastly the study reported that 2.7% patients developed wound dehiscence in Limberg flap group versus 5.88% patients in Karydakís repair group which was statistically non-significant ($p=0.590$). Arslan et al¹⁸ also reported a statistically significant difference between Limberg flap

group and Karydakias repair group in terms of seroma formation ($p=0.002$). However the results of wound infection ($p=0.322$) and hematoma formation ($p=0.919$) were comparable to our study.

We followed our patients for a mean duration of 6 months and found that the frequency of recurrence varied by a non-significant difference between the two groups ($p=0.268$). Can et al¹⁹ also reported that the recurrence rate was 5.4% in Limberg flap group versus 4.8% in Karydakias repair group with a non-significant difference ($p=1.000$). Ates et al⁶ reported a recurrence rate of 3.1% with Karydakias repair and 6.9% with Limberg flap, but the difference was statistically non-significant ($p=0.151$). (11) Comparable results were reported by Tokac et al⁶ who reported a recurrence rate of 6.5% with Limberg flap and 4.4% with Karydakias repair ($p>0.05$). On the contrary, Arslan et al¹⁸ reported a recurrence rate of 6.3% with Limberg flap and 11.0% with Karydakias repair, with the difference being statistically significant (0.027).

On the basis of our findings, we favor the Karydakias repair technique for being simpler, quick to perform and having comparable results to the Limberg flap technique for sacrococcygeal pilonidal sinus. Studies on pilonidal sinus are limited in our population. Our study had a healthy sample size of 204 patients. The limitation of the study was the shorter follow up duration. We also did not compare the patients on the basis of number of sinuses and infection at the time of presentation. We recommend more studies on the topic with longer follow up durations and inclusion of more variables to ascertain the better technique in terms of management of pilonidal sinus disease..

CONCLUSION

Both Limberg flap and Karydakias repair are effective surgical options for the management of pilonidal sinus disease. The two techniques have a comparable complication and recurrence rate. However Karydakias repair stands out as the better technique in terms of lesser operation time and lesser frequency of wound dehiscence while Limberg flap technique is associated with lesser post-operative pain.

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Determine the Outcomes of External Rectal Prolapse

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ABSTRACT

Objective: To determine the outcomes in patients with external rectal prolapse.

Study Design: Observational study

Place and Duration of Study: This study was conducted at the Department of General Surgery, Bhatti International Teaching Hospital and Central Park Hospital, Lahore from 01-06-2016 to 30-11-2017.

Materials and Methods: Thirty patients above age of 12 years both males and females with complete rectal prolapse were included. Patients who were below the age of twelve years, recurrent prolapse, colorectal cancer, with medical issue like renal failure, acute disease of liver were excluded. Patients with lower gastrointestinal symptoms e.g. pain, something coming out from anus, bleeding per rectum and tenesmus were diagnosed on history basis and examination. Resection, Wells rectopexy and thiersch stitch was performed in patients

Results: There were 22 (73.33%) male patients and 8 (26.67%) female patients. Wells Rectopexy was done in 25 patients, thiersch stitch was applied in 2 patient and 3 patients had anterior resection. Post-operative complications such as pelvic abscess found in 2 (6.67%), constipation in 6 (20%) patients and wound infection in 2 (6.67%) patients. Recurrence found in 1 (3.33%). No mortality was recorded.

Conclusion: The Wells rectopexy was the safe and effective procedure with very low rate of complications.

Key Words: Wells rectopexy, Prolene mesh, Complete rectal prolapse, Anterior resection

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INTRODUCTION

Complete rectal prolapse is the protuberance of all rectal layers by the anal sphincters.¹ Treatment of rectal prolapse depends on the severity of the disorder. Degree of severity is categorized into complete full thickness, mucosal and occult prolapse.²⁻³ The most common clinical presentation of rectal prolapse is protrusion. Severe constipation, incomplete evacuation, bleeding, pain and incontinence are other major symptoms of this disorder.⁴ In prolapse patients, fecal incontinence and constipation are reported in 75% and 30 to 50%.⁵ Among the main reasons of rectal prolapse are history of obstetric trauma and previous anorectal surgery. Rectal prolapse is found in both the pediatric and adult population. Elderly women between 50 to 70 years have high rate of incidence as compared to men.⁶

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Men with ages 20 to 35 years have high rate of incidence.⁷

Pelvic floor weakness, a usually related phenomenon, is possibly secondary to reoccurring incident of prolapse or strain over prolonged periods.⁸

Many surgical options have been described for the treatment of complete rectal prolapse. Most of the earlier techniques have been deserted by surgeons because of their unfavorable long term outcomes. Presently the operation in practice is to fix the rectum to sacrum. Rectopexy is the most prevalent procedure in United Kingdom, firstly described by Wells in 1959.⁹ We desire to state the experience of complete rectal prolapse in 30 patients.

MATERIALS AND METHODS

This observational study was conducted at Department of General Surgery, Bhatti International Teaching Hospital and Central Park Hospital, Lahore from 01-06-2016 to 30-11-2017. Thirty patients of both genders were selected for this study. Patients with complete rectal prolapse and above the age of 12 years were included in this study. Patients who were below the age of twelve years, recurrent prolapse, colorectal cancer, with medical issues like renal failure, acute disease of liver were excluded from the study. The patients were admitted from outpatient and emergency department or in some cases referred from other primary and secondary centers. All 30 patients with lower gastrointestinal symptoms e.g. pain, something coming out from anus, bleeding per rectum and tenesmus were

diagnosed on basis of history and examination including proctosigmoidoscopy. Necessary related laboratory analysis was done. Patients were kept on clear fluids a day before the surgery and mechanical bowel preparation was done. We performed anterior resection, thiersch stitch and wells abdominal rectopexy. Prolene mesh was used where required. Postoperatively intravenous antibiotic and analgesic were given for five days and then shifted to oral medication. The patients were monitored carefully and judicious follow up was done after discharge for the development of complications. All the data was analyzed using SPSS 20.

RESULTS

Out of 30 patients, 22 (73.33%) were male patients and 8 (26.67%) were females (Table 1). Five (16.67%) patients were ages <20 years, 13 (43.33%) patients were ages between 21 to 30. years, 6 (20%) patients were ages 31 to 40 years, 3 (10%) patients had ages 41 to 50 years and 3 (10%) had ages above 50 years (Table 2). Five (16.67%) patients had symptoms duration <2

Table No.1: Frequency of genders (n=30)

Gender	No.	%
Female	8	26.67%
Male	22	73.33%

Table No.2: Frequency of age

Age(years)	No.	%
<20	5	16.66
21 to 30	13	43.33
31 to 40	6	20.0
41 to 50	3	10.0
>50	3	10.0

Table No.3: Frequency of duration of symptoms

Duration of symptoms (years)	No.	%
>4	7	23.33
2 – 4	18	60
<2	5	16.67

Table No.4: Frequency of repair type

Repair type	No.	%
Wells Posterior rectopexy	25	83.33
Anterior resection	3	10
Thiersch Stitch	2	6.67

Table No.5: Post-operative complications

Complication	No.	%
Constipation	6	20
Wound Infection	2	6.67
Pelvic Abscess	2	6.67
Recurrence	1	3.33

years, 7 (23.33%) had duration >4 years and 18 (60%) had duration 2 to 4 years (Table 3). Wells rectopexy was done in 25 (83.33%) patients, anterior resection in 3 (10%) patients and thiersch stitch was applied in 2

(6.67%) patients (Table 4). Post-operative complication such as pelvic abscess found in 2 (6.67%), constipation in 6 (20%) patients and wound infection in 2 (6.67%) patients. Recurrence found in 1 (3.33%). No mortality was recorded (Table 5).

DISCUSSION

There is no ideal and standard procedure to treat complete rectal prolapse. One unanimous opinion that we have managed to grasp is that abdominal procedures are linked with a low reappearance rate than perineal one which was also demonstrated by Habr-Gama et al¹⁰ in their study. Abdominal procedures are linked with high morbidity and preferred for young patients with no comorbidities as stated by Madoff¹¹ and Kim et al.¹² On the other hand, perineal procedures are linked with low morbidity but have high reappearance rate and therefore, should be considered in elderly patients with comorbidities. Abdominal rectopexy is the most favored procedure by many surgeons due to low morbidity and recurrence as we also prove in this study. Though literature states that prolapse is a predominantly female disease in our study as compared to 26.67% female patients, 73.33% were male patients, which may be clarified on the basis of our male dominating society and also failure to seek medical advice by female patients. Huber et al¹³ and Boutsis et al¹⁴ also prove the male dominance in their studies.

Regarding the presentation no difference was noted between both genders and something coming out of the anus was the chief complaint in our series. Only in 6.7% patients peroperative bleeding was noticed which was because of sutures placement in presacral fascia resulting in injury to veins. By manual pressure & packing the bleeding was secured successfully. Another complication noted peroperatively was difficulty in placement of meshes which was probably due to diverse anatomy as Magruder et al¹⁵ documented in his study.

Constipation is a major postoperative drawback of abdominal rectopexy. A high incidence of postoperative constipation 50% is reported by previous studies and also documented by Shamim¹⁶ and Gomes et al.¹⁷ Post-operative constipation occurred in 6 (20%) patients in our study, which was successfully treated with enriched fiber diet and use of bulk forming agents. Adequate outcome regarding postoperative constipation can be explained by the fact that we preserved the lateral rectal ligaments and nervi erigentes in our study. The sensitivity of rectum was thus not impaired in patients after operation as documented by Portier et al.¹⁸ We observed that it is significant to spare lateral ligaments. In the present study, wound infection was found in 6.7% patients and pelvic abscess in 6.7% patients. These patients were treated successfully with antibiotics but their hospital stay got prolonged. There was one week median hospital stay during our study. At one

week total 90% patients were discharged while 10% patients were discharged on seventeenth postoperative day. In our study, recurrence was observed in only one patient at 4 months follow up who had been treated with perineal technique. This patient was later reoperated and underwent Wells rectopexy..

CONCLUSION

Technically feasible procedure is Wells abdominal rectopexy with nil rate of reappearance, improved continence and shorter hospital stay in most patients. Continence grade in patients significantly increase and constipation is treated successfully with enriched fiber diet and use of bulk forming agents..

Author's Contribution:

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Ventral Hernia Repair: Compare the Outcomes of Onlay Versus Sublay Mesh Procedure

Amna Shahab¹, Muhammad Aqil Razzaq² and Muhammad Tanvir Iqbal³

ABSTRACT

Objective: To examine the outcomes of onlay mesh technique and sublay mesh technique in patients undergoing ventral hernia repair and compare the findings between both procedures.

Study Design: Randomized control study.

Place and Duration of Study: This study was conducted at the Department of General Surgery, CMH Lahore from August 2017 to July 2018.

Methods: One hundred and forty patients of both genders having ages 18 to 70 years who were undergoing ventral hernia repair were included. Patients were equally divided into two groups Group A and Group B. Group A patients received onlay mesh technique and Group B received sublay technique. Outcomes such as post-operative pain, wound infection, seroma formation and hospital stay were recorded and the results compared between both groups.

Results: There were 39 (55.71%) and 37 (52.86%) female patients in Group A and B respectively. Paraumbilical hernia was the commonest type between both groups. There was significant difference in terms of post-operative pain 5.23 ± 1.54 vs 3.01 ± 1.01 (P-value < 0.05), wound infection found in 11 (15.71%) vs 5 (7.14%) patients in both groups. 6 (8.57%) patients in Group A and 2 (2.86%) patients in Group B had seroma formation ($p = < 0.05$). Mean Hospital stay in days was high in Group A patients compared to Group B 4.01 ± 1.95 vs 2.01 ± 0.65 ($p = < 0.05$).

Conclusion: Sublay mesh technique for ventral hernia repair was safe and effective with very low rate of complications as compared to onlay mesh procedure.

Key Words: Ventral Hernia Repair, Onlay Mesh Technique, Sublay Mesh Technique, Outcomes

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INTRODUCTION

Repair of ventral hernia is one of the most commonly performed surgical procedure. These may be congenital or acquired i.e. can occur during or after pregnancy, or as a result of weakening of abdominal muscles following abdominal incision.¹ Incidence ranges from 10-20% after abdominal surgery.^{2,3} Mesh repair has improved surgical outcomes as compared to primary repair. However post-operative complications after hernia repair still exist and advancements are being made to reduce their frequency.

Sublay and onlay mesh repair are two most popular techniques of ventral hernia repair. In onlay technique mesh is secured on exposed anterior rectus sheath while in sublay technique mesh is secured between the rectus sheath and peritoneum.^{4,5}

Commonly reported complications after ventral hernia repair are wound infections, recurrence, mesh infections, seroma and fistula formation.⁶

Sublay technique is more beneficial as compared to the onlay technique as it has a lower rate of recurrence and wound complications. However, sublay technique requires more expertise, longer operative time and sometimes it is associated with chronic abdominal pain.^{8,9,10} Many studies have been conducted to examine the outcomes of onlay and sublay mesh repair technique for ventral hernia repair but still there is controversy for the choice of technique. The present study was conducted to examine the outcome of onlay and sublay mesh technique and compare the findings between both techniques..

MATERIALS AND METHODS

This study was conducted at Department of General Surgery, CMH, Lahore from 1-08-2017 to 31-07-2018. One hundred and forty patients of both genders between 18 to 70 years of age who were undergoing ventral hernia repair were included after informed consent.

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Patients less than 18 years, those not signed the consent and patients with chronic liver disease were excluded. Patients were randomly allocated into two groups Group A and Group B. Group A had 70 patients who underwent onlay mesh technique whereas Group B also had 70 patients who received sublay technique. Surgery was performed under general anaesthesia and Prolene mesh was used. All patients received a 2nd generation Cephalosporin at the time of induction of anaesthesia and for two post-operative days. Outcomes such as post-operative pain, wound infection, seroma formation and hospital stay were recorded and the results compared between both groups. Data was analyzed by SPSS 20. Student t-test and Chi-square test was applied. P-value <0.05 was set as significant difference.

RESULTS

There were 39 (55.71%) females and 31 (44.29%) male patients in Group A and 37 (52.86%) females and 33 (47.14%) males in Group B. Mean age of patients in Group A was 46.85±8.42 years and in Group B it was 47.95±9.75 years (Table 1).

Para-umbilical hernia was most common type found in 34 (48.57%) patients in Group A and 36 (51.43%) patients in Group B followed by incisional in 15 (21.43%) and 14 (20%) in Group A and B, epigastric in 12 (17.14%) and 13 (18.57%) in both groups and umbilical in 9 (12.86%) and 7 (10%) in both groups respectively (Table 2).

Table No.1: Age and gender wise distribution

Variable	Group A	Group B	P-value
Mean age	46.85±8.42	47.95±9.75	>0.05
Gender			
Male	31 (44.29%)	33 (47.14%)	>0.05
Female	39 (55.71%)	37 (52.86%)	>0.05

Table No.2: Type of ventral hernia among both groups

Types	Group A	Group B	P-value
Paraumbilical	34 (48.57%)	36 (51.43%)	>0.05
Incisional	15 (21.43%)	14 (20%)	>0.05
Epigastric	12 (17.14%)	13 (18.57%)	>0.05
Umbilical	9 (12.86%)	7 (10%)	>0.05

Table No.3: Postoperative outcomes between both groups

Outcomes	Group A	Group B	P-value
Post-op pain	5.23±1.54	3.01±1.01	0.002
Wound Infection	11 (15.71%)	5 (7.14%)	0.05
Seroma	6 (8.57%)	2 (2.86%)	0.32
Mean Hospital Stay (days)	5.01±1.95	3.01±1.65	0.024

There was significant difference in terms of post-operative pain 5.23±1.54 vs 3.01±1.01 (P-value <0.05). Wound infection rate was high in Group A patients than Group B 11 (15.71%) vs 5 (7.14%). 6 (8.57%) patients in Group A and 2 (2.86%) patients in Group B developed seroma (p=<0.32). Mean Hospital stay in

days was high in Group A patients compared to Group B 5.01±1.95 vs 3.01±1.65 [p=<0.05] (Table 3).

DISCUSSION

Surgical treatment of ventral hernia is one of the most performed surgical procedure all over the world.¹¹ Ventral hernia repair with lesser complications is challenging for surgeons and many advancements have been made to avoid complications.^{12,13} Mesh technique is considered as effective and safe with very low rate of complications. Sublay and onlay are two most commonly used techniques of mesh placement during hernia repair. According to some studies sublay technique should be declared as gold standard because there is less risk of mesh infections and seroma formation.^{14,15} Present study was conducted to examine the outcomes of both techniques. In this study total 140 patients underwent ventral hernia repair. We randomly allocated patients in two groups. There were 39 (55.71%) females and 31 (44.29%) males in Group A and 37 (52.86%) females and 33 (47.14%) males in Group B. Mean age of patients in Group A was 46.85±8.42 years and in Group B it was 47.95±9.75 years. A study conducted by Ahsan et al¹⁶ reported female patients population was high in number as compared to males 64% in onlay group and 60% in sublay groups with mean age 51.4±9.8 years and 52.3±10.1 years. Some other studies demonstrated female patients population was high as compared to males and most of patients were ages 30 to 50 years.¹⁷

In present study para-umbilical hernia was most common type in both groups followed by incisional, epigastric and umbilical hernia. These results were similar to many other studies in which para-umbilical was the most common type of ventral hernia repaired 50 to 60% followed by incisional and umbilical.^{18,19}

In our study we found that there was significant difference in terms of post-operative pain 5.23±1.54 vs 3.01±1.01 (P-value <0.05). Wound infection rate was high in Group A patients than Group B 11 (15.71%) vs 5 (7.14%). 6 (8.57%) patients in Group A and 2 (2.86%) patients in Group B developed seroma (p=<0.32). Mean Hospital stay in days was high in Group A patients compared to Group B 5.01±1.95 vs 3.01±1.65 (p=<0.05). These results were comparable to many other studies regarding ventral hernia repair in which sublay mesh technique was demonstrated as effective and safe procedure in terms of postoperative pain, wound infection and seroma formation as compared to onlay mesh procedure.²⁰⁻²²

CONCLUSION

Sublay mesh technique for ventral hernia repair was safe and effective in term of postoperative pain, wound infection and seroma formation with less hospital stay as compared to onlay mesh procedure..

Author's Contribution:

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Success of External Cephalic Version and Frequency of Cesarean Section in Patients

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ABSTRACT

Objective: Frequency of success in patients undergoing external cephalic version and assesses rate of C-section after successful external cephalic version.

Study Design: Descriptive Case Series.

Place and Duration of Study: This study was conducted at the Department of Obstetrics & Gynaecology, M. Islam Medical College Gujranwala from October 2018 to March 2019.

Materials and Methods: Seventy patients with gestational ages between 34 to 40 weeks were included. Patients underwent external cephalic version in labour room by a single consultant.

Results: 58% patients underwent successful external cephalic version and 41% patient's external cephalic version were not successful. Among patients undergoing successful external cephalic version, 39% were delivered by cesarean section and 61% were delivered by spontaneous vaginal delivery. There was no maternal and fetal complication noted.

Conclusion: External cephalic version is a safe and effective treatment modality with high rate of success and also effective for reducing the rate of cesarean sections.

Key Words: External cephalic version, Frequency, Cesarean section

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INTRODUCTION

External cephalic version (ECV) is a procedure in which a fetus that is lying in a breech position is turned so that the head enters the birth canal first.¹ External cephalic version is considered safe and effective method of turning the baby from breech to head first.² It is very useful and effective methods for reducing the frequency term breech delivery also helpful for reducing the complications associated to term breech presentation. In developing and developed countries ECV is considered effective for reducing the rate of cesarean delivery.³

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Breech presentation is associated with increase rate of morbidity and mortality, it complicates 3 to 4% of term deliveries. It is a most common risk factor of preterm deliveries. From last two decades the rate of C-sections has been increased due to breech presentation. Globally the rate of cesarean deliveries is increases due to breech presentation.⁵ Several studies demonstrated that External Cephalic Version is safe and effective for reducing the rate of cesarean deliveries.⁶ Approximately 8% of primigravid women has spontaneous version rate after 36 weeks of gestation.⁷ Success rates of ECV is accounted 30 to 80% and less than 5% of women after successful ECV has reversion of spontaneous breech presentation.^{8,9}

The success rates for ECV vary widely but ranges from 35-86% (average 58%). Approximately 47% of women whom had received ECV had a cephalic presentation at birth. Studies reported that multiparous women had a high rate of successful ECV as compared to nulliparous.¹¹ The success of ECV depends upon various factors. Race, parity, uterine tone, liquor volume, engagement of breech, whether the head is palpable and the use of tocolysis all effects the success rate of ECV.¹² The success rate of ECV is increased by the use if tocolysis and increase in success rate is evident with epidural but not with spinal analgesia.¹³

External Cephalic Version has fewer rate of complications. No major complications have been reported due to ECV. Many of previous studies reported that ECV procedure is very safe and effective

for lowering the rate of cesarean deliveries with no major complications.¹⁴

This study focuses on the success of ECV and reducing the frequency of cesarean sections in these pts. Thus decreasing the morbidity, expenditure and hospital stay of the patients..

MATERIALS AND METHODS

This descriptive case series was carried out at Department of Obstetrics & Gynaecology, M. Islam Medical College Gujranwala from 1st October 2018 to 31st March 2019. Seventy pregnant females with breech presentation undergoing ECV were included. Patients 20-35 years of age with any parity, gestational age between 34-40 weeks, breech presentation, singleton pregnancy, thin and relax abdominal wall were included. Women with placenta previa, confirmed on scan, history of anti-partum hemorrhage, IUGR, significant fetal anomalies, ruptured membranes, elective cesarean section is indicated and previous one cesarean section were excluded. Patients were explained aims, methods, benefits and potential hazards of the study. Subjects were informed that their participation was voluntarily and that they may withdraw at any time during the study. An informed consent was taken. The patient was instructed to empty her bladder first and then was allowed to rest and relax on the couch with a mild degree of head down tilt. The whole procedure was explained to the patient in a sympathetic manner to allay her anxiety. An USG was performed to confirm the presenting part, fetal cardiac activity and location of placenta. Fetal wellbeing was assessed by NST. The breech was then held in right hand while the left hand was placed over the fetal head. A sustained pressure was applied by both hands simultaneously in the direction which would promote fetal flexion and simultaneously rotating the fetus. After that, the attitude of the fetus was maintained manually for few minutes. No analgesia, anesthesia or sedation will be used during the procedure. After that, an USG was performed to confirm the fetal position. CTG was performed to assess the fetal well being. The patient was made to lie on the couch for about 15-30min. If NST was fine and the patient was stable, she was sent and followed in OPD after one week to confirm the presenting part. She was counselled about signs and symptoms of labor. Her labour was monitored and maternal outcome was noted in the form of cesarean section. The data was analysed using SPSS-20..

RESULTS

The parity and gestational age of patients undergoing external cephalic version showed in Tables 1-2. There were 41 (58.5%) patients were successful external cephalic version and 29 (41.5%) were failed external cephalic version (Table 3). Regarding mode of delivery in patients with successful external version, 16 (39%)

patients were caesarean delivery and 25 (61%) normal vaginal delivery (Table 4).

Table No. 1: Parity of patients undergoing ECV (n=70)

Parity	No.	%
PG	30	42.9
Para 1	19	27.1
Para 2	11	15.7
Para 3	5	7.1
Para 4	4	5.7
Para 5	1	1.5

Table No.2: Patients undergoing ECV according to gestational age (n=70)

Gestational age (weeks)	No.	%
34-36	45	64.3
37 – 38	23	32.8
39-40	2	2.9

Table No.3: Results of ECG (n=70)

ECV	No.	%
Successful	41	58.5
Failed	29	41.5

Table No.4: Mode of delivery in pts with successful ECV (n=41)

Mode of delivery	No.	%
Cesarean delivery	16	39.0
Normal vaginal delivery	25	61.0

DISCUSSION

External cephalic version is one of the safest procedures of decreasing the number of cesarean section due to breech presentation. Success rates will be higher when the pt. presents one or more good prognostic factors, as described previously.¹⁵ Globally, ECV is considered a cost effective procedure in the management of breech presentation at term; however there is a wide variation in the success rate, with a range between 30-80%, the ECV technique has remained unchanged for many generations without any modifications.¹⁶

In the present study, success of ECV was about 58%. This observation is similar to those of Ranjon¹⁷, Wise et al¹⁸, but differ from Ben-Meir et al¹⁹ and Rauf et al.²⁰ On the other hand, the success rate of ECV in this study was higher than those done by Nassar et al²¹ and Zeck et al.²²

In this study, among the successful ECVs, 61% were delivered vaginally which differ from the study of Zeck et al²² and Wise et al¹⁸, who reported much more cases who deliver vaginally after successful ECV. As discussed earlier, in this study following successful ECV, spontaneous vaginal delivery was attained by 61% and 39% underwent cesarean section due to various indications, which was slightly different from the study done at Hayatabad Medical Complex Peshawar, which shows that after successful ECV, spontaneous vaginal delivery was attained in 77.7% of the pts.²⁰

As far as the parity in success of ECV is concerned, this study shows that ECV was more successful in multi gravidas, i.e. 76% as compared to nulliparous women which was just 24%. These findings were slightly different from those of Ben-Meir et al¹⁹ in which success rates were 72.3% and 46.1% in multi-paras and nulli-paras respectively.

There were no complications related to ECV in this study, as also seen in the study of Grootsholten et al²³, but in the study of Flamm et al²⁴, there was a risk of detectable fetomaternal hemorrhage during ECV in 2.4% of cases and in the study of Collins et al²⁵, there was 0.5% risk of emergency cesarean section after the procedure.

The study also shows that beginning of ECV between 34-35 wks may have some benefit in terms of decreasing the rate of non-cephalic presentation and cesarean section, as also shown in the study of Hutton EK & Hofmeyr GJ.²⁶

CONCLUSION

External cephalic version is very useful and effective method for reducing the rate of cesarean deliveries. We concluded from this study that the rate to successful External cephalic version rate is 58% and it is satisfactory and comparable to other studies. Also we found that after ECV the rate of normal vaginal deliveries was high and this procedure concluded safe and effective for reducing the rate of C-sections. No major complication and mortality was recorded.

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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 Wound Infection And Hospital Stay Between Primary Closure And Delayed Primary Closure In Patients With Perforated Appendicitis

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ABSTRACT

Objective: To compare the outcomes of primary closure and delayed primary closure in term of wound infection and hospital stay in patients treated perforated appendicitis.

Study Design: Comparative study.

Place and Duration of Study: This study was conducted at the Department of General Surgery, Bhatti International Teaching Hospital and Central Park Hospital, Lahore from September 2017 to August 2018.

Materials and Methods: Eighty patients of both genders with ages >15 years with clinical suspicion of perforated appendicitis which was later confirmed peroperatively were included in this study after written consent. Patients were randomly divided into two groups and were scheduled for conventional appendectomy. Group I consist of 40 patients in which wound was closed primarily at the time of surgery. Group II consist of 40 patients and underwent delayed primary closure on 3rd post-operative day. Outcomes such as wound infection and hospital stay were analyzed.

Results: In Group I 21 (52.5%) were males and 19 (47.5%) were females with mean age 35.21 ± 9.80 years while in Group B 23 (57.5%) were males and 42.5% were females with mean age 36.25 ± 10.45 years. Wound infection was found in 18(22.5%) patients. 14 patients in Group-I as compared to 4 patients in Group II (delayed primary closure). Patients with primary closure had less hospital stay as compared to patients with delayed primary closure 5.35 ± 1.02 vs 7.65 ± 1.15 days p-value 0.002.

Conclusion: Patients treated with primary closure had high rate of wound infection as compared to delayed primary closure and patients with primary closure had less hospital stay as compared to patients with delayed primary closure.

Key Words: Perforated appendicitis, Primary closure, Delayed primary closure, Wound infection, Hospital stay

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INTRODUCTION

One of the commonest reason of emergency abdominal surgery is acute appendicitis. It is more common in males with a male to female ratio of 1.3:1. The incidence of appendicitis is at its peak in early childhood.¹

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Thereafter it decreases with age. Perforated appendix tends to occur more in males and also at extremes of ages.²

Luminal obstruction is the main causative factor in the perforation of appendix whereas fecoliths are implicated in about 90% of the cases.^{3,4} There are many contributing factors, the most important being the late presentation of the patients.⁵ Among the many postoperative complications wound infection is the most common and its incidence substantially increases with the severity of the appendicitis treated, particularly after emergency appendectomy for perforated appendicitis.^{6,7}

The method of skin closure is an important factor influencing post-operative wound infection. Two commonly used methods are delayed primary closure (DPC) and primary closure (PC) however there is no consensus as to the optimal method. Management of contaminated wounds by keeping them open has been practiced for centuries.⁸ Bhangu et al¹⁰ advocate the primary closure of all appendectomy wounds under good antibiotic cover, despite data suggesting that

contaminated wounds have a higher rate of wound infection.

The present study was conducted to examine the outcomes of primary closure and delayed primary closure in terms of wound infection and duration of hospital stay in patients with perforated appendicitis undergoing appendectomy.

MATERIALS AND METHODS

This comparative study was conducted in the Department of General Surgery, Bhatti International Teaching Hospital and Central Park Hospital, Lahore from 1st September 2017 to 31st August 2018. In this study total 80 patients of both genders with clinical suspicion of perforated appendicitis which was later confirmed peroperatively were included after written consent. Patients less than 15 years of age, cirrhotic and diabetic, and pregnant women were excluded. Patients were randomly allocated into two groups. All the patients received conventional appendectomy under general anesthesia. A standard dose of antibiotic was given intravenously preoperatively and continued for 3 days postoperatively. Group I of 40 patients was the Primary Closure group in which external oblique was closed by continuous vicryl I. Wound was washed with normal saline and skin closed with interrupted prolene stitches. Group II of 40 patients was delayed primary closure group in which skin was left open. Daily dressing was done till the 3rd postoperative day and skin closed. Appendectomy wound in all patients was examined daily and noted particularly on 3rd, 5th and 7th postoperative day for development of infection. Wound infection was managed by antibiotics, dressings and removal of stitches as the need may be. Outcomes measures were wound infection and hospital stay. Data was analyzed by SPSS 21.0. Chi square test and student t' test was used to compare the findings among both groups. Consider p-value <0.05 as statistically significant.

RESULTS

Table No.1: Age and gender-wise distribution among both groups (n=80)

Variable	Group I	Group II	P value
Mean age	35.21±9.80	36.25±10.45	>0.05
Gender			
Male	21 (52.5%)	23 (57.5%)	>0.05
Female	19 (47.5%)	17 (42.5%)	>0.05

In Group I 21 (52.5%) were males and 19 (47.5%) Females with mean age 35.21±9.80 years while in Group II 23 (57.5%) were males and 17 (42.5%) females with mean age 36.25±10.45 years (Table 1). Post-operatively wound infection was found in 18 (22.5%) patients while 62 (77.5%) patients did not develop wound infection. 14 (35%) patients in Group I as compared to 4 (10%) patients in Group II (delayed primary closure) had infection of wound (Table 2).

Patients with primary closure generally had less hospital stay as compared to patients with delayed primary closure 5.35±1.02 vs 7.65±1.15 days p-value 0.002. Development of wound infection prolonged the hospital in both groups (Table 3).

Table No.2: Comparison of wound infection among both groups (n=80)

Wound infection	Group I	Group II	Total
Yes	14 (35%)	4 (10%)	18 (22.5%)
No	26 (65%)	36 (90%)	62 (77.5%)

P-value 0.001

Table No.3: Comparison of hospital stay

Hospital stay (days)	Group I	Group II	P value
	5.35±1.02	7.65±1.15	0.002

DISCUSSION

Acute appendicitis is an extremely common surgical emergency and appendectomy is the most performed surgical procedure all over the world.¹¹ Wound infection is a common complication occurring after appendectomy and the type of wound closure influences its occurrence to a considerable extent. We conducted this study to evaluate the outcomes in terms of wound infection and hospital stay of primary closure and delayed primary closure after appendectomy in patients with perforated appendicitis. In this study 80 patients of perforated appendicitis who underwent appendectomy were included. The patients were randomly allocated into two equal groups, Group I underwent Primary Closure and Group II Delayed Primary Closure of the wound. 55% patients were male while 45% patients were female with mean age 36.01±11.65 years. These results were similar to many other studies in which male patients was higher in number as compared to female.^{12,13} Abou-Nukta et al¹⁴ have reported a high population of female patients.

In the present study, we found that 18 (22.5%) patients developed wound infection on 5th post-operative day. Patients who received primary closure were more prone to wound infection 35% as compared to delayed primary closure group 10%. A study conducted by Ali et al¹⁵ reported that patients who received primary closure after appendectomy had higher rate of wound infection 36.67% as compared to patients who received delayed primary closure 6.67%. Chiang et al¹⁶ demonstrated that primary closure was associated with low infection rates following appendectomy for perforated appendicitis.

In our study, we observed that patients with primary closure had shorter hospital stay as compared to patients with delayed primary closure 5.35±1.02 vs 7.65±1.15 days (p-value 0.002). In comparison to the other study length of hospital stay was 2.30±0.51 and 3.94±0.84 days in primary closure and delayed primary closure patients after appendectomy.¹⁷

Meka and Anasuri¹⁸ reported a low infection rate in delayed primary closure 2.9% versus primary closure 38.9% which is comparable with our study. However in contrast to our study the hospital stay was shorter in DPC versus PC.

CONCLUSION

Wound infection after appendectomy is one of the major complications that increase the length of hospital stay and treatment cost. We concluded from this study that patients treated with primary closure had high rate of wound infection as compared to delayed primary closure and patients with primary closure had shorter hospital stay as compared to patients with delayed primary closure..

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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Study the Correlation Between Serum Intact Parathyroid Hormone Levels and Erythropoiesis Resistance Index (ER) in Patients on Maintenance Hemodialysis (MHD)

Parathyroid &
Erythropoiesis
Levels in
Hemodialysis
Patients

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ABSTRACT

Objective: To find the correlation between serum intact parathyroid hormone levels and erythropoiesis resistance index (ER) in patients on Maintenance Hemodialysis (MHD)

Study Design: Analytical / Cross-Sectional Study

Place and Duration of Study: This study was conducted at the Dialysis Center and Nephrology OPD of Idris Teaching Hospital, Sialkot Medical College Sialkot from May 2018 to May 2019.

Materials and Methods: About 70 chronic kidney disease patients presenting to the Dialysis Unit and OPD Department and fulfilling the selection criteria were enrolled. Serum iPTH levels were measured by taking a fasting venous sample. Hb was calculated from CBC. ERI was calculated by the formula mentioned earlier. Data were used to calculate the correlation between iPTH levels and ERI using Karl Pearson coefficient with statistically p-value <0.05. Data were stratified for Age, Gender, BMI and Duration of MHD to address effect modifiers. Post stratification Pearson's correlation was applied with p-value < 0.05 was considered as significant.

Results: The mean age of the patients was 43.82 ± 15.89 years. 16(22.9%) of the patients had age 16-35 years, while 32(45.7%) and 22(31.4%) of patients had ages between 36-55 and >55 years respectively. Gender distribution showed that 48(68.6%) were males while 22(31.4%) were females. The mean duration of patients on maintenance hemodialysis was 5.45 ± 1.12 years. The mean BMI of patients on maintenance hemodialysis was 28.3 ± 6.36 . The mean iPTH and ERI was 67.54 ± 22.69 and 9.11 ± 4.24 respectively.

Conclusion: It was concluded that intact parathyroid hormone levels (iPTH) is positively correlated with erythropoiesis resistance index (ERI) in patients on Maintenance Hemodialysis (MHD).

Key Words: intact parathyroid hormone levels (iPTH), erythropoiesis resistance index (ERI), Maintenance Hemodialysis (MHD)

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INTRODUCTION

Anemia in chronic kidney disease (CKD) is very common; especially when the effective glomerular filtration rate (eGFR) is less than $35 \text{ ml/min/1.73m}^2$. The main cause of anemia of CKD is decrease Erythropoietin (EPO) production by the kidneys.

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By the invention of Erythropoietin Stimulating Agents (ESAs), there is significant reduction in the requirement of blood transfusions in patients of CKD.^{1,2,3,4,5} Normally the erythropoietin is produced by peritubular interstitial fibroblasts in outer medulla and deep cortex. Hypoxia is a main stimulus for EPO production. EPO is essential for production and maturation of erythrocytes. There are different guidelines for target hemoglobin in ESRD. Generally accepted one is KDIGO. They recommend target Hb level is 10-12g/dl in ESRD. They also recommend the initiation of ESAs if Hb is less than 10g/dl, and can be initiated when Hb is above 10g/dl to improve the quality of life, they don't recommend the use of ESAs to increase Hb above 11.5g/dl due to increase mortality.^{2,6,7,8,9} While some studies suggest the level of 13g/dl is associated with increase in mortality due to thrombosis, hypertension and cardiovascular events.^{3-4,10-14} In spite of extensive use of ESAs, 7-14% of all patients with End Stage Renal Disease (ESRD) show suboptimal or no response to ESAs (i.e. the desired Hemoglobin concentration is not

achieved and remains below 10g/dl).^{5,16-18} There are several factors which can be the cause of ESAs non responsiveness. These include active inflammation, vitamin B12 deficiency,⁶ folate deficiency, malignancies, secondary hyperparathyroidism hyperphosphatemia⁷ and iron deficiency.⁸ However if these conditions are excluded, there is significant proportion of patients who still exhibit Primary ESA-resistant anemia. Intact parathyroid hormone is a marker of bone marrow suppression and previous studies have shown positive correlation between iPTH and erythropoiesis resistance index with a correlation coefficient 0.76 and p-value of < 0.001.⁹ This study is designed to see the correlation between iPTH and primary resistance to ESAs (by measuring ERI) in patients on Maintenance Hemodialysis (MHD) in our population. This will help up to guide management of anemia in patients on maintenance dialysis.

MATERIALS AND METHODS

This cross-sectional analytical study with non-probability consecutive sampling was conducted at Dialysis Center and Nephrology OPD of Idris Teaching Hospital, Sialkot Medical College Sialkot during May 2018 to May 2019.

Sample size: Sample size of 70 cases was calculated with 5% type I error and 10% type II error and taking expected correlation of 0.76 between intact PTH and ERI in patients on maintenance hemodialysis.⁹

RESULTS

A total of 70 patients fulfilling the inclusion/exclusion criteria were enrolled in the study to calculate the correlation between iPTH and ERI in patients on maintenance hemodialysis. The mean age of the patients was 43.82±15.89 years. 16(22.9%) of the patients had age 16-35 years, while 32(45.7%) and 22(31.4%) of patients had ages between 36-55 and >55 years respectively. Gender distribution showed that 48(68.6%) were males while 22(31.4%) were females. The mean duration of patients on maintenance hemodialysis was 5.45±1.12 years. The mean BMI of patients on maintenance hemodialysis was 28.3±6.36. The mean iPTH and ERI was 67.54±22.69 and 9.11±4.24 respectively. There was a positive correlation between iPTH levels and ERI with a Karl Pearson correlation coefficient of 0.370 with p-value 0.02. When stratified for age, the correlation coefficient between iPTH levels and ERI was 0.078 (p=0.77), 0.026 (p=0.92) and 0.930 (p=0.0001) in patients aged 16-35, 36-55 years and >55 years respectively. After stratifying the data for gender the correlation coefficient between iPTH levels and ERI was 0.650 (p=0.001) in males and 0.020 (p=0.92) in females. When stratified with respect to duration of MHD, the correlation coefficient between iPTH levels and ERI was 0.294 (p=0.03) in patients having MHD for >2 years, while the coefficient was 0.036 (p=0.88) and 0.204

(p=0.32) in patients having MHD for 2-4 years and >4 years respectively. When stratified with respect to BMI, the correlation coefficient between iPTH levels and ERI was 0.096 (p=0.67) in patients having BMI 19-24, while the coefficient was 0.743 (p=0.002) and 0.687 (p=0.2) in patients having BMI for 25-29 and 30-39 respectively.

Table No.1: Frequency distribution of Gender

Gender	Frequency	Percent
Male	48	68.6
Female	22	31.4
Total	70	100.0

Table No.2: Frequency distribution of Age groups

Age Groups	Frequency	Percent
16-35	16	22.9
36-55	32	45.7
>55	22	31.4
Total	70	100.0

Table No.3: Frequency distribution of BMI

BMI	Frequency	Percent
19-24	31	44.3
25-29	34	48.6
30-39	5	7.1
Total	70	100.0

Table No.4: Frequency distribution of Duration of MHD

Duration of MHD	Frequency	Percent
<2 years	25	35.7
2-4 years	20	28.6
>4 years	25	35.7
Total	70	100.0

Table No.5: Mean±S.D of different variables

Statistics	Age	BMI	iPTH	ERI
Mean	43.83	28.30	67.54	9.11
Std. Deviation	15.90	6.37	22.70	4.24
Minimum	16.00	19.00	31.00	2.00
Maximum	70.00	39.00	112.00	15.00

Table No.6: Correlation Between iPTH levels and ERI

Correlation Between iPTH levels and ERI	n	70
	r	0.370
	p-value	0.02

n= number of patients r = correlation co-efficient

Table No.7: Stratification with respect to Gender of Correlation Between iPTH levels and ERI

Correlation Between iPTH levels and ERI in Males	n	48
	r	0.650
	p-value	0.001
Correlation Between iPTH levels and ERI in Females	n	22
	r	0.020
	p-value	0.92

n= number of patients r= correlation co-efficient

Table No.8: Stratification with respect to Age groups of Correlation Between iPTH levels and ERI

Correlation Between iPTH levels and ERI in 16-35 age group	n	16
	r	0.078
	p-value	0.77
Correlation Between iPTH levels and ERI in 36-55 age group	n	32
	r	0.026
	p-value	0.92
Correlation Between iPTH levels and ERI in >55 age group	n	22
	r	0.930
	p-value	0.0001

n= number of patients r= correlation co-efficient

Table No.9: Stratification with respect to BMI groups of Correlation Between iPTH levels and ERI

Correlation Between iPTH levels and ERI in 19-24 BMI group	n	31
	r	0.096
	p-value	0.67
Correlation Between iPTH levels and ERI in 25-29 BMI group	n	34
	r	0.743
	p-value	0.002
Correlation Between iPTH levels and ERI in 30-39 BMI group	n	5
	r	0.687
	p-value	0.200

n= number of patients r= correlation co-efficient

Table No.10: Stratification with respect to Duration of MHD of Correlation Between iPTH levels and ERI

Correlation Between iPTH levels and ERI in <2 years duration of MHD	n	25
	r	0.294
	p-value	0.03
Correlation Between iPTH levels and ERI in 2-4 years duration of MHD	n	20
	r	0.036
	p-value	0.880
Correlation Between iPTH levels and ERI in >4 years duration of MHD	n	25
	r	0.020
	p-value	0.328

n= number of patients r= correlation co-efficient

Inclusion Criteria: (1)Age >16 years and < 70 years (2) ESRD patients with Hemodialysis thrice a week for more than 3 months(3)Patients on weight based erythropoietin for at least 8 weeks(4)Hemoglobin <12 g/dl

Exclusion Criteria: (1)Patients having transferrin saturation < 30%.(2)Patients having vitamin B12 levels < 200 pg/ml(3)Patients having plasma folate levels < 4.5 ng/ml(4)Patients with history of myocardial infarction in the previous 3 months.(5)Patients with history of malignancy and active infection.

DISCUSSION

Anemia of ESRD is a multi-factorial disorder.^{19,20} There is some evidence suggesting that elevated levels of parathyroid hormone may inhibit the endogenous production of erythropoietin or the responsiveness to

erythropoietin.^{21,22} In our present study, we found that patients on MHD had positive correlation between iPTH value and ERI. Meyteset al²³ stated that iPTH directly inhibits human peripheral blood erythroid colony formation. Furthermore, ERI levels and blood reticulocytes were noted to be dramatically increased one to two weeks after parathyroidectomy in some HD patients.^{24,25} These results were matched with the results from Shih et al,²⁶ who found that the iPTH levels in MHD patients had the better responsiveness to ERI. Age >55 years had any influence on the responsiveness to ERI in our study. This is in agreement with the results from Jinn et al,¹⁰⁵ who found an influence of age >60 years, and Ishimura et al²⁷ suggested that Obesity is a risk factor for the severity of anemia in patients with renal failure not yet receiving dialysis. Power et al^{5,6} stated that the ERI response to anemia in the elderly is not similar to that in the young. In contrast, Yun et al^{6,7} found that a reduced ERI response to anemia could explain the anemia present in diabetics having no advanced diabetic nephropathy. Kario et al^{1,2} suggested that a decreased ERI responsiveness to low iPTH in the elderly. A higher percentage of male gender was found in this study; however, a direct causal relation or association between male gender and hyperparathyroidism needs further clarification.

CONCLUSION

It was concluded that intact parathyroid hormone levels (iPTH) is positively correlated with erythropoiesis resistance index (ERI) in patients on Maintenance Hemodialysis (MHD).

Author's Contribution:

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

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Study of the frequency of Hypomagnesemia in Hemodialysis patients using Proton Pump Inhibitors (PPI)

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ABSTRACT

Objective: To study the frequency of Hypomagnesemia in Hemodialysis patients using Proton Pump Inhibitors (PPI)

Study Design: Observational Study

Place and Duration of Study: This study was conducted at the Idrees Teaching Hospital of Sialkot Medical College, Sialkot from January 2018 to January 2019.

Materials and Methods: A total of 135 patients were selected in Hemodialysis Unit, Idris teaching Hospital, Sialkot with proper written informed consent. Information was then collected using Performa. Participants were selected through non probability consecutive sampling technique. Samples for serum magnesium levels were taken immediately before dialysis. Serum magnesium levels were measured using photometric methods.

Results: A total of 135 patients fulfilling the inclusion/exclusion criteria were enrolled in the study to calculate the frequency of hypomagnesemia in End Stage Renal Disease patients using PPI.

Conclusion: We conclude that frequency of hypomagnesemia in hemodialysis patients using PPI is 79.3%.

Key Words: Hypomagnesemia, Hemodialysis, Proton pump inhibitors

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INTRODUCTION

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation. It is one of the most essential elements in the human body and is involved in majority of the metabolic processes. Magnesium plays pivotal role in mitochondrial function, inflammatory and immune processes and stress. It regulates neuromuscular transmission, cardiac excitability, vasomotor tone and blood pressure¹.

Average daily intake of magnesium in an adult is about 360 mg. Various factors modify intestinal magnesium absorption like serum magnesium and calcium levels, activity of aldosterone and atrial natriuretic peptide (ANP)².

Magnesium is excreted mainly through the kidneys and also to some extent through intestine.

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Normal daily magnesium elimination through the kidneys is 100mg³. Hypomagnesemia is a very important and usually under diagnosed electrolyte abnormality. Hypomagnesemia has been found to have detrimental effects in critically ill patients. It is associated with other electrolyte abnormalities like hypocalcemia, hypophosphatemia and hypokalemia, and leads to neuromuscular abnormalities including hyperexcitability and respiratory muscle weakness⁴. Hypomagnesemia can be caused by decreased magnesium intake, redistribution of magnesium into the cells, increased intestinal and renal losses. Drugs like proton pump inhibitors, aminoglycosides, amphotericin B and cyclosporine are notorious in causing hypomagnesemia⁵. Proton pump inhibitors (PPI) are one of the most commonly used drugs. They are used for the treatment of gastroduodenal ulcers, gastroesophageal reflux and H. pylori eradication. PPI are routinely used in hemodialysis patients for the relief of symptoms of uremic gastritis. PPI is a documented cause of hypomagnesemia⁶.

In the face of decreased oral magnesium intake, normally there is increased active intestinal absorption of magnesium, which is mediated by the transient receptor potential melastatin-6 (TRPM6) and -7 (TRPM7) transport system. This prevents the development of hypomagnesemia when dietary intake is low. PPIs impair intestinal magnesium

absorption by disrupting active transport by TRPM 6 and 7 channels. PPIs lower the gut pH, which in turns decrease the affinity of TRPM channels with magnesium⁷.

Hypomagnesemia has been associated with increased cardiovascular and all-cause mortality in hemodialysis patients.

MATERIALS AND METHODS

It was a cross sectional study. : Study was conducted in Hemodialysis Unit, Idris Teaching Hospital Sialkot
Sample size: The sample size was of 135 by using 95% confidence level, 7% margin of error with expected percentage of hypomagnesemia in ESRD patients using PPI to be 79%. It was non-probability consecutive sampling.

Inclusion criteria:

1. Patient having age ≥ 18 years and ≤ 80 years.
2. Patients who were on twice weekly maintenance hemodialysis for at least 1 year.
3. Patients who were using PPI for at least 3 months.

The minimum doses of PPI was:

- A)Omeprazole 20 mg daily(B)Esomeprazole 20 mg daily(C)Lansoprazole 15mg daily
(D)Pantoprazole 20mg daily

Exclusion criteria:

1. Patients who had history of chronic diarrhea in the preceding 3 months.
2. Patients with history of heavy alcohol consumption.
3. Patients with serum calcium levels ≥ 10.5 mg/dl
4. Patients using any loop or thiazide diuretics.
5. Patients with history of Parathyroidectomy in the preceding 3 months.

Data collection: Patients were selected in Hemodialysis Unit, Shaikh Zayed Hospital Lahore with proper written informed consent. Information was then be collected using Performa (as shown in Annexure I).Participants were selected through non probability consecutive sampling technique.

Samples for serum magnesium levels were taken immediately before dialysis. Serum magnesium levels were measured using photometric methods.

Data Analysis: Data was entered and analyzed in SPSS v23.0. Quantitative variables include age, duration of dialysis and duration of PPI use and were expressed as mean \pm standard deviation. Qualitative variables include gender and presence of hypomagnesemia and were expressed as frequencies and percentages. Data was stratified for age, gender, duration of dialysis, duration of PPI use and type of PPI used to deal with effect modifiers. Post-stratification, Chi-square test was used. $P \leq 0.05$ will be considered significant.

RESULTS

A total of 135 patients fulfilling the inclusion/exclusion criteria were enrolled in the study to calculate the

frequency of hypomagnesemia in End Stage Renal Disease patients using PPI. The mean age of the patients was 52.42 ± 13.63 years. 50.4 % (n=68) of the patients had age 18-49 years, while 49.6 % (n=67) of patients had age 50-80 years.(Table No. 1).

Gender distribution shows that 60% (n=81) were males while 40 % (n=54) were females. (Table No. 2). The mean duration of dialysis was 6.28 years. (Table No. 3) The mean duration of PPI use was 10.31 months. (Table No. 4). The frequency of use of different types of PPI was Omeprazole 20.7 %, Esomeprazole 50.4%, Lansoprazole 19.3% and pantoprazole 9.6%. (Table 5).

The frequency of hypomagnesemia in hemodialysis patients using PPI was 79.3% (n=107) (Table No. 6).

When stratified with respect to age 44.8% (n=48) of the patients with hypomagnesemia had age 18-49 while 55.2% (n=59) had age 50-80 years. (Table No. 7).

When stratified with respect to gender 63.5% (n=68) of the hypomagnesemic patients were males and 36.5% (n=39) were females. (Table 8). When data was stratified with respect to duration of dialysis, 42.9% (n=46) of patients had duration of dialysis 1-6 years while 57.1% (n=61) had duration of dialysis 7-12 years. (Table 9).

When data was stratified with respect to duration of PPI use, 54.2% (n=58) of patients had duration of dialysis 1-9 months while 45.8% (n=49) had duration of dialysis 10-18 months. (Table 10). When data was stratified with respect to the type of PPI used, it showed that 57.1% (n=16) of patients using omeprazole developed hypomagnesemia, 76% (n=52) of patients using esomeprazole developed hypomagnesemia, 100% (n=26) of patients using lansoprazole developed hypomagnesemia while 100% (n=13) of patients taking pantoprazole also developed hypomagnesemia. (Table 11).

Table No. 1: Age Distribution (n=135)

Age(in years)	No. of patients	%
18-49	68	50.4
50-80	67	49.6
Total	135	100
Mean \pm SD	52.42 \pm 13.63	

Table No. 2: Gender Distribution (n=135)

Gender	No. of patients	%
Male	81	60
Female	54	40
Total	135	100

Table No. 3: Mean Duration of Dialysis (n=135)

Duration of Dialysis (Years)	Mean	SD
	6.28	3.10

Table No. 4: Mean Duration of PPI use (n=135)

Duration of PPI use (Months)	Mean	SD
	10.31	4.36

Table No. 5: Frequency of use of different types of PPIs (n=135)

Type of PPI	Frequency	Percentage
Omeprazole	28	20.7%
Esomeprazole	68	50.4%
Lansoprazole	26	19.3%
Pantoprazole	13	9.6%
Total	135	100.0%

Table No. 6: Frequency of hypomagnesemia in hemodialysis patients using PPI (n=135)

Hypomagnesemia	Frequency	Percentage
Yes	107	79.3%
No	28	20.7%
Total	135	100.0%

Table No. 7: stratification frequency of hypomagnesemia in hemodialysis patients using PPI with respect to age (n=135)

Hypomagnesemia	Age		Total
	18-49	50-80	
Yes	48	59	107
No	20	8	28
Total	68	67	135

Table No. 8: Stratification frequency of hypomagnesemia in hemodialysis patients using ppi with respect to gender (n=135)

		Gender		Total
		Male	Female	
Hypomagnesemia	Yes	68	39	107
	No	13	15	28
Total		81	54	135

Table No. 9: Stratification frequency of hypomagnesemia in hemodialysis patients using ppi with respect to duration of dialysis (N=135)

		Duration of dialysis		Total
		1-6 years	7-12 years	
Hypomagnesemia	Yes	46	61	107
	No	22	6	28
Total		68	67	135

Table No. 10: Stratification frequency of hypomagnesemia in hemodialysis patients using ppi with respect to duration of PPI use (n=135)

		Duration of PPI use		Total
		1-9 months	10-18 months	
Hypomagnesemia	Yes	58	49	107
	No	22	6	28
Total		80	55	135

Table No. 11: Stratification frequency of hypomagnesemia in hemodialysis patients using PPI with respect to type of PPI used (n=135)

		PPI used				Total
		Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole	
Hypomagnesemia	Yes	16	52	26	13	107
	No	12	16	0	0	28
Total		28	68	26	13	135

DISCUSSION

This cross sectional study was carried out to calculate the frequency of hypomagnesemia in hemodialysis patients using PPI. PPI are widely used in ESRD patients for the treatment of dyspepsia and uremic gastritis. They have been associated with the development of hypomagnesemia, which is associated with significant cardiovascular mortality in ESRD patients.

A total of 135 patients fulfilling the inclusion/exclusion criteria were enrolled in the study to calculate the frequency of hypomagnesemia in End Stage Renal Disease patients using PPI.

The mean age of the patients was 52.42 ± 13.63 years. 50.4 % (n=68) of the patients had age 18-49 years, while 49.6 % (n=67) of patients had age 50-80 years. Gender distribution shows that 60 % (n=81) were males while 40 % (n=54) were females. The mean duration of dialysis was 6.28 years.

The mean duration of PPI use was 10.31 months. The frequency of use of different types of PPI was Omeprazole 20.7 %, Esomeprazole 50.4%, Lansoprazole 19.3% and pantoprazole 9.6%.

The frequency of hypomagnesemia in hemodialysis patients using PPI was 79.3% (n=107). This figure is in accordance with previous studies. When stratified with respect to age 44.8% (n=48) of the patients with hypomagnesemia had age 18-49 while 55.2% (n=59) had age 50-80 years. These figures show that frequency of hypomagnesemia is not dependent on age of the patient. When stratified with respect to gender 63.5% (n=68) of the hypomagnesemic patients were males and 36.5% (n=39) were females. Hypomagnesemia turned out to be more common in males than in females.

When data was stratified with respect to duration of dialysis, 42.9% (n=46) of patients had duration of dialysis 1-6 years while 57.1% (n=61) had duration of dialysis 7-12 years. Thus hypomagnesemia was more common in patients with long duration of dialysis. When data was stratified with respect to duration of PPI use, 54.2% (n=58) of patients had duration of dialysis 1-9 months while 45.8% (n=49) had duration of dialysis 10-18 months. Duration of duration of PPI use had no effect on frequency of hypomagnesemia.

When data was stratified with respect to the type of PPI used, it showed that 57.1% (n=16) of patients using omeprazole developed hypomagnesemia, 76% (n=52) of patients using esomeprazole developed hypomagnesemia, 100% (n=26) of patients using

lansoprazole developed hypomagnesemia while 100% (n=13) of patients taking pantoprazole also developed hypomagnesemia. Frequency of hypomagnesemia was more common in patients using lansoprazole and pantoprazole. In this observational study, Our data suggest an overall trend toward hypomagnesemia and increased all-cause mortality and CV mortality in HD patients on PPIs. Our findings are consistent with those of previous studies that also found increased hazards of CV disease and death with PPI use in other populations. Maggio et al. investigated the relationship between PPI use and study outcomes in patients 65 years or older who were discharged from acute care medical wards.^{9,10,11,12,13} The authors concluded that high-dose PPI use was associated with increased 1-year mortality. Charlot et al. studied aspirin-treated patients with first-time myocardial infarction and found that treatment with PPIs was associated with an increased risk of adverse CV events.^(10,14-16) Bell et al. observed that baseline PPI use was associated with all-cause mortality in 2 cohorts of institutionalized older persons.^{11,17-20}

CONCLUSION

We conclude that frequency of hypomagnesemia is 79.3% in hemodialysis patients using PPI.

Author's Contribution:

Concept & Design of Study:	Salman Yaqoub
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The Effect of Pre-Infarct Angina on Post-Myocardial Infarction Left Ventricular Ejection Fraction in Patients of Acute ST-Elevation Myocardial Infarction Treated With Streptokinase

Shehzad Ahmad, Asif Ali and Anwaar-ul-Hasan

ABSTRACT

Objective: To determine the effect of pre-infarct angina on post-MI left ventricular function in patients with acute STEMI.

Study Design: Comparative study

Place and Duration of Study: This study was conducted at the Department of Cardiology, Bahawal Victoria Hospital, Bahawalpur, from May 2018 to October 2018.

Materials and Methods: Two hundred and thirty patients admitted to the Cardiology Department with the diagnosis of acute STMI who subsequently received thrombolytic therapy were enrolled in the study. The data were recorded on a performa which included demographic characteristics, history of risk factors for coronary artery disease, time from symptom onset to presentation; and the presence or absence of pre-infarction angina. All the enrolled patients underwent 2-dimensional echocardiography to assess left ventricular ejection fraction before discharge. The data was entered and analyzed with SPSS version 20. The patients were divided into two groups depending upon the presence or absence of pre-infarct angina. The categorical variables were compared between the two groups with chi-square test. The left ventricular ejection fraction was compared between the two groups with two-tailed t-test. A p value of <0.05 was considered to be significant.

Results: Pre-infarct angina was present in 58.7 % of the patients. There were no significant differences with regards to baseline characteristics in patients who experienced pre-infarct angina as compared to those who didn't have pre-infarct angina. Post-MI ejection fraction was significantly higher in patients who experienced pre-infarct angina.

Conclusion: The patients with pre-infarct angina have better post-MI left ventricular ejection fraction.

Key Words: Pre-infarct angina, Post-MI left ventricular ejection fraction

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INTRODUCTION

Transient myocardial ischemic episodes are supposed to protect the myocardium against a subsequent prolonged episode of myocardial ischemia; this is termed ischemic preconditioning (IP).¹ IP is the most potent mechanism of myocardial protection described so far. It has been established by the results of several studies conducted earlier that the pre-infarct angina has an ischemic preconditioning effect.²⁻⁴

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This ischemic pre-conditioning effect as a result of pre-infarct angina, plays an important role in preserving left ventricular function, improving microvascular reperfusion, limiting infarct size and enhancing survival.⁵⁻¹⁰ One possible mechanism of this ischemic preconditioning is that it stimulates adenosine receptors and simultaneously decreases the influx of calcium into the myocardial cells; this leads to reduction in myocardial energy demands and hence limits the extent of myocardial injury.¹¹ Some authors have suggested that ischemic preconditioning increases the likelihood of successful thrombolytic therapy, which results in earlier reperfusion and hence limits myocardial damage.¹² Others have concluded that increases in pressure distal to a subtotal occlusion during episodes of unstable angina likely result in opening and development of thin-walled coronary collateral vessels.¹³ This mechanism apparently plays an important role among diabetic individuals.¹⁴ However, even in the absence of significant collateral circulation, some studies have documented the protective role of

pre-infarct angina. These functional effects in turn result in better post –myocardial infarction left ventricular function, greater regional and global left ventricular functional recovery and account for the favorable clinical outcomes in patients who have experienced pre-infarct angina. In this clinical background, we planned a study to determine the effects of pre-infarct angina on post-myocardial infarction left ventricular function.

MATERIALS AND METHODS

This comparative study was conducted in the department of Cardiology, Bahawal Victoria Hospital, Bahawalpur, from 1st May 2018 to 31st October 2018. The objective of the study was to determine the effect of pre-infarct angina on post-MI left ventricular ejection fraction in patients with acute ST-segment elevation myocardial infarction (STEMI) who underwent thrombolytic therapy with streptokinase given as an infusion of 150,000 Units over one hour. Two hundred and thirty patients admitted to the Cardiology Department with the diagnosis of acute ST-segment elevation myocardial infarction who subsequently received thrombolytic therapy were enrolled in the study. STEMI was defined as chest pain of more than 30 minutes duration with ST-segment elevation ≥ 2 mm in precordial leads V_2 and V_3 , or ≥ 1 mm in all other leads except aVR in at least two leads of a contiguous lead group. Pre-infarct angina was defined as intermittent chest pain or other chest discomfort lasting less than 20 minutes that had occurred within 60 days before presentation to the emergency department for acute myocardial infarction (AMI). This included the patients who had chest pain only within 24 hours before AMI. Patients with valvular heart disease, previous myocardial infarction, cardiomyopathy, contra-indications to thrombolytic therapy, cognitive impairment or diagnosed renal or hepatic impairment were excluded from the study. Contra-indications to thrombolytic therapy included intracranial tumor, previous intracranial hemorrhage, ischemic CVA within three months of admission, recent major surgery within 3 weeks, active bleeding, and severe uncontrolled hypertension refractory to emergency anti-hypertensive therapy. Informed consent was taken from the enrolled patients. The data were recorded on a performa which included demographic characteristics of the patients like age and gender; history of risk factors for coronary artery disease like diabetes mellitus, hypertension, smoking, and family history of ischemic heart disease; time from symptom onset to presentation; and the presence or absence of pre-infarct angina. All the enrolled patients underwent 2-dimensional echocardiography to assess left ventricular ejection fraction before discharge. The data was entered and analyzed with SPSS version 20. The patients were divided into two groups; one comprising

of those who had pre-infarct angina and the other comprising of those who didn't have pre-infarct angina. The categorical variables were compared between the two groups with chi-square test. The left ventricular ejection fraction was compared between the two groups with two-tailed t-test. A p value of <0.05 was considered to be significant.

RESULTS

A total of 230 patients were enrolled in the study, out of which 150 (65.2%) were males. The most common risk factor for coronary artery disease encountered in our study population was hypertension which was found in 162 patients (70.4 %), followed by smoking in 140 patients (60.8 %), diabetes mellitus in 50 patients (21.7 %), and family history of ischemic heart disease in 50 patients (21.7 %). Pre-infarct angina was reported in 58.7 % of the patients (Table 1). There were no significant differences with regards to baseline characteristics including age, gender, risk factors for coronary artery disease like diabetes mellitus, hypertension, smoking, as well as time to presentation in patients who experienced pre-infarct angina as compared to those who didn't have pre-infarct angina (Table 2). Post-MI ejection fraction was significantly higher in patients who experienced pre-infarct angina (Table 3).

Table No 1: Frequency of Pre-infarct angina

Pre-infarct angina	No. of patients	Percent
Yes	135	58.7
No	95	41.3
Total	230	100.0

Table No 2: Baseline characteristics of the patients

Variable	Pre-infarct angina (n=135)	No Pre-infarct angina (n=95)	p Value
Age (yrs)	49.24 \pm 10.45	50.64 \pm 9.88	0.301
Males	85	65	0.392
Diabetes Mellitus	30	20	0.832
Hypertension	97	65	0.575
Smoking	80	60	0.551
Family history	30	20	0.832
Time to presentation (hrs)	4.5 \pm 2.2	4.7 \pm 1.9	0.532

Table No 3: Left ventricular ejection fraction in patients of STEMI with and without pre-infarct angina

	Pre-infarct angina	No pre-infarct angina	p Value
LVEF (%)	44.0 \pm 6.5	35.2 \pm 5.6	0.000

DISCUSSION

The protective role of pre-infarct angina on myocardium is well established. A number of studies¹⁵⁻¹⁷ have reported significantly lesser infarct size, better left ventricular function, and a protective effect on arrhythmias after acute myocardial infarction. Mladenovic et al¹⁵ reported that there was no significant difference in baseline left ventricular ejection

fraction (LVEF) and wall motion score index (WMSI) between the patients having pre-infarct angina as compared to those without pre-infarct angina. However, the recovery of LVEF after a period of 7-12 months was significantly greater in those who had experienced pre-infarct angina. In this background of established importance of pre-infarct angina, its frequency has widely varied between different studies. In Itoh et al,¹⁷ it was 66.36%, while 32.24% in Reiter et al,¹⁶ 45.57% in Kiziltunc et al,¹⁸ and 58.7% in Mladenovic et al.¹⁵ The frequency of pre-infarct angina in our study matches that of Mladenovic et al.¹⁵

Reiter et al¹⁶ reported decreased infarct size as measured with peak creatine kinase level, and greater LVEF assessed by echocardiography within 48 hours of admission in patients who had a history of pre-infarct angina. The results of our study support the results of Reiter et al¹⁶ in that post-MI LVEF was significantly higher in patients who had pre-infarct angina. However, our study differs from that done by Reiter et al¹⁶ because we included the patients who had ischemic chest pain at any time during 60 days prior to admission for acute myocardial infarction, while the study conducted by Reiter et al¹⁶ considered pre-infarct angina as chest pain occurring within 24 hours before admission. Moreover, our study focused on LVEF only, and creatine kinase level was not taken into account.

Our study was limited by the problems in retrieving the proper documentation of previous angina episodes as well as the treatment record. There is a possibility that the drugs prescribed for previous angina episodes may contribute to better LVEF after acute myocardial infarction. Secondly, our study did not take into account the presence of silent ischemia. It is possible that silent ischemia may be present in some of the patients who were labeled not to have pre-infarct angina and may have pre-conditioning effect.

CONCLUSION

The patients with pre-infarct angina have better post-MI left ventricular ejection fraction as compared to those who do not have pre-infarct angina..

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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Outcome of Ureteroscopy (URS) in Paediatric Age at Tertiary Care Hospital

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ABSTRACT

Objective: The aim is to detect the outcome of ureteroscopy in paediatric age group .

Study Design: Cross sectional study.

Place and Duration of Study: This study was conducted at the Tertiary Care Hospital of Sind PMCH Nawabshah from September 2016 to September 2018.

Materials and Methods: Total 30 patients of middle and lower ureteric stones were admitted through OPD of Urology Department for this study. They were optimized accordingly and selected for the procedure of URS. Stones were removed through URS. Stone size and stone free rate was assessed.

Results: A total of 30 patients were included in this study. There were 18(60%) males and 12(40%) females. Sex difference was found. Males were more affected than females. Age ranged from 2 to 10 years. 10 (33.33) patients had stone in middle ureter and 20(66.66%) had in lower ureter. The size of stones was different also. In middle ureter, size of single stones was found from 3 mm to 7 mm and in multiple stones, it was 8 mm to 10 mm. in lower ureter, the size of the stones were from 4mm to 14mm

Conclusion: It can be summed up that ureteroscopy is the best minimally invasive procedure for children with least complications and recurrence.

Key Words: Ureteroscopy, Ureter, Calculi, Paediatric Age.

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INTRODUCTION

Paediatric urolithiasis is uncommon condition with lower incidence of 2-3%. Ureteric stones also establish the little proportion of the urological stones. Now a days, its incidence is rising and its recurrence is increased up to 50% so it is imperative to decide the mode of treatment decided that should be safe, effective and lessens recurrence rate.¹

Ureteroscopy was first performed in 1929 by Young and McKay. In 1970s, rigid ureteroscope was used. It was in 1982 that clinically it was introduced by Perez-Castro Ellendt and Martinez-Pineiro which with passage of time improved a lot and nowadays it is commonly used as minimally invasive procedure.²

The evolution of surgical procedures has revolutionized the methods of treatments. The introduction of

endoscopic options has not only facilitated the mankind but it has also written a new history in the field of urology in the world. Ureteroscopy (URS) has contributed a lot in evolution of the management of urology especially in Paediatric age groups since its first application in 1988 by Ritchey et al.³

Ureteroscopy is of two types that are flexible and rigid fiberoptic. In obstructed kidney, ureteral stent is placed in order to save the kidney by restoring its function by normalizing the hydrostatic pressure, swelling and infection. There are different sizes of ureteral stents varying in length from 24 to 30 cm. they have shapes of Double J or Double pigtail.⁴

A ureteroscopy is the minimal Invasive surgery to cure the stones in the ureter. An instrument called ureteroscope is used to remove the stone from the ureter. The success rate of clearing small stones upto to maximum size of 1.5 cm is 50-80% as compared to lithotripsy. This procedure does not remove larger stones. In this procedure, a small telescope is passed through urethra and into ureter to remove stones.⁵ Mostly, fragmentation is needed so that the fragment stones could be removed through grasping device. Only 10-15% requires surgical therapy. In lower ureteric stones, its successful rate is 95% and 85-90% in upper ureteric stones.⁶

The advantages of URS is the visual inspection of stones, very effective method of removing stones, stricture of ureter and injuries detections, biopsies and capturing of stones by baskets through this scope.⁷

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The complications of URS includes iatrogenic perforation of Urinary Bladder, stuck up of stent, and formation of stricture after weeks or months. Re-implantation is needed when there is major perforation of ureter. Avulsion of ureter is the major complication that is repaired by replacement of ureter by intestine. The common complication is the stent pain that is among 50% of patients. A warm tingling sensation is felt along with pain. An urgency to urinate is also observed among patients with stent.^{8,9}

There are certain risks of undergoing URS which includes urinary tract infection, bleeding for short period of time and burning sensation.¹⁰

The rationale of our study to see the benefits of Ureteroscopy apart from saving patient from the major open surgical interventions and making the patient possible to return early to home and work.

MATERIALS AND METHODS

This study was conducted at urology department of PMC Hospital Nawabshah. All the patients were admitted through Emergency/ urological Outpatient department (UOPD) in Department of Urology Peoples Medical College Hospital Nawabshah. This study was conducted from September 2016 to September 2018. This is tertiary care hospital of Sindh dealing patients of not only Sindh but also other provinces of Pakistan.

A detailed history was taken from the patients regarding the pain in lumbar region, nausea/vomiting, discomfort, blood or pus in urine or any symptom or sign of renal system. Thorough clinical examination is done. Systemic examination included abdominal examination was done. Apart from routine biochemical investigations, radiological assessment was also done. Ultrasound was also obtained to find out the size of kidney, level of obstruction, number of stones if present or any other pathology. Patients were prepared for the required procedure and Ureteroscopy was done in all patients. Most of the patients were discharged after 2 to 5 days and called on for follow up accordingly..

RESULTS

A total of 30 patients were included in this study. There were 18(60%) males and 12(40%) females. Sex difference was found. Males were more affected than females.

Table No 1: Showing The Presence Of Urolithiasis According To Site Size

S.No:	Ureter	No of stones	Size of Stones
1	Middle Ureter	Single	3mm to 7 mm
2	Middle Ureter	Multiple	8mm to 10mm
3	Lower Ureter	Single/multiple	4mm to 14 mm

Age ranged from 2 to 10 years. 10 (33.33) patients had stone in middle ureter and 20(66.66%) had in lower ureter. The size of stones was different also. In middle ureter, size of single stones was found from 3 mm to 7

mm and in multiple stones, it was 8 mm to 10 mm. In lower ureter, the size of the stones were from 4mm to 14mm.

Table No. 2: Showing Size And Site Of Stone With Location.

S.No.	No of patients	%	Site of stone	Size of Stone
1	2	6.66%	Middle Ureter	3-5 mm
2	3	10%	Middle Ureter	6-7 mm
3	5	16.6%	Middle Ureter	7-10mm
4	7	23.33%	Lower Ureter	4-6mm
5	9	30%	Lower Ureter	7mm to 10mm
6	4	13.33%	Lower Ureter	11mm to 14mm
Total	30	100%		

Ureteric stones are common in lower part. In middle ureter, 2(6.66%) patients had 3-5 mm stones, 3(10%) had 6-7 mm and 7-10mm stones were found in 5(16.6%) babies. In lower ureter, 7(23.33%) had stone size from 4mm to 6 mm, 9(30%) had size of stone from 7mm to 10 mm, 4(13.33%) had stone size from 11mm to 14 mm.

Table No 3: Complications Of Urs

S.NO:	Complication	No of Patients	percentage
1	Hematuria	2	6.66%
2	Urinary Infection	3	10%
3	Residual Stones	1	3.33%
Total		6	19.99%

This has also complications that develop post operatively early or late. These were noted within 30 days and readmissions were done within 90 days if needed. Injury to urinary bladder was common in our study and it was among 6 (20%) patients. Urinary infection was observed among 11 (36.66) patients. In only 2 (6.66) patient's blood in urine was found. Not single patients had immediate surgical repair and none of the patients had complained of residual stones.

DISCUSSION

The invention of MIS not in urology but also in other surgical fields has made dramatic changes in postoperative outcomes. The unveiling of ureteroscopy has really made the urolithiasis easy with good outcomes. Generally, the endoscopic treatment is considered to be challenging and is reserved as a salvage treatment option of last resort.¹¹

In symptomatic patients with ureteric stones, the first line therapy considered is Shock Wave Lithotripsy. Now there have occurred concerns about long term effects of SWL on developing kidneys including the risk of renal scarring, hyperoxaluria, hypertension and later on chronic renal failure.¹²

Paediatric Ureteroscopy requires endoscopes with small diameter along with lithotripsy. In a study of 21

patients, 90.7% achieved stone free status. In our study, only 1 (3.33%) residual stone was found within 90 days after admission. Another study revealed stone free rate of 77% and 100%. Their stones were found in lower ureter. Same is found in our study.¹³

Stent placement sometimes causes discomfort. Schuester and coworkers suggested external string stent which can be removed in OPD. They also suggested that stent should be avoided if the procedure lasts less than 90 minutes. In a study of 21 patients, 3 (14.2%) were treated with stents. Kurzrock et al used stents in 29% of his patients. Shroff and Watson did it in 4 out of 13 patients. In our study same results are found, stents are placed 4 out 30 patients.¹⁴

Seldom is morbidity detected with paediatric ureteroscopy. In study, ureteral perforation was found among 4.7% patients but in our study no any such case was found. Another study showed ureteral perforation in 5% of patients.¹⁵

URS is deemed to be the safe procedure for pediatric patients. The failure rates and complications are higher in babies aged less than 6 years. Comparison of PCNL, SWL with URS proved the efficacy of URS and announced it as the suitable for ureteric stones. This is the reason that URS is increasingly being used throughout the world nowadays. Georgescu with colleagues showed the complication rate up to 3.9% but in our study the complication rate is 29.98% only.¹⁶

CONCLUSION

It is concluded that ureteroscopy in paediatric age group is highly beneficial and having good outcomes. It has proved to be the procedure with least complication rate. Residual stones and recurrence was found to be negligible. In hands of expertise, this seems to be the best ever option of treatment in cases of ureteric stones..

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Impact on Creatinine Clearance in Obstructive Kidney After Percutaneous Nephrostomy

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ABSTRACT

Objective: To detect the impact of creatinine clearance after percutaneous nephrostomy done in obstructive kidney at People's Medical College Hospital Nawabshah.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Urological Department and Urology OPD of People's Medical College Hospital Nawabshah from January 2017 to August 2018

Materials and Methods: All the patients were admitted through Emergency/urological Outpatient Department of the Hospital. History, examination and required investigations were done. PCN was done in all patients and outcome was assessed according to the follow up visits.

Results: A total of 70 patients were included in this study. There were 40(57.14%) males and 30(42.86%) females. Age ranged from 12 to 70 years. 15 (21.42%) patients aged from 12 to 15 years. 20 (28.57%) patients were of 17 to 30 years and 35(50%) patients age was from 31 to 70 as is shown in table 1 below. The average age was 35 to 40 years. In 71.42% patients, Pre PCN creatinine was 2-3.5mg/dl but post PCN was 0.8-1.2mg/dl. Pre PCN clearance was 30-35ml/m in 77.14%.

Conclusion: The conclusion is that PCN is the best procedure to revive the function of kidney.

Key Words: Creatinine, Percutaneous Nephrostomy, Clearance.

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INTRODUCTION

Percutaneous nephrostomy is the procedure of interventional radiology by which pelvis of kidney is punctured with help of imaging. Images are obtained by ante grade pyelogram. Calcifications are seen through the contrast. This tube is used to allow the drainage.¹ Percutaneous nephrostomy (PCN) was unveiled by urologist Dr. Willard Goodwin in 1955. It was used as a minimally invasive; radio logically guided temporary or permanent procedural. It is alternative to conventional surgery in patients suffering from hydronephrosis. Since then, it has become a gold standard procedure.²

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Anatomically, kidney is at the level of T12 and L3 vertebrae. Its position at this site can cause injuries to surrounding structures while placing PCN. Injuries can be to pleura, diaphragm, colon, spleen and liver. The most common of these is pleura and diaphragm. The pleura are at the level of lower margin at the level of 12th rib therefore injury is minimized while doing the procedure PCN. Its placement above 12th rib can puncture the diaphragm.^{3,4}

PCN is indicated for drainage, stone treatment, urine diversion and diagnosis of obstruction. It is the procedure of choice when transurethral approach is impossible or has failed to relieve obstructing urinary system due to external factors like pregnancy, carcinoma, cysts, abscesses or urinomas. Internal blockage is due to benign or malignant strictures.⁵ The most common indication of PCN is drainage of obstructed kidney for about 85-90% of all cases. The absence if infection is not indication for emergency placement of the Tube but the time matters. If obstruction exceeds one week, there are less chances of good improvement in renal function. Bilateral nephrostomy is rarely indicated particularly in cases like severe hemorrhagic cystitis and bilateral benign or malignant diseases.⁶

The common indication of emergency PCN is to provide drainage in pyonephrotic kidney with

septicemia with risk of permanent renal dysfunction. In these cases, PCN and D-J stenting is recommended. PCN is mostly done in severe state keeping in view the obstructed and infected ureter. In obese patients with minimal hydronephrosis, transurethral D-J stenting is indicated.⁷

PCN is also used as the first step to approach kidney's collecting system in order to provide access to devices for treating renal stones. It creates a tract by which lasers, ultrasonic probes and retractable baskets are used for mechanical crushing, vaporization and stone removal. Now a day, interventional radiology is using commonly PCN before PCNL. PCN is safe method to treat pregnant lady with nephrolithiasis not manageable on conservative therapy.⁸

Direct percutaneous access to the renal collecting system is the least likely invasive method of treating fistulas, strictures and infections. Pyeloplasty/urethroplasty, stent insertion and direct insertion of medication for treatment of highly resistant infection is done by direct access.⁹

There are certain conditions in which PCN cannot be done. Untreated UTI are relative contraindications. Non dilated system, risk factors of hemorrhage and complications from sedation are also contraindications. In patients with obstructed kidney having renal dysfunction can develop hyperkalemia so hemodialysis should be performed before PCN.¹⁰

The rationale of our study is to detect the outcome of PCN in obstructed kidney and post PCN impact on creatinine clearance.

MATERIALS AND METHODS

This study was conducted at urology department of PMC Hospital Nawabshah. All the patients were admitted through Emergency/ urological Outpatient department (UOPD) in Department of Urology Peoples Medical College Hospital Nawabshah This study was conducted from January 2017 to August 2018. This is tertiary care hospital of Sindh dealing patients of not only Sindh but also other provinces of Pakistan.

A detailed history was taken from the patients regarding the pain in lumbar region, nausea/vomiting, discomfort, blood or pus in urine or any symptom or sign of renal failure. Thorough clinical examination is done. Systemic examination included abdominal examination including inguinal and per rectal examination is done. Palpable mass in lumbar regions were found in majority of the patients.

Apart from routine investigations like blood sugar, blood urea, serum creatinine was done to find out any element of uropathology. Serum electrolytes were also done to see hyponatremia and hyperchloremic metabolic acidosis. Urinalysis showed elevated PH.

Ultrasound was also obtained to find out the size of kidney, level of obstruction, number of stones if present or any other pathology.

Patients were prepared for the required procedure and PCN was done in all patients. Most of the patients were discharged after 2 to 5 days and called on for follow up after 3 to 4 weeks and creatinine clearance was done by the following calculation formula

Creatinine Clearance = $\frac{\text{age(yr)} \times \text{weight(kg)}}{[72 \times \text{serum Cr(mg/dL)}]}$ (multiply by 0.85 for women). All the patients had normal creatinine clearance of 88–128 mL/min for healthy women and 97–137 mL/min for healthy men.

RESULTS

A total of 70 patients were included in this study. There were 40(57.14%) males and 30(42.86%) females. Sex difference was found. Males were victims of this disease more as compared to females..

Table No 1: Age of Patients Percentages

S.No	Age	No of patients	Percentage
1	12 -15	15	21.42%
2	17-30	20	28.58%
3	31-70	35	50%
total		70 n= 70	100%

Age ranged from 12 to 70 years. 15 (21.42%) patients aged from 12 to 15 years. 20 (28.57%) patients were of 17 to 30 years and 35(50%) patients age was from 31 to 70 as is shown in table 1 below. The average age was 35 to 40 years.

This procedure also resulted in some complications that were dealt with accordingly. Major complications occurred 5.69% whereas minor complications ranged up to 67.13%.

Table No. 2: Complications of Patients Percentages

S.No	Complications	No of patients	Percentage
3	Pneumothorax	1	1.42%
4	Hematuria	4	5.71%
5	Infected wound	2	2.85%
Total		7 n=7	9.98%

Table No. 3: Out Come of PCN on Creatinine

S. No.	Pre PCN	Post PCN	No of Patients	Percentage
1	2-3.5 mg/dl	0.8-1.2mg/dl	50	71.42%
2	4.5-5 mg/dl	1.3-1.6mg/dl	15	21.42%
3	5.0-5.5 mg/dl	1.8-2.8mg/dl	5	7.14%

Table No. 4: Out Come of PCN on Clearance/ GFR

S. No.	Pre PCN	Post PCN	No of Patients	Percentage
1	30-35ml/m	60-80ml/m	54	77.14%
2	20-30ml/m	50-60ml/m	13	18.57%
3	10-20ml/m	30-45ml/m	3	4.28%

DISCUSSION

Percutaneous Nephrostomy is the commonly done aimed at diverting the upper urinary system and decompression of the renal collecting system in various clinical scenarios. PCN is the surgical procedure in which renal pelvis is punctured and nephrostomy tube is kept to drain. Though it is the basic urological technique but is challenging technically to place it into appropriate site. It can be done under fluoroscopy, USG or CT guided.¹¹

Surajit Samsol et al conducted study and concluded that by PCN patient is relatively fit for further therapeutic management improving the patients' outcome and quality of life. In a study conducted on outcome of PCN, renal biochemical parameters were assessed on post operative day 1,3 and 7 then 1st and 3rd month. A significant decline was seen in creatinine level with enormous increase in urine output. In our study, 71% patients showed decline in creatinine level and 77% patients showed great improvement in clearance.¹²

There are multiple factors that can influence the function of kidney even after releasing obstruction. These are age, duration of obstruction, function of opposite kidney and compliance of ureter and renal pelvis. Moreover, the factors affecting the kidney function recovery are the presence/absence of infection, use of nephrotoxic agents and contrast materials. But the dysplasia has enormous effect on the recovery of renal function especially in children.¹³

Gillenwater expressed opinion that the best way to detect the level and depth of injury and recoverability is to relieve obstruction with PCN Tube and later on concluding the outcome. In our study, same methodology is applied and renal function recovery was observed in follow up visits. Some investigators are of the opinion that surgical intervention should be done to predict the recovery of the renal function. In one study, the determination of recoverability of the kidney function is done by calculating GFR by MDRD formula due to lack of resources and financial constraints.¹⁴

Recently, new non invasive predictors of recoverability have been suggested like Urinary N acetyl-glucosaminidase and TGF-beta. Still the studies are required to explore its advantages. In one study, the factors predicting the renal function were CT, RS, Pre Rx GFR, Hb, Pre Rx, urine output, presence of infection and co morbid factors. Other variables such as degree of hydronephrosis, time duration between start of disease and intervention were also observed. Same was also seen in our study.¹⁵

To ascertain the obstruction, ultrasonography, intravenous urogram and computed tomogram are suggested. Diagnostic ureteroscopy is also done in doubtful cases. Insertion of PCN is the measurement of creatinine clearance. In our study, ultrasonography was

done in every case but IVU and CT scans were suggested wherever required.¹⁶

Gillenwater considers PCN as the best way to detect the degree of injury and recovery so that obstruction is to be relieved by this temporary procedure to save the life of kidney. Bassiouny has discouraged the placement of this tube in neonates with poor kidney function owing to risk of infection, retraction of renal pelvis and more kidney injury. Some studies have concluded that the age at the time of obstruction occupies significance to detect the damage. Provost et al concludes that immature kidneys are prone to develop pathology as compared to mature ones. Koff and Campbell studies resulted in good recovery in obstructed kidney. Our study also showed excellent results. Bassiouny also showed good recovery in hydronephrotic kidneys of children.¹⁷

CONCLUSION

Percutaneous nephrostomy is the best procedure in our study with good results in obstructed kidneys. It showed good recovery in serum creatinine and clearance indicating the excellent restoration/revival of renal function.

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To Investigate the Effects of Nicotine on Morphology of an In-Vitro Reconstituted Model of Normal Healthy Uninflamed Oral Mucosa

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ABSTRACT

Objective: The objective of this study was to investigate the effect of nicotine on morphology of an uninflamed reconstituted oral mucosa in vitro when treated for 5 minutes and 24 hours respectively.

Study Design: Observational study.

Place and Duration of Study: This study was conducted at the Department of Oral Pathology Bart's and the London Queen Mary School of Med. and Dentistry Queen Mary, University of London from July 2018 to July 2019.

Materials and Methods: This study focuses on the effects of nicotine on an in vitro reconstituted model of oral mucosa. The reconstituted human epithelium model used in this study was prepared and supplied by Skin Ethic Laboratories, Nice, France. The effect of the different treatments of nicotine on tissue morphology was assessed using formalin fixed paraffin wax sections and hematoxylin and eosin staining.

Results: It was found that the effect of nicotine after 5 minutes and 24 hours with working solutions (10µM and 1mM) used on uninflamed oral mucosal did not significantly effect on the gross morphology.

Conclusion: This study has confirmed that all the concentration of nicotine used after 5 minutes and 24 hours had no effect on tissue morphology.

Key Words: Tobacco, Nicotine, Oral mucosa, Morphology.

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INTRODUCTION

The Tobacco consumption is directly responsible for nearly 6 million deaths annually and a further 600,000 people die each year from exposure to second-hand smoke (SHS).¹

Tobacco is killing 1 in 10 adults worldwide and its quantity of consumption is increasing globally especially in developing countries according to WHO statistical data.² The genus tobacco comes from a source named after Jean Nicot, a French ambassador that is being credited for the shipment of tobacco from

Portugal to Paris in the year 1560.³ The frequency of smoking in countries like Western Europe, Australasia, and the United States and the developing world is rising.⁴ Eriksen et al. concluded that tobacco smoking has serious adverse health consequences in all of the countries of the world irrespective of social, economic, personal, and political influences in determination of the smoking prevalence and cessation patterns.⁵

People consume different types of tobacco products which can be smoked, chewed or sniffed.⁶ These include products that are smoked such as cigars, cigarettes, pipe tobacco and roll- your-own or consumed smokeless as chewing tobacco and snuff.⁷ Tobacco smoking is a very popular habit and is associated with the development of cancers in humans.⁸ The incidence of oral cancer is correlated to the use of tobacco products.⁹ Cigarette smoking and tobacco use are also associated with development of other cancers in humans, including cancer of the oesophagus and the lungs.¹⁰ Nicotine is an important component of tobacco, it is the addictive substance in tobacco and the main reason why people continue to use tobacco related products and it is highly suggested that it may be associated with tobacco related diseases.¹¹ Nicotine addiction results in exposure to various carcinogens and bioactive compounds present in tobacco.¹² Nicotine (C10 H14 N2) is a naturally

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occurring alkaloid present in the tobacco leaves and makes up about 5% of a tobacco plant by weight, and it acts as a botanical insecticide and is highly addictive.^{13,14}

Tobacco smoking delivers rapid doses of nicotine into the brain following each inhalation, 15-20 minutes is its distribution half-life with a terminal half-life of two hours in the blood and nicotine has a penetrating effect on brain neurochemistry causing activation of nicotinic acetylcholine receptors, and releases dopamine in the nucleus accumbent.¹⁵ Nicotine is a type of psychomotor stimulant and helps smokers to calm down when they are under stress and enables them to work more effectively and with a higher concentration.¹⁵ Nicotine is associated with a variety of lesions within the oral cavity.⁹ It is suggested that nicotine might be associated with the pathogenesis of oral white pre-malignant lesions.¹⁶ Many Oral lesions and conditions associated with tobacco use include oral precancerous lesions such as leukoplakia, erythroplakia and smokeless tobacco keratosis, oral cancers such as squamous cell carcinoma of the tongue, floor of the mouth, lip and gingiva. It is further associated with verrucous carcinomas of the buccal mucosa gingival and alveolar ridge.¹⁷

The excessive consumption of tobacco has also been associated with other lesions within the oral cavity such as tooth stains, abrasions, smoker's melanosis, acute necrotizing ulcerative gingivitis, burns, keratotic patches, nicotinic stomatitis, peri-implantitis and other periodontal conditions including increased plaque and calculus depositions, gingival recession and alveolar bone loss.¹⁸ Carcinogens found in the tobacco smoke are responsible for the developing of oral diseases and cancer.¹⁹ Nicotine can contribute to cancer etiology when it is nitro sated and in turn, makes carcinogenic tobacco-sp. edifice nitrosamines.¹² In vivo studies showed that when 0.216M of nicotine is applied topically to the oral mucosa for a period of two hours leads to alterations within the epithelium like acantholysis and nuclear shrinkage.²⁰ Oral keratinocytes are the first cells in contact with tobacco components, thus keratinocyte inflammation has been stated as a critical step in tumor promotion.²¹ Recent study has shown that when 6% nicotine alone or in combination of other tobacco-specific nitrosamines such as 0.01% NNN, 0.01% NNK was applied on hamster cheek pouch and gastric mucosa, off them the cheek pouch epithelium showed signs of hyperplasia, hyperkeratosis and moderate dysplasia.²² Nicotine is associated with increase the permeability of oral mucosa to N-nitrosomonicotine.²³ Nicotine agents by acting on nicotine acetylcholine receptors, directly modulates the stimulated release of calcitonin gene related peptide (CGRP). This modulation can contribute to inflammatory processes within the oral cavity.²⁴ As oral keratinocytes are the first cells in contact with tobacco

components, thus keratinocyte inflammation has been stated as a critical step in tumor promotion.²¹

MATERIALS AND METHODS

This study was conducted at Department of Oral Pathology Bart's and the London Queen Mary School of Medicine and Dentistry Queen Mary, University of London. The study focused on the effects of nicotine on an uninflamed stratified epithelial layer, when applied for a period of 5 minutes and over 24 hours respectively.

The reconstituted human epithelium model used in the study was prepared and supplied by Skin Ethic Laboratories, Nice, France. It is a three-dimensional tissue culture model obtained by culturing transformed oral keratinocytes (TR146) derived from a buccal carcinoma. The cells were seeded and cultivated in a defined medium for 14. The resulting culture formed a stratified epithelium with 5-7 cell layers devoid of stratum corneum (Fig 1). Skin Ethic Laboratories also supplied maintenance medium (MCDB 153 containing 5µg/ml insulin and 1.5mM Ca²⁺) for use in the experiments. The Model cultures were transferred into a new 24 well culture plates (Costar, UK) containing 500µl maintenance medium per well and incubated for 2 hours at 37°C in 5% CO₂ in a humidified atmosphere. The cultures were transferred to a new 24 well plate containing fresh media for all experiments. Working solutions (10µM and 1mM) of nicotine were prepared from a 2.5M stock solution (Sigma, UK). The working solutions were diluted in phosphate buffered saline immediately before use. The morphology of the stratified oral mucosal model was examined using formalin fixed paraffin processed tissue. The culture was fixed by submerging in excess neutral buffered formalin for 24 hours at room temperature. The epithelium, with supporting polycarbonate membrane was dissected out of the inserts and the tissue processed to paraffin wax using an automatic tissue processor (Shandon Hyper Centre II). 5µm sections were cut and stained with hematoxylin and eosin, examined by light microscopy whilst the image was recorded with digital photography.

RESULTS

In order to confirm the effect of nicotine on an epithelial layer of the different treatments on tissue morphology was assessed using formalin fixed paraffin wax sections and hematoxylin and eosin staining. All the samples of nicotine treated uninflamed tissue were stratified with the presence of 10-15 epithelial layers and the absence of a stratum corneum (Figure 2-5) respectively.

The results showed no evidence of damage or alteration to the surface layers or the basal layer of the stratified squamous epithelial models.

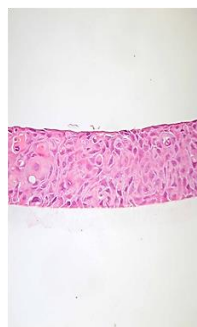


Figure No.1: Haematoxylin and eosin stained section of mucosal model (original magnification x63)

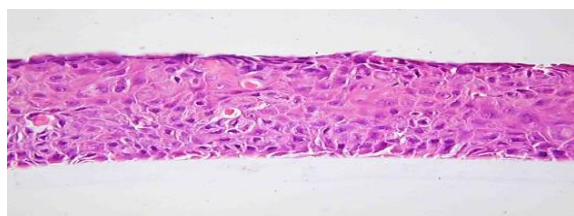


Figure No.2: Haematoxylin and eosin stained section of Mucosal model (original magnification x63)

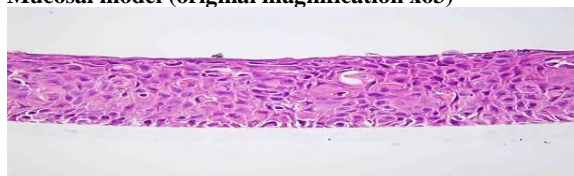


Figure No.3: Haematoxylin and eosin stained of uninflamed mucosatreated with 1mM nicotine for 5 minutes; original magnification x63

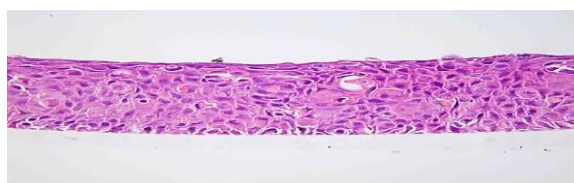


Figure No.4: Haematoxylin and eosin stained section of uninflamed mucosatreated with 10µM nicotine for 24 hours; original magnification x63

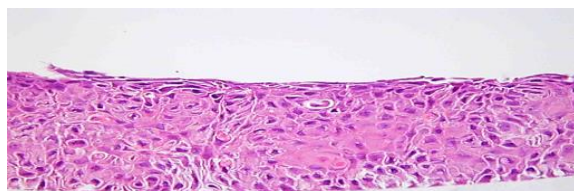


Figure No.5: Haematoxylin and eosin stained section of uninflamed mucosa treated with 1mM nicotine for 24 hours; original magnification x63

DISCUSSION

The aim of this study has been to investigate the effect of nicotine on an uninflamed reconstituted oral mucosa. The epithelial model allowed us to consider the effect of nicotine on an epithelial layer in the absence of any influence from mesenchyme. Stratified cultures were treated for 5 minutes and 24 hours respectively. Tissue morphology was assessed using formalin fixed paraffin wax sections and hematoxylin and eosin staining. The results from morphology studies suggested that nicotine treatment of uninflamed reconstituted oral mucosa after 5 minutes and 24 hours respectively had no significant effect on the morphological structure of the epithelium.

The results from morphological studies suggest that nicotine induces only a subtle change in membrane integrity, and also of important note was the fact that there were no gross changes in the appearance of the epithelium. This was surprising, in fact, nicotine has been shown to alter viability and morphology. In a previous in vivo study by Anderson and Warfving,²⁵ revealed that nicotine exerts its biological effect on the oral mucosa and resulted in changes in the appearance of the epithelium. Alpar et al. in their study showed that 4mM nicotine dose caused significant morphological alterations of microtubules and vimentin filaments which than lead to atypical and vacuoles formation within the oral fibroblasts.²⁶

However in a similar type of study conducted on a reconstituted oral mucosa by Kwon et al.¹⁶ revealed that nicotine had no effect on the viability of the cells although decreased, dose-dependently, mucosal epithelial thickness at 10µM, and 100µM concentration, but nicotine reduced cell viability in the epidermal keratinocyte at a concentration 100µM. Previously Alpar et al.²⁶ had also linked higher doses of nicotine (10.5-15.5mM) to be responsible for causing irreversible changes in morphological appearance of the cells. Squier and Johnson²⁷, also showed that when 0.2M nicotine was applied topically to the oral mucosa, after 2 hours it induced acantholysis and nuclear shrinkage within the epithelium. There may be some factors that may limit the significance of the findings in this study. It may be due to the permeabilizing effect of nicotine on mucosa, and it may be due to the reason that we used in vitro tissue culture models, whereas most of the studies were conducted in vivo. Alternatively, these results could suggest that it was not possible to quantify the amount of mitochondrial disruption by nicotine at the concentration range used.

CONCLUSION

In these experiments the tissue morphology was assessed by conventional light microscopy. Results showed that application of nicotine after 5 minutes and 24 hours treatment on uninflamed tissue with different concentrations used, did not have a significant effect on gross morphology. None of the treatments caused a

significant effect on the morphological structure of the epithelium.

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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Study of Insulin Resistance and Glucose Transporter Protein 4 in Polycystic Ovarian Syndrome

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ABSTRACT

Objective: To evaluate the relationship of Glucose transporter protein 4 and insulin resistance in patients of polycystic ovarian syndrome of various age groups.

Study Design: Case control study

Place and Duration of Study: This study was conducted at the Department of Gynaecology, Jinnah Hospital, Lahore from November 2018 to April 2019.

Materials and Methods: This study included 58 polycystic ovarian syndrome women with age ranging between 18-45 years, subdivided into three age groups. Rotterdam's criteria were used to confirm the diagnosis of Polycystic ovarian syndrome.

Results: The interpretation of the results revealed significantly high level of serum insulin and insulin resistance in patients suffering from Polycystic Ovarian Disease. Glucose transporter protein-4 levels in patient group were not found to be statistically significantly different in comparison to control.

Conclusion: Insulin level in serum and insulin resistance is strongly associated with poly cystic ovarian syndrome. However, deranged glucose transporter protein- 4 is not always the case.

Key Words: Serum Insulin, Insulin resistance, Glucose Transporter Protein, Polycystic ovarian Syndrome

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a multifactorial, multigenic condition and its occurrence is increasing with time in our society.¹ A large number of environmental and genetic factors are associated with PCOS.² In addition, it's the commonest endocrine disorder and a well known causative factor for infertility caused by in ovulation.³

Polycystic ovarian syndrome is well known to girls and women of reproductive age, who belong to every races and nationality. In developed countries PCOS is affecting 14% of women. Its more prevalent in developing countries like India, where 31% of the females between 20-40 years of age are effected.⁴

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Prevalence rate of 20.7% has been found amongst women of reproductive age in Pakistan.⁵

Commonest associated factor with PCOS is insulin resistance (IR). In one study IR is found to be present in nearly 70% of patients suffering from PSOC. High body mass index and hyperinsulinemia are also present along with IR.⁶ Homeostatic Model Assessment (HOMA) is an effective arithmetic method for calculating insulin resistance. It is calculated from the product of serum insulin level and fasting blood glucose level (fasting blood glucose-level x serum insulin- level/22.5).⁷

Major insulin dependent transporter in tissue, Glucose Transporter 4(GLUT-4), plays a key role in regulation of body's glucose metabolism. GLUT-4 levels have been found to be decreased to a considerable level in insulin resistant patients of PCOS.⁸ Secondary to resistance to human insulin, GLUT-4 do not travel effectively to cell surface and start to accumulate in membrane compartments inside the cell.⁹ In PCOS effected women GLUT-4 decrease of 50 % causes similar decrease in adipocyte GLUT-4 translocation in spite of obesity and IR.¹⁰

MATERIALS AND METHODS

The present study included 58 PCOS affected women between 18-45 years of age. Patients were selected from Gynaecology Department of Jinnah Hospital, Lahore, Pakistan, both from outdoor and indoor

facility, in a time period of six months from 1st November 2018 to 30th April 2019. Rotterdam's criterion was applied to select polycystic ovarian syndrome patients. This criterion takes into consideration presence of hyperandrogenism, anovulation and ultrasonographic finding of polycystic ovaries. Women suffering from other endocrinological abnormalities including thyroid dysfunction, hyperprolactinaemia, Cushing's syndrome and tumours of endocrine origin were excluded from the study. Depending upon the age, individuals were categorized further into Patient and Control group having age between 18-24 year, Patient and Control group with age in between 25-35 years and Patient and Control group with age ranging between 36-45 years. SPSS 17 software was used for data analysis. Student t test and Pearson coefficient correlation was applied to express and compare various variables between control and patient group of all three age categories.

RESULTS

Table 1 enlists the mean value of variables along with significance levels. In present study, levels of BMI, Fasting blood sugar level, fasting insulin level and insulin resistance seems to increase with age i.e. lowest in patient age 18-24 and highest in patient age 36-45 year old. Significant differences ($P < 0.05$) were observed, in between Patient and Control group of all ages, for fasting serum insulin level, fasting serum

glucose level and HOMA insulin resistance calculation. However, GLUT-4 levels did not show a consistent increase with age increase and the difference was statistically not significant in all age groups in present study.

The blood glucose was more significantly altered in child bearing age to 119 mg% serum insulin, 33.83 IU/ml as compared to controls in the same age group the values of which were 94 mg% insulin, 3.3 IU/ml respectively. For young girls aged 18-24, glucose was 98 mg% and insulin was 9.31 IU/ml while the values for glucose and insulin in controls of this group were 79 mg% and 3.34 IU/ml respectively. For 36-45 years, the values were glucose 122 mg% and insulin, 42.40 IU/ml while for the controls they were 92 mg%, 3.31 IU/ml. Glucose insulin ratio was 3.44 in the child bearing age (25-35), while for controls it was 28.48. In young girls aged 18-24, it was 10.63, while the value for controls was 24.24. For ages 36-45, the glucose insulin ratio was 2.88 and for controls it was 27.86.

By looking at the table 2 of Pearson Coefficient Correlation, it can be observed that a significant negative correlation exist between parameters serum fasting insulin level and GLUT-4 only in patients of 18-24 years of age ($r = -0.51$). The only significant positive correlation can be seen between Glucose Insulin Ratio and GLUT-4 in patients of age group 36-45 years ($r = 0.6$).

Table No.1: BMI & Biochemical Parameters of PSOC Patients vs Control (age in yrs).

Variable	Patient Age 18-24 (n=15)	Control Age 18-24 (n=20)	Patient Age 25-35 (n=39)	Control Age 25-35 (n=20)	Patient Age 36-45 (n=16)	Control Age 36-45 (n=10)
Body Mass Index (kg/m ²)	26.86±0.86	23.60±1.94	29.77±4.39	28.60±1.12	32.63±4.22**	23.60±2.1
Blood glucose Fasting (mg/dl)	98.74±20.27*	80.1±8.4	119.16±14.94**	94.0±8.5	122.93±5.02**	92.0±8.5
Serum Insulin Fasting (μU/ml)	9.32±0.33**	3.6±2.5	23.83±15.83**	3.3 ± 2.6	42.4±6.87**	3.5±2.1
Glucose insulin ratio (GIR)	10.60	24.24	3.52	28.48	2.90	27.87
HOMA- IR	1.23±0.12**	0.43±0.06	4.46±2.7**	0.44 ± 0.6	5.56±1.1**	0.43 ± 0.6
GLUT-4 (arb. Units)	5.01±4.43	4.28±2.43	4.77±4.08	4.22±0.54	6.37±5.89	4.28±2.43

* $P < 0.05$ = Significant ** $P < 0.001$ = Highly significant

Table No. 2: Pearson correlation PSOC Patients VS Control

Coefficient of determination (r value) between variables	Age (years)		
	18-24	25-35	36-45
Body Mass Index and GLUT-4	0.06	0.09	-0.14
Fasting insulin & GLUT-4	-0.51	0.2	0.25
Glucose insulin ratio & GLUT-4	-0.34	0.18	0.62

DISCUSSION

Polycystic ovarian syndrome is a common well recognized condition in women with child bearing age.^{11,12} The present study delineated that PCOS is commoner in patients belonging to age 25-35 years

.Nevertheless, previous studies have reported that PCOS effects a vast range of women of reproductive age ranging from 15-45 years.¹³ It was noted in another study that PCOS is more prevalent in younger age group ranging between 18-24 years.¹⁴

In our present study it was noticed that fasting blood glucose levels and fasting serum insulin levels were not only significantly high amongst all age groups in comparison to control but these levels also increased consistently with age. It was also observed that insulin resistance increases with age being lowest in youngest age group and highest in oldest age group. It is consistent with previous studies in which 1/3 of the

PCOS patients under study had increased IR at mean age of 40 years.¹⁵ It was observed in an invitro study that hormone levels and ovarian morphology changes as age advances. Possibility lies that metabolic abnormalities including insulin resistance worsen as age advances in patients of PCOS.¹⁶

Glucose transporter protein-4 was determined in all age groups, both in PCOS women and control, and it was found out that GLUT-4 was significantly low only in the child bearing age (25-35 years). GLUT-4 was 4.77 arbitrary units in this age group as compared to others as around 5-6 arbitrary units. Previous studies demonstrated the role of GLUT-4 in the muscles of the uterus for the transport of glucose as reported by Bryant et al.¹⁷ The expression of GLUT-4 is seemed to be well maintained in menstrual cycle dependent way in the uterine endometrium.¹⁸

Since GLUT-4 is insulin dependent transporter level of insulin is also measured and compared with it.¹⁹ The correlation of with GLUT-4 with other parameters is positive for ages 25-35 years but non significant in our study. Previous studies demonstrated variation in insulin secretion.²⁰ It is a consistent finding in our study in comparison to previous literature that metabolic abnormalities may worsen with age in women having PCOS.¹⁶

CONCLUSION

Patients of all age groups with polycystic ovarian syndrome had significantly raised fasting blood glucose level, fasting serum insulin level and also significantly increased insulin resistance. And an upward trend has been noticed with increasing age. However GLUT -4 levels were not found to be raised significantly in any age group and also did not show a significant correlation pattern with other parameters in various age groups.

Author's Contribution:

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

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Study of Circulating Oxidative Stress Markers and Level of Antioxidant in Non-Alcoholic Fatty Liver Disease (NAFLD)

Oxidative and
Antioxidant level
In Non Alcoholic
Fatty Liver
Disease

Zunaira Kanwal¹, Mohammad Faheem Siddiqui², Sohaib Farooq³ and Mujahid Israr⁴

ABSTRACT

Objective: To document the markers of oxidative stress and state of endogenous and exogenous antioxidants levels in non-alcoholic fatty liver disease.

Study Design: Case control study.

Place and Duration of Study: This study was conducted at the Department of Medicine, Services Hospital Lahore from December 2018 to May 2019.

Materials and Methods: Fifty non-alcoholic fatty liver disease patients with elevated aminotransferases and presence of fatty liver on ultrasound were included in the study. Fifty healthy individuals of same age and sex matched healthy were selected as control. Patients with positive viral serology, alcohol use and known diabetics were excluded.

Results: Oxidative stress determinants including malondialdehyde (5.44 nmol/ml) and nitric oxide (15.5µmol/l) levels are found to be statistically significantly raised and endogenous antioxidants including glutathione (4.91 mg/dl), catalase (1.43 mmol/mol of protein), superoxide dismutase (0.24 nmol/ml) as well as exogenous antioxidants including vitamin C (0.33 mg/dl) and vitamin E (0.22 mg/dl) were reduced significantly in non-alcoholic fatty liver disease patients.

Conclusion: Non-alcoholic fatty liver disease is associated with derangement of multiple circulatory oxidative stress parameters and antioxidant thus depicting a significant role of oxidative stress in disease mechanism.

Key Words: Non-alcoholic fatty liver disease, Oxidative stress, Antioxidants, Oxidative stress

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INTRODUCTION

It is an established fact that Non-alcoholic fatty liver disease (NAFLD) is the commonest disorder of liver in developed world.¹ NAFLD embraces a spectrum of disorders, from just steatosis in liver to steatohepatitis, Steatohepatitis can also lead to cirrhosis, liver failure and even hepatocellular carcinoma.² Fatty liver is characterized by macrovesicular fat accumulation in Hepatocytes. Whereas, non alcoholic steatohepatitis (NASH) is characterized by hepatocellular injury, inflammatory changes and varying degree of hepatic fibrosis.^{3,4}

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In present times, NAFLD is known to affect 20% to 40% of general population in western industrialized countries.⁵ However, NASH effects 10% to 30% of effected individuals only.⁶ NAFLD is now also well recognized as a common problem in Asia Pacific region.⁷ In general population of countries in Asia Pacific, the prevalence of NAFLD ranges from 2% to 37%. Larger surveys conducted in Japan, China and Korea showed a prevalence rate of 10% to 29%, which are comparable to the figures described in Western Surveys.^{8,9}

The most common cause of elevated liver enzymes remains NAFLD.¹⁰ Important associated factors associated with NAFLD are dyslipidaemias and toxins exposure.¹¹ Both dislipidaemia and toxin exposure cause oxidative stress and increased production of malondialdehyde (MDA) leading to mitochondrial damage.¹² In addition antioxidants like catalase and glutathione (GSH) are found to be reduced in these patients.¹³ Reduced activity of antioxidant enzyme super oxide dismutase (SOD) is associated with increased reactive oxygen substances (ROS) production leading to increased susceptibility to NASH and hepatic fibrosis.¹⁴ Research studies have shown that levels of antioxidant vitamins C and E decrease in NAFLD patients exhibiting a compromised antioxidant protection status.¹⁵

MATERIALS AND METHODS

Fifty NAFLD patients from outpatient department at Services Hospital Lahore were selected from 1st December 2018 to 31st May 2019. Detailed history of alcohol intake, diabetes mellitus, known hepatitis C or B clinical complications if any was collected by help of a questionnaire from all individuals of the study. Clinical diagnoses of the patient were also taken into consideration. Fifty age and sex-matched clinically apparently healthy individuals were included as controls. Patients with elevated LFTs especially ALT and AST having fatty liver on ultrasound examination were included in present study. Alcoholics, smokers and known diabetics and individuals with positive hepatitis B or C were not included in the study. 5ml blood was collected from control and study group in EDTA and red top vacutainers and processed. All chemical reagents used for analysis were sourced from Sigma Chemical Co. (St. Louis, Mo, USA). Results have been expressed as mean±SD. Independent sample t test was used for statistical analysis. The difference were considered significant at $p<0.05$.

RESULTS

Table No. 1: Oxidative stress markers profile of control vs NAFLD

Parameter	Groups	Mean±SD	No.	p value
MDA	Control	1.36±0.38	50	.000
	NAFLD	5.44±1.14	50	
NO	Control	11.28±1.34	50	.000
	NAFLD	15.50±1.64	50	

Table No. 2: Antioxidant profiles of control vs NAFLD

Parameter	Groups	Mean±SD	No.	p value
SOD	Control	0.73±0.25	50	.007
	NAFLD	0.24±0.11	50	
GSH	Control	9.77±1.17	50	.000
	NAFLD	4.91±1.11	50	
Catalase	Control	4.27±0.73	50	.000
	NAFLD	1.43±0.35	50	
Vitamin E	Control	0.29±0.067	50	.000
	NAFLD	0.22±0.073	50	
Vitamin C	Control	0.57±0.08	50	.000
	NAFLD	0.33±0.07	50	

The level of plasma Malondialdehyde (MDA) was determined to be 5.44±1.13 nmol/ml in NAFLD patients and 1.36±0.38 nmol/ml in control group. This difference in values between NAFLD and control group is found to be statistically significant ($p<0.05$). Level of nitric oxide (15.50±1.64 μ mol/l) at ($p<0.001$), indirectly measured as nitrites and nitrates has also found to be statistically significant raised in NAFLD patient group (Table 1).

Data regarding stress antioxidants including superoxide dismutase (SOD), glutathion (GSH), catalase (CAT), vitamin C and vitamin E has been depicted in Table 2. Levels of endogenous antioxidant components of serum

including SOD (0.243±0.1 nmol/ml) at ($p<0.05$), CAT (1.43±0.36 nmol/mol) at ($p<0.001$) and GSH (4.91±1.1 mg/dl) at ($p<0.001$) were found to be decreased in the NAFLD patient group than in the control group. This difference was statistically significant. Moreover in group having NAFLD effected patient, exogenous antioxidant level including vitamin C (0.34±0.07 mg/dl) at ($p<0.001$) and Vitamin E (0.22±0.07 mg/l) at ($p<0.001$) are statistically significantly decreased as compared to controls.

DISCUSSION

Oxidative stress is usually delineated as a condition which results because of either uncontrolled increase in reactive oxygen species or insufficient antioxidant defence system due to any pathological cause. Reactive oxygen species and reactive nitrogen species, mainly hydroxyl radical and nitric oxide, exert significant hazardous and toxic effects. Superoxide anion causes peroxidation of lipids in membranes thus causing formation of end products like MDA. These substances can directly injure hepatocytes and in turn leads to production of proinflammatory cytokines, spindle cell activation into fibroblast and myofibroblasts and fibrogenesis responsible for NASH.^{16,17}

Parameters representing lipid peroxidation like MDA and NO show significant upward trend from control to NAFLD group with statistically significant increase in values in NAFLD patients as compared to control in present study. A previous study has document similar results and has associated high levels of these markers as a prognostic marker in patients with steatosis and NASH.¹⁸ Deranged NO levels enhance the production of reactive oxygen substances and impose oxidative stress on liver cells in NAFLD patients.¹⁹

Glutathione, CAT and SOD are the best recognized constituents of the body's own antioxidant defence system. Glutathione prevent the oxidative damage of free radicals via direct non-catalytic reaction by helping SH group containing proteins to remain in reduced form. All these markers show statistically highly significant differences between the NAFLD and control group in present study. Both endogenous antioxidants like SOD, GSH and CAT as well as exogenous antioxidants like Vitamin E and Vitamin C have seen to be significantly decreased in NAFLD group in comparison to control group. Decreased levels of endogenous defence antioxidants like low vitamin C and decreased vitamin E play a significant role in pathogenesis of NAFLD.²⁰ Decreased hepatic GSH levels have been reported in most of NASH pathogenesis models.^{21,22} Super oxide dismutase and Catalase has also found to be increased in plasma in another study conducted by Yesilova et al.²³

Findings of the present study are consistent with the literature and show increased lipid peroxidation and consequential suppression of antioxidant capacity as

result of its consumption.¹⁷ This imbalance between oxidative stress and antioxidant capacity of the body has a pivotal role in development of NAFLD and NASH.²⁴

CONCLUSION

Non-alcoholic fatty liver disease accompanies a variety of changes in both oxidant and antioxidant system of the body. Increased lipid peroxidation, as depicted by elevated levels of malondialdehyde and nitric oxide and depletion of endogenous and exogenous antioxidants, importantly glutathione, catalase and vitamin C, occurs as a result of free radical formation secondary to excessive fat accumulation in liver.

Author's Contribution:

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Frequency of Radiologically Confirmed Pneumonia in Children with First Time Wheezing at Pediatric Emergency Department, Liaquat University Hospital Hyderabad

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ABSTRACT

Objective: To assess the frequency of radiologically confirmed pneumonia in children with first time wheezing at pediatric emergency department, Liaquat University Hospital Hyderabad.

Study Design: Descriptive Cross Sectional Study

Place and Duration of Study: This study was conducted at the at Department of Pediatric Liaquat University Hospital, Hyderabad from January to June 2017.

Materials and Methods: A Descriptive Cross Sectional Study was conducted at Department of Pediatric Liaquat University Hospital, Hyderabad, total six months' duration from 1st January to 30 June 2017. The child who came first time with wheeze with signs of fast breathing and chest in drawing as per operational definition were nebulized with rapid acting inhaled bronchodilator i.e. Ventolin solution upto three times 20 minutes apart. According to standard/IMNCI protocol soon after three times nebulization, they were reassessed for persistence of fast breathing and chest indrawing and reclassified as Pneumonia if fast breathing and/or chest indrawing persisted. The chest radiography was done in all of the children to confirm the radiological finding suggestive of pneumonia.

Results: Mean \pm SD of age was 21.13 ± 12.06 with C.I (19.02-23.24) months. Mean \pm SD of duration of symptoms was 2.34 ± 1.11 with C.I (2.15-2.54) days. Out of 128 patients 67 (52.3%) were male and 61 (47.7%) were female. Radiologically proven Pneumonia was present in 54 (42.2%) patients.

Conclusion: Our study shows that out of 128 children who presented with first time wheeze; 42.2% had radiologically proven pneumonia while 57.8% did not have radiological findings of pneumonia. Boys had higher proportion of pneumonia than girls. Based on our study findings, it is suggested that all children who present first time with wheeze and signs of fast breathing and chest indrawing should be screened for pneumonia.

Key Words: Fast breathing, Children, Chest indrawing, Chest Radiography, Ventolin Nebulization

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INTRODUCTION

Pneumonia cause lot of morbidity and mortality in children younger than the 5 years of age worldwide.¹ Globally there are about 120 million cases of pneumonia annually, resulting in 1.3 million deaths. The prevalence of Childhood Pneumonia in India is about 36%.²

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In Pakistan prevalence of Pneumonia in children is 20% and it is a primary cause of under-five mortality.³

The presentation of Pneumonia is non-specific, including cough, fever, fast breathing and breathing difficulties. Though no isolated physical examination finding can accurately diagnose pneumonia but Chest auscultation for crepitations/rhonchi can aid in diagnosis.⁴ Although there are no clear guidelines for performing chest x-ray for the diagnosis of Pneumonia in children but the chest x-ray can be helpful in the diagnosis of pneumonia.⁵

Wheezing is a common problem in children. About 25% to 50% children have the history of atleast one wheezing episode by the age of 5 years. Other than the Pneumonia the cause of wheezing may be; Reactive Airway Disease, gastro esophageal reflux disease, and bronchiolitis. In an American study 20.4% patients had radiographic evidence of Pneumonia with wheeze.⁶ While an Indian study showed that 8.7% children had radiological evidence for pneumonia in children having wheeze.⁷

In 1980 World Health Organization developed a Pneumonia control strategy for developing countries with limited resources. Simple signs (respiratory rate and chest indrawing) were included for the identification of Pneumonia in settings with little or no access to diagnostic technology. According to revised classification (WHO 2012) children who has chest indrawing with or without fast breathing are classified as having "pneumonia". For last 30 years, many countries have implemented these WHO case management protocols, after that there is reduction in the mortality in these developing countries. Neonatal mortality decreased from 42% to 27%, infantile mortality decreased from 36% to 20% and among children mortality decreased from 36% to 24%.⁸ However, there is the possibility of virus induced wheezing illness or asthma, rather than pneumonia. That's why a careful review of the existing evidence about management of wheezing illness in children is needed. Children having the history of recurrent wheezing episodes or a single episode of wheezing that not responding to bronchodilators should undergo chest radiography.⁹

The rationale of this study is that as, history and clinical examination findings in wheezy children may not distinguish pneumonia from those without pneumonia and there is limited data exist regarding importance of wheezing in children without pneumonia. Keeping this possibility, we conducted a study to see the frequency of radiologically proven Pneumonia in children who admitted with clinical diagnosis of pneumonia according to IMNCI strategy. By knowing the frequency of wheezing in pneumonia the results of the study will help the pediatrician in efficiently diagnosing the pneumonia clinically by observing wheezing & other sign and symptoms and hence the patients care will be improved..

MATERIALS AND METHODS

Pneumonia According to IMNCI It is defined as fast breathing and/or chest indrawing with age specific cut off values for increased respiratory rate (≥ 50 /min if age 2-11 months and ≥ 40 if age 12-59 months).

Chest indrawing: It is the inward movement of lower chest wall when the child breaths in.

Wheeze: It is the whistling or rattling sound on chest auscultation. **Radiologically confirmed pneumonia:** It is defined as if air bronchogram or diffuse infiltrate or lobar consolidation seen on chest x-ray.

A Descriptive Cross-sectional study was done by Non-Probability Consecutive Sampling technique at Department of Pediatrics, Liaquat University Hospital Hyderabad from 1st January to 30th June 2017 (total 6 months' duration). By using W.H.O sample size calculator using prevalence of pneumonia=20.4%¹⁰ Confidence interval = 95%, margin of error (d) = 7% then the estimated sample size was 128. Patient's age

between 2 months to 5 years admitted to the pediatric emergency department with first time wheeze with increased breathing rate and chest indrawing (as defined in operational definition) of both gender was included in the study. Children already on treatment for pneumonia or wheeze, known cases of chronic lung disease (e.g. cystic fibrosis, tuberculosis) and congenital heart disease on previous available medical record, failure to get informed consent, children having recurrent wheeze and who had used inhaled bronchodilators with in last 6 hours were excluded from the study.

Study was conducted after the approval from the Research evaluation unit CPSP, Karachi. Patients meeting the selection criteria attending emergency department of Liaquat University Hospital Hyderabad were enrolled in the study. Prior to inclusion the purpose, procedure, benefits and risks involved in the study were explained and informed consent was obtained by the parents/guardian. The Child who came first time with wheeze with signs of fast breathing and Chest Indrawing as per operational definition was nebulized with rapid acting inhaled bronchodilator i.e. Ventolin solution (0.5 ml) for up to three times 20 minutes apart according to standard IMNCI protocol and soon after three times nebulization child was reassessed for persistence of fast breathing and chest indrawing and reclassified as pneumonia as per operational definition. The chest radiography was conducted in all of the patients who were classified as pneumonia. The main outcome variables and demographics were entered in the proforma.

All the data was entered into SPSS version 20.0. Mean \pm SD were calculated for age, weight & duration of symptoms. Frequencies and percentages were calculated for gender & outcome variable i.e. Pneumonia. Effect modifiers were controlled through stratification of age, gender, duration of symptoms and weight to assess the effect on these on outcome variables. Post stratification appropriate Chi square was applied considered $P \leq 0.05$ as statistically significant..

RESULTS

In this study 128 children were included to assess the frequency of radiological proven pneumonia in patients presented with wheeze and the results were analyzed as Mean \pm SD of age was 21.13 ± 12.06 with C.I (19.02-23.24) Table 1. Mean \pm SD of duration of symptoms was 2.34 ± 1.11 with C.I (2.15-2.54) days **Table 1.** Mean \pm SD of weight was 9.58 ± 3.45 with C.I (8.97.....10.18) kg Table 2. Out of 128 patients 67 (52.3%) were male and 61 (47.7%) were female Table 2. Positive radiological pneumonia was found to be 54 (42.2%) patients Table 2. Stratification of pneumonia with respect to effect modifier of the study i.e. age, gender, duration of symptoms and weight were done from (Table 2).

Table No. 1: Descriptive Statistics n=128

Descriptive Statistics		Statistic
AGE (In months)	Mean	21.13
	Std. Deviation	12.066
DURATION (In Days)	Mean	2.34
	Std. Deviation	1.111
WEIGHT (In Kg)	Mean	9.58
	Std. Deviation	3.452
FREQUENCY OF PNEOMONIA		N (%)
Radiological Proven Pneumonia		54 (42.2%)
Pneumonia having no radiological findings		74 (57.8%)

Table No. 2: Stratification of Age Group N=128

Characteristics		Pneumonia		Total
		Yes	No	
Age Group (In Months)				
4--21	Count	31	38	0.4947
	% Of Total	24.2%	29.7%	
> 21	Count	23	36	
	% Of Total	18.0%	28.1%	
Total	Count	54	74	100.0%
	% Of Total	42.2%	57.8%	
Gender				
MALE 67 (52.3%)	Count	30	37	0.534
	% Of Total	23.4%	28.9%	
FEMALE 61 (47.7%)	Count	24	37	
	% Of Total	18.8%	28.9%	
Total	Count	54	74	100.0%
	% Of Total	42.2%	57.8%	
DURATION (In Days)				
1---3	Count	40	67	0.013
	% Of Total	31.2%	52.3%	
>3	Count	14	7	
	% Of Total	10.9%	5.5%	
Total	Count	54	74	100.0%
	% Of Total	42.2%	57.8%	
WEIGHT (In Kg)				
4---10	Count	39	51	0.686
	% Of Total	30.5%	39.8%	
>10	Count	15	23	
	% Of Total	11.47%	18.0%	
Total	Count	54	74	100.0%
	% Of Total	42.2%	57.8%	

DISCUSSION

Pneumonia is a second leading cause of childhood death (under 5 years of age) in Pakistan.¹¹ The incidence of Pneumonia is more in younger age children (age 2-6 months).¹² Other common associations of pneumonia include male gender, undernutrition, micronutrient deficiency, low immunization status, poverty, overcrowding, poor breastfeeding and exposure to indoor air pollution. Chest radiographs are advised frequently at Clinics for suspected pneumonia in children.¹³ According to an international study chest radiographs were performed in upto 94% of cases to confirm the diagnosis of suspected pneumonia.¹⁴ Guidelines for the developed countries cannot be applied to the developing countries, hence

requiring regular review in the context of new information.

As the clinical features of lower respiratory tract infections are nonspecific, it causes a problem for clinicians in making the diagnosis. That's why imaging is justified for making the final diagnosis of Pneumonia.¹⁵

Some guidelines advocate chest xray only in severe pneumonia having the need of hospitalization, while the others advocate performing chest xray in suspected pneumonia having the less reliable history and examination.¹⁶ In infants advising chest xray for the diagnosis of Pneumonia is the best decision because the signs and symptoms are usually non-specific or subtle). In our study there were more male children, out of 128 patients 67 (52.3%) were male and 61 (47.7%) were female. The male to female ratio was 1.09: 1. An international study also showed the similar gender distribution, 311 (50.6%) were males and the median age was 27.2months.¹⁷ Out of 128 children with wheeze, 54 [42.2%] diagnosed to have radiologically proven pneumonia while 74 [57.8%] did not have radiological findings of pneumonia. Children 4-21 months had higher proportion of radiological proven pneumonia than children > 21 months of age, and this difference was not statistically significant [p=0.668]. In an unsimilar international study Chest Xray done in children with first time wheeze, among them 24% children showed radiological findings of Pneumonia while 76% showed no radiological finding of Pneumonia. Radiological findings were more in children having elevated temperature, an absence of a family history of asthma, and localized wheezes or rales by auscultatory examination.¹⁸

Although there have been previous studies that have identified some clinical factors that predict the presence of radiographic pneumonia, there is still no validated clinical rule that informs the clinician as to which patients should get a CXR.¹⁹ In an international study high grade fever was significantly associated with radiological confirmed Pneumonia 63 (51.6%).²⁰ In another international multicenter study fever, fast breathing, crepitations and hypoxemia was associated with radiological proven pneumonia, while wheeze was not present in most of the children with radiological proven pneumonia.²¹ In another study fever within 48 hours of admission was directly associated with radiological proven pneumonia, 109 (38.5%) children had radiological confirmation and 143 (50.5%) had no radiological confirmation. Children without radiologically-confirmed pneumonia were younger than those with radiologically-confirmed pneumonia.²²

Regarding the etiological agent Pneumococci was more common in radiologically confirmed pneumonia in comparison with patients with normal CXRs (24.2% vs 8.3%, P = .04).²³ A Local study from Lahore showed that X-ray findings were present in 91(39.6%) cases

while in 139(60.4%) children chest xray was normal. Ronchi were present in 42(18.3%) children (p-value <0.001).²⁴

In an international study the combination of fast breathing and oxygen saturation <96% in children (>12 months old) and nasal flaring in children (<12 months old) was strongly associated with radiologically proven pneumonia.²⁵ In a study Chest Xray performed in children with viral induced wheeze (fever and wheeze), 14% of chest Xray showed findings suggestive of bacterial Pneumonia.²⁶

In present study age, gender, duration of symptoms and weight played as a role of confounders / effect modifiers. In univariate analysis of age group (4-21) and (> 21) months pneumonia was found in 31 (24.2%) and 23(18%) respectively and P value found to be non-significant i.e. (P=0.497); Similarly, in stratification of gender 30(23.4%) pneumonia was found in male whereas 24 (18.8%) was found in female and P value found to be non-significant i.e. (P=0.534). On the other hand, significant difference was found in stratification for duration of symptoms in days (1-3) and (> 3) days radiologically proven pneumonia was found in 40 (31.2%) and 14(10.9%) respectively and P value found to be significant i.e. (P=0.013). In analysis of weight group (4-10) and (> 10) kg pneumonia was found in 39 (30.5%) and 15(11.47%) respectively and P value found to be non-significant i.e. (P=0.686).

CONCLUSION

Our study shows that out of 128 children who presented with first time wheeze; 42.2% had radiologically proven pneumonia while 57.8% did not have radiologically proven pneumonia. Based on our study findings, it is suggested that pneumonia commonly presents with wheeze and there is a need to screen all children for Pneumonia who admit with wheeze. However, there is a need to conduct more studies using large sample size with multiple study sites in Pakistan to validate these results.

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Significance of LA Volume in Cardiac Patients with Diastolic Dysfunction and Renal Failure and their LV Measurements

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ABSTRACT

Objective: Left atrial size and volume is significant clinical tool for testing diastolic function and chronicity of diastolic dysfunction by echocardiography. It involves measuring diameter in end systole internally and LA volume by prolate ellipse method.

Study Design: Cross-sectional study.

Place and Duration of Study: This study was conducted at the Department of Cardiology, Shaikh Zayed Hospital Lahore from July 2018 to December 2018.

Materials and Methods: One hundred and forty seven renal failure patients from both genders within an age group of 15-75 years were undergone echocardiography. The related clinical history and findings were recorded.

Results: There were 76 males and 71 females. The data analysis suggested that mean LA size was highest 38.35 in patients >50 years of age. Highest left ventricle ejection fraction (mean 69) and LV mass (mean 173) was presented in 31-40 years of age group. The greatest mean LA size (41.7 ± 3.93) was noticed in severe graded patients.

Conclusion: The LV measurements showed that 41-50 years of age was most vulnerable for abnormal echocardiographical findings and The LA measurement is the HbA1C% of diastolic dysfunction.

Key Words: Ejection fraction, LV diameter, End stage renal failure, LA volume

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INTRODUCTION

There is a major burden of deaths caused by heart diseases and renal failure all over the globe. The prevalence of cardiac arrests is very high in developing countries due to multiple reasons including comorbidities, late diagnosis and unhealthy lifestyle.¹ Left atrial (LA) size is an independent predictor of cardiovascular events such as congestive heart failure, myocardial infarction, atrial fibrillation, stroke, and cardiovascular death.² Three commonly used methods for evaluation of LA volume are the biplane area length (AL), the biplane modified Simpson (SIMP), and the prolate ellipse (PE) methods. Each mathematical calculation assumes the LA to be a fixed shape, which may result either in over- or underestimation of true volume.³ The standard and most suitable reporting method of LA size is through measuring internal

diameter in end systole and LA volume by prolate ellipse method in echocardiographic patients.² It has a high significance in diagnosis of cardiac complications and their prognostic status.^{1,4,5} In few cases such as valvular cardiac diseases the LA dimensions are very important in critical identifying and managing the schedule of surgical intervention.⁶⁻⁸ Overall LA measurements are an efficient and simple method for assessing cardiac dysfunctioning.⁹⁻¹¹ The left atrial diameter measurements can easily be gained at the time of Echocardiography/LVEF measurements. Past studies has proven the significance of LA and LV measurements and size in respect to cardiac morbidities. The increased left ventricle end systolic diameter is directly associated with higher frequency of cardiac failure.¹⁰ There is a strong association between LV diastolic function and heart failure. The conventional electrocardiographic measurements and radiography of chest are not sufficient for diagnosing LV diastolic dysfunction. The more appropriate method of diagnosis becomes echocardiography for attaining LV measurements and diagnosis of LV diastolic dysfunction.

The present study focuses on assessing the reliability of LA measurements during echocardiographic examine and also gradating the values of LA measurements in different age groups by categorizing them on the basis of LA dilation. This study is conducted for better diagnosis and early identification of issues with cardiac

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complications involving left ventricle dysfunction and to minimize the rate of cardiac mortalities related with late and inefficient diagnosis.

MATERIALS AND METHODS

This cross-sectional study conducted at Cardiology Department of Sheikh Zayed Hospital, Lahore from 31st July 2018 to 31st December 2018. The study included 147 patients from both genders. The age of the patients was <18 years upto 65 years. . Known cases of ischemic heart disease (confirmed on history and echocardiography) and known cases of organic valvular heart disease (confirmed on history and echocardiography) were excluded from this study. The patients having end stage renal failure and with LVEF greater than 50% were included in this study. The study was approved from Ethical Board of hospital. A written informed consent was taken from each participant before enrolling in this study. The information regarding demographic, clinical history was entered on a well prepared questionnaire by interviewing the patients. The most important variables included age, gender, LV measurements (LVIDD, LVPW, LV MASS and LA size). The data was entered and analyzed by using SPSS version 21. The formula used for measuring LA volume by the prolate ellipse (PE) method is $L/A \text{ volume} = 0.523 \times D1 \times D2 \times D3$.

RESULTS

The left ventricle (LV) measurements were taken through echocardiograms of 147 patients having disturbed diastolic dysfunction. The echocardiogram reading contained two dimensional measurements, Doppler scan and M. Mode modalities. The minimum age of patients was <18 years while 53 patients were such which belonged to an age group >51 years. This group also had highest number of patients enrolled. An increasing patient's frequency could be clearly noticed with increasing age (Table 1). In present study it was noticed that more male were admitted in cardiology department than females in relevance with cardiac diseases. Out of 147 patients 51.7% were males (Table 2).

Each enrolled patient was assessed for their diastolic functioning by echocardiographic reporting. The different left ventricle measurements showed that there was no significance difference among LVIDD of different age groups. However mean LVIDS was highest in 31-40 years patients while and IVS was highest in 41-50 years of patients. The LV mass also showed an increasing trend with increasing age with highest value recorded in 31-40 years patients. The LA size was greatest in patients above 50 years of age (Table 3).

The grading of diastolic dysfunction was as unchanged, mild, moderate, and severely abnormal. LA volume has no direct association with grading of diastolic dysfunction. However it was recorded that duration of diastolic dysfunction had a direct correlation with LA volumes and also had significant association with age, however 18-20 years of age showed higher LA volume with a history of \pm two years of hemodialysis. There were 53 cases who were having normal LA volume, 39 cases who were having mild LA volume, 32 cases having moderate LA volume and 23 cases of severe LA volume Table 4.

Table No.1: Age distribution of the patients (n=147)

Age (years)	No.	%
<18	3	2.04
18-20	5	3.4
21-30	20	13.6
31-40	19	12.92
41-50	47	31.97
>51	53	36.05
Mean \pm SD	45.98 \pm 6.43	

Table No.2: Gender distribution of the patients (n=147)

Gender	No.	%
Male	76	51.7
Female	71	48.29

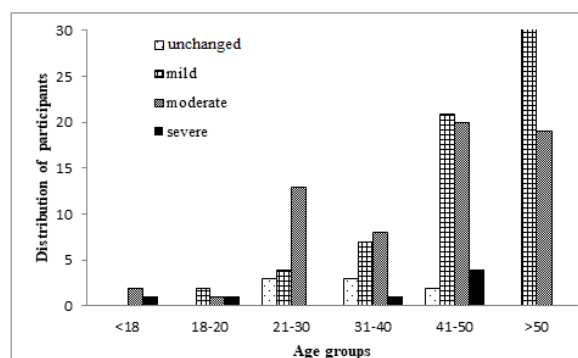


Figure No. 1: Frequency of diastolic dysfunction grade according to age

An association of age with grading (normal, mild, moderate or severe) of diastolic dysfunction was compared for better understanding of its effects. Majority of participants had mild diastolic dysfunction grade while 41-50 years of age was most vulnerable age with highest number of moderate and diastolic dysfunction grade cases. The severe diastolic dysfunction grade was also presented in two patients with a very young age (Fig. 1).

The LV grading showed that mean LV mass was highest in mild graded patients while LA size was highest in severe graded patients. Left ventricle ejection fraction was insignificantly changed between mild and moderate diastolic dysfunction grades with lowest mean value of severe graded cases (Table 5).

Table No. 3: Stratification of LV measurements according to age (n=147)

LV measurement	Age (years)					
	<18 (n=3)	18-20 (n=5)	21-30 (n=20)	31-40 (n=19)	41-50 (n=47)	>50 (n=53)
LVIDD	47±7.55	47.13±5.643	45.65±7.72	46.47±6.74	45.98±6.43	45.34±6.33
LVIDS	24.67±19.42	28.88±11.76	29.70±7.09	31.65±6.84	30.32±6.85	31.04±6.43
IVS	11.00±1.00	11.00±3.46	11.45±1.95	12.47±1.90	15.51±19.97	12.72±2.29
LVPW	12.00±3.60	10.75±2.60	11.00±1.74	12.00±1.90	12.30±1.66	12.11±1.62
LVEF	62.00±20.78	65.13±14.50	67.50±14.75	69.00±9.50	68.57±10.34	65.49±8.52
FS	28.67±11.93	31.25±9.49	33.60±5.09	33.65±5.75	33.30±6.32	37.40±41.20
LV mass	144.33±16.01	129.86±19.11	146.68±37.30	173.59±35.40	165.86±39.19	170.11±39.34
LA size	36.67±3.05	32.43±5.85	35.05±6.14	36.82±5.19	37.89±3.95	38.25±4.94

Table No.4: Comparison of age with LA volume and hemodialysis duration

Age (years)	LA volume	Hemodialysis duration
<18	25.53±9.76	2.00±1.15
18-20	30.75±16.20	2.80±2.49
21-30	32.19±17.37	3.81±2.54
31-40	29.40±10.69	3.84±3.04
41-50	33.81±10.36	4.06±2.74
>51	33.59±10.33	4.39±2.89

Table No. 5: The mean LV measurements in different LV grades

Diastolic dysfunction grade	LV Measurements							
	Unchanged	Mild	Moderate	Severe	Unchanged	Mild	Moderate	Severe
Unchanged	43±2.8	31.5±4.9	12±1.4	13.5±0.7	72±24	28±5.6	165.5±3.5	34±5.6
Mild	45.19±6.2	29.35±6.3	12.90±2.2	12.32±1.8	67.54±11.1	33.46±5.4	169.46±43.6	37.31±4.7
Moderate	46.7±7	31.5±7.3	12.0±2.1	11.8±1.6	68.4±9.9	32.9±6.1	155.5±32.9	37.3±5.4
Severe	49.5±5.4	36.8±6.1	12.5±2.07	10.8±2.2	61.7±8.35	29.0±3.4	159.5±21.2	41.7±3.93

DISCUSSION

Precise assessment of LA volumes is fundamental cardio logical practice, the present study suggests that LA size is an independent factor of LVEF and is strongly associated with diastolic dysfunction in renal impaired patients. The demographic variables of patients showed a significant number of males affected by cardiac complications than females. Another study also found a significant correlation between male gender and LV diastolic dysfunction with almost 50% men affected.¹²

St. John Sutton et al¹³ have proven that declined ejection fraction has a direct association with increased incidence of heart failures. The present study analyzes diastolic dysfunction as an independent factor for heart failure in patients with preserved ejection fractions. This study reports that increasing age had more cases of patients with diastolic dysfunction and renal impairment with a mean age as 34.54±6.21. A study elsewhere has also reported similar findings with a mean age of patients as 48±13 years as mean age. More men might be affected due to their hectic workloads and lifestyle disparities.

Left atrial volume is most reliable method in measuring LA diameters and represents the true picture of duration of diastolic dysfunction. If the duration of diastolic dysfunction is longer than LA volume will represent more severity in volumetric size. Left atrial volume is most reliably measure by prolate ellipse method as used in present study. Ujino et al¹⁴ also shown that ellipsoid method is based on three different diameters and can be characterized as prolate ellipse methods. This method is

most frequently used for better representation of LA volume.¹⁵

An evident cross sectional association can be reported between age and diastolic dysfunction depending upon left ventricle dilation grades. Aging declines diastolic dysfunction as reported in international studies.¹⁶⁻¹⁸ Diastolic function measurements attained by echocardiography shows almost 7% of patients > 45 years to have diastolic dysfunction between moderate to severe grades¹⁹⁻²¹, however in present study patients above 41 years had more chances of having severe diastolic dysfunction than patients above 50 years who had mild to moderate diastolic dysfunction.

CONCLUSION

The LA measurement is the HbA1C% of diastolic dysfunction and is more reliable in identifying diastolic dysfunction. The LA size increased with increase in age while LV mass has an independent significance irrelevant of age.

Author's Contribution:

Concept & Design of Study: Abubakar Hilal
 Drafting: Qazi M. Tufail
 Data Analysis: Rida Fatima,
 Qazi Abdul Saboor and
 Revisiting Critically: Abdubakar Hilal,
 Qazi M. Tufail
 Final Approval of version: Abubakar Hilal

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

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Assessment of Determinants Leading to Salmonella Resistance to Ciprofloxacin in Patients Presenting with Typhoid Fever

Salmonella Resistance
to Ciprofloxacin in
Typhoid Fever

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ABSTRACT

Objective: To determine the frequency and common factors leading to ciprofloxacin resistance to salmonella among patients presenting with typhoid fever.

Study Design: Descriptive / Cross Sectional Study

Place and Duration of Study: This study was conducted at the Department of Medicine, Qazi Hussain Ahmad Medical Complex, Nowshera from 23-01-2018 to 22-07-2018.

Materials and Methods: Through a Descriptive Cross Sectional Study Design, a total of 195 patients with typhoid fever were selected in a consecutive manner from Medical Wards and tested for resistance of salmonella to ciprofloxacin and common risk factors leading to it such as prior use of ciprofloxacin and recurrent typhoid fever were also scrutinized.

Results: The mean age of patients was 29.4 ± 11.56 years with 63% male gender predominating the overall sample of typhoid fever. On disc diffusion (Kirby Beur) method salmonella resistance to ciprofloxacin was found in 72 (36.9%) of patients with 36-45 years of age group most commonly affected age group (47%) and male (72.2%) commonly affected gender. The distribution of common factors leading to salmonella resistance to ciprofloxacin are: 46 (63.9%) had history of prior use of ciprofloxacin and 26 (36.1%) had recurrent typhoid fever.

Conclusion: As in many other parts of the world, salmonella resistance to ciprofloxacin is also common in our local population and the most common factor responsible for it is prior use of ciprofloxacin.

Key Words: Typhoid fever, ciprofloxacin, salmonella.

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INTRODUCTION

Typhoid fever is an important determinant of morbidity and mortality in many developing countries of the world especially in Asia¹. It is estimated that world over 16 to 33 million cases of typhoid fever cause deaths of 500,000 to 600,000 yearly². Indian subcontinent is considered to have the highest incidence of typhoid fever world-wide³.

Typhoid fever is a systemic infection. It is caused by the bacterium "Salmonella enterica" serotype "typhi"⁵. Pakistan is thus one of the hyper-endemic areas for this disease⁶.

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This bacterium is disseminated through oro-fecal route after ingestion of infected food or water by the feces or urine of the infected people⁶. Typhoid Fever is diagnosed through blood culture. Serological investigations are in use but having low sensitivity and specificity. As blood culture takes many days, it is usual to start treatment in any patient with suspected typhoid fever on the basis of clinical findings and positive serology⁷.

Typhoid fever can cause complications in many parts of the body. However the most serious complications are intestinal hemorrhage and perforation. Typhoid ileal perforation is recognized as a dominant reason of morbidity and mortality in patients with typhoid fever⁸. In order to prevent these complications and hence morbidity and mortality of this disease, it is important to diagnose the disease early and then to start appropriate antibiotic⁹.

The choice of drug for typhoid fever treatment is a fluoroquinolone like ciprofloxacin. However recent studies have shown that ciprofloxacin resistance salmonella is increasing due to the widespread and irrational use of ciprofloxacin in many different conditions¹⁰. It is estimated that prevalence of ciprofloxacin resistance may be as high as 38 percent in Pakistan¹¹. In a recent study in Ontario, Canada,

decreased susceptibility of salmonella to ciprofloxacin was found in 80% of patients. Majority of these patients belonged to Indian subcontinent¹². Another study carried out in India regarding anti-microbial resistance of salmonella typhi showed reduced susceptibility to ciprofloxacin in 24% of cases¹³. So there are dramatic geographic variations in ciprofloxacin resistance salmonella.

There are some factors that may lead to ciprofloxacin resistance salmonella like irrational use of ciprofloxacin in about 40% of cases and recurrent typhoid fever in about 14% of cases¹⁴. The optimal management of typhoid fever depends on understanding of local pattern of resistance to different drugs¹⁵.

Although patients with suspected typhoid fever are empirically treated with ciprofloxacin but no research has been formulated on ciprofloxacin resistance in local population. My study will determine the frequency of ciprofloxacin resistance in patients with typhoid fever which is important for us because ciprofloxacin resistance has vast geographical variation and also to identify common factors involved which will contribute to local magnitude of the problem. The study results will be compared with previous national and international data, so as to provide guidance for an improved empirical treatment in our local population with typhoid fever.

MATERIALS AND METHODS

This study was conducted in the in the Department of Medicine, Qazi Hussain Ahmad Medical Complex, Nowshera from 23-01-2018 to 22-07-2018. Through a Descriptive Cross Sectional Study Design, a total of 195 patients using proportion of ciprofloxacin resistance salmonella as 24%¹³, 95% confidence level and 6% margin of error using WHO sample size calculation, with typhoid fever were selected in a consecutive manner from Medical Wards and tested for resistance of salmonella to ciprofloxacin and common risk factors leading to it such as prior use of ciprofloxacin and recurrent typhoid fever were also scrutinized.

Inclusion Criteria:

- All patients with typhoid fever with salmonella positive blood cultures.
- Both genders (male and females) were included.
- All patients with age greater than 13 years.

Exclusion Criteria:

- Patients with co-morbid conditions like diabetes mellitus, AIDS, transplant recipients. Detected on the basis of patients previous medical history.
- The above conditions act as confounders and if included, will institute bias in the results.

Data Collection Procedure: Data was collected through specially designed proforma. Informed written consent was sought from all the patients. Final approval from the ethical review committee was taken. All

admitted patients in department of medicine, whether from OPD or casualty were included in the study presenting with typhoid fever with IgM positive and having salmonella positivity on blood cultures. A detailed relevant history was taken from the patients. Special enquiry was made about the prior ciprofloxacin use and past history of typhoid fever.

10ml of venous blood sample was taken from every patient under strict aseptic technique. The blood was immediately injected into blood culture bottle and sent to hospital laboratory for the detection of ciprofloxacin resistance to salmonella. Among those patients in whom ciprofloxacin resistance to salmonella is detected were carefully scrutinized for the detection of common factors leading to it (recurrent typhoid fever and history of prior use of ciprofloxacin)

All patients were started on empirical antibiotics and blood culture and sensitivity report were followed. All the above information including name, age, gender and address were recorded in a pre-designed Performa. Exclusion criteria was strictly followed to control confounders and biases. All the laboratory procedures are conducted under strict supervision of single expert "Pathologist" having experience minimum of 5 years.

Data Analysis: Data was collected through specially designed Performa and analyzed using SPSS 13. Frequencies, percentages were calculated for categorical variables like gender, ciprofloxacin resistance to salmonella and common factors (recurrent typhoid fever and history of prior use of ciprofloxacin). Mean and SD was calculated for numerical variables like age. Ciprofloxacin resistance and common factors were stratified among age and gender to see the effect modifications. Results are presented in the form of tables and charts.

RESULTS

A total of 195 patients of typhoid fever were enrolled in the study. There were 123 (63%) male and 72 (37%) females.

The mean age of the patients was 29.4 ± 11.56 years. While distributing the sample of typhoid patients in different age groups, we found that in the age group 13-25 years there were 48 (24.6%), in the age group 26-35 years there were 102 (52.3%), in the age group 36-45 years there were 34 (17.4%) while in the age group 45+ years there were only 11 (5.6%) patients. (Table 1). On Disk Diffusion method (Kirby Bauer) out of 195 patients with typhoid fever, 72 (36.9%) patients were found to have salmonella Resistance to ciprofloxacin and out of which 52 (72.2%) were males and 20 (27.8%) were females (Table 2).

On stratification we found that out of total 123 males, 52 (42.3%) were having salmonella resistance to ciprofloxacin and out of total 72 females with typhoid fever 20 (27.8%) were resistant to Ciprofloxacin

showing resistance pattern in more in male as compared to females. (Table 3).

While stratifying the salmonella resistance to ciprofloxacin, out of total 48 patients in the age group 13-25 years 7 (14.6%) were resistant, in the age group 26-35 years out of total 102 patients 45 (44%) were resistant, in the age group 36-45 years out of total 34 patients 16 (47%) were resistant and in the age group 45+ years out of total 11 patients 4 (36.4%) were resistant. (Table 4)

Out of 72 patients with salmonella resistance to ciprofloxacin, history of prior use of ciprofloxacin was found to be the most common factor leading it with total 46 patients in that group (63.9%) while recurrent typhoid fever contributed 26 (36.1%) of the resistance. (Table 5)

While stratifying the common factors among gender, we found that in among total 52 male patients with ciprofloxacin resistance to salmonella, 33 (63.5%) patients had used ciprofloxacin in the past while 19 (36.5%) had history of recurrent typhoid fever. Among 20 female patients with ciprofloxacin resistance, 13 (65%) had history of ciprofloxacin use in the past while 7 (35%) had history of recurrent typhoid which shows that gender has no effect on factors. (Table 6)

While stratifying the common factors among different age groups, we found that different factors have different relations with the age groups. In the age group 13-25 years out of total 7 resistant cases 2 (28.6%) had history of prior use of ciprofloxacin while remaining 5 (71.4%) had recurrent typhoid fever. In the age group 26-35 years out of total 45 resistant cases 34 (75.6%) had history of prior use of ciprofloxacin while remaining 11 (24.4%) had recurrent typhoid fever. In the age group 36-45 years out of total 16 resistant cases 9 (56.3%) had history of prior use of ciprofloxacin while remaining 7 (43.7%) had recurrent typhoid fever. In the age group 45+ years out of total 4 resistant cases 1 (25%) had history of prior use of ciprofloxacin while remaining 3 (75%) had recurrent typhoid fever. (Table 7).

Table No. 1: Age-Wise Distribution of Sample (n=195) [DMJK1]

Age Ranges [In Years]		Percentage
13-25	48	24.6%
26-35	102	52.3%
36-45	34	17.4%
45+	11	5.6%
Total	195	100%

Table No. 2: Salmonella Resistance to Ciprofloxacin (N=195)

Salmonella Resistance	No of Patients	Percentage
Yes	72	36.9%
No	123	63.1%
Total	195	100%

Table No. 3: Gender Wise Stratification of Salmonella Resistant Patients (n=72)

Gender	Total No of Patients	Resistant Cases	Percentage
Male	123	52	42.3%
Female	72	20	27.8%
Total	195	72	

Table No. 4: Age-wise stratification of resistant cases (n=72)

Age ranges [in years]	Total No of Patients	Resistant Cases	Percentage
13-25	48	7	14.6%
26-35	102	45	44%
36-45	34	16	47%
45+	11	4	36.4%
Total	195	72	

Table No. 5: Common factors leading to resistance (n=72)

Risk factor	No. of cases	Percentage
History of Ciprofloxacin Use	46	63.9%
Recurrent Typhoid Fever	26	36.1%
Total	72	100%

Table No. 6: Gender wise stratification of common factors (n=72)

Gender	Resistant Cases	Prior use of Ciprofloxacin	Recurrent Typhoid Fever
Male	52	33 (63.5%)	19 (36.5%)
Female	20	13 (65%)	7 (35%)
Total	72	46 (63.9%)	26 (36.1%)

Table No. 7: Age wise stratification of common factors (n=72)

Age Range	Resistant Cases	Prior use of Ciprofloxacin	Recurrent Typhoid Fever
13-25	7	2 (28.6%)	5 (71.4%)
26-35	45	34 (75.6%)	11 (24.4%)
36-45	16	9 (56.3%)	7 (43.7%)
45+	4	1 (25%)	3 (75%)
Total	72	46 (63.9%)	26 (36.1%)

DISCUSSION

Typhoid fever caused by “Salmonella enterica”, Serovar typhi (*S. typhi*), remains a significant problem in developing countries¹⁴. It is approximated that, typhoid fever causes more than 20 million cases and 700,000 deaths worldwide every year¹⁵. In developing countries, the antibiotics most easily available for treatment of typhoid are chloramphenicol, ampicillin, and cotrimoxazole¹⁴. In *S. typhi* plasmid-incoded resistance to these three drugs were reported from South-East-Asia.

The rate of drug resistant *Salmonella typhi* is increasing rapidly, notably in the Indian subcontinent and South-East Asia. Ciprofloxacin has remained the drug of choice for enteric fever for the last many years¹⁶. However, isolates of *Salmonella enterica* Serovars typhi and Paratyphi A with decreased susceptibility to fluoroquinolones have now appeared in the subcontinent, Vietnam and Tajikistan, and the treatment failures with fluoroquinolones have also been noted¹⁷.

The public health community has a suspicion about the probability that animals which are given antibiotics are then utilized by humans may play role in resistance of human pathogens.^{18,19}

Several antibiotics are important to human medicine because they are effective against resistant pathogens. Fluoroquinolones are among these important antibiotics, so the emergence of fluoroquinolone-resistant *Salmonella Typhi* is potentially an alarming problem. A recent survey by the National Health Research Institute of Taiwan found that five antibiotics important to human medicine, including a fluoroquinolone (ciprofloxacin), have been widely added to animal feed for years²⁰.

The emergence of fluoroquinolone resistance would change the policy for the treatment of *S. Typhi* infections. Because the majority of *S. Typhi* isolates are also resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, the third-generation cephalosporins are now the only antibiotics with reliable activity against²¹.

This study was designed to determine the frequency of salmonella resistance to ciprofloxacin and common factors leading to it. In our study a total of 195 patients presenting with typhoid fever were included. In our study, there were 63% males and 37% females. This was in contrast in a study by Wain J et al²² as in his study out of 132 patients with typhoid fever, 51.5% were males while 48.5% were female gender. The mean age group in our study was 29.4 ± 11.56 years and again it was in contrast with the study by Wain J et al²² as the range of age in his study was 7-21 years only.

On Disk Diffusion method (Kirby Bauer) out of 195 patients with typhoid fever, 36.9% patients were found to have salmonella Resistance to ciprofloxacin. Various studies have been done in the literature not only on resistance of various species of salmonella on ciprofloxacin but also on the multiple drugs. Although the proportion of this resistance is not low in our population but even higher proportion were observed in various studies like Chiu C et al²¹ reporting ciprofloxacin resistance was found in 60% of isolates of salmonella, Morris SK et al¹² reported it to be 80% in Canada. Another study from Pakistan reported salmonella resistance to ciprofloxacin to be 38%¹¹ which was a bit comparable to our study and another study from India reported this resistance of 24% somewhat less than what was observed in our study

however, another study from New Delhi India by Chandel DS²³ et al reported none of resistance of salmonella to ciprofloxacin though they found 32% isolates resistant to chloramphenicol and cotrimaxazole while another 13% to multi-drugs. A similar result of no ciprofloxacin resistance was observed by Anjum P et al²⁴ in Rawalpindi. Another local study from Pakistan by Mirza SH et al¹⁶, they reported the salmonella resistance to ciprofloxacin was observed in 65.5% of cases of typhoid fever. Yet another study by Ahmad D et al²⁵ reporting from Dhaka, a very high 90.6% of salmonella typhi isolates were found resistant to ciprofloxacin.

The above statistics explain a wide geographical variation in the resistance to ciprofloxacin and this further is supported by a strong evidence by Frost JA et al²⁶ who carried out a long study from 1991-1994 in England and Wales and showed the trend of changing resistance of salmonella to ciprofloxacin. In their study Resistance to ciprofloxacin, which increased from 0.3% in 1991 to 0.6% in 1992 and 0.8% in 1993 has doubled to 2.1% in 1994. In another study by Wain J et al²² the number of patients who were found to be having salmonella multi-drug resistance were 63% which also included ciprofloxacin. Another study by Threlfall EJ et al²⁷ 23% of *Salmonella enterica* serotype Typhi isolates from patients in the United Kingdom exhibited decreased susceptibility to ciprofloxacin, more than half were also resistant to chloramphenicol, ampicillin, and trimethoprim and important thing in their study was that most of the resistant cases had traveled to UK from India and Pakistan. The same study also reported an increasing resistance of salmonella to ciprofloxacin from 0% in 1990 to 23% in 1999.

Treatment failures with quinolones were significantly prevalent in infected patients with "nalidixic acid resistant *Salmonella typhi*" (NARST), than in those infected with "nalidixic acid sensitive *Salmonella typhi*" (NASST). Viet Nam study showed 2.1% isolates resistant to nalidixic acid with raised MICs to ciprofloxacin²². In recent years studies have been focused on fluoroquinolone resistance in *Salmonella* isolates with special reference to strains for which ciprofloxacin MICs were >0.125 mg/ml^{23,28}.

The common factors leading to salmonella resistance to ciprofloxacin reported in our study were history of ciprofloxacin use in the past (63.9%) and recurrent typhoid fever (36.1%). The reported frequency of these risk factors are bit higher if we compare them to study reported by Crump JA et al¹⁰ who observed 40% cases of ciprofloxacin resistance was caused by prior use of ciprofloxacin and 14% were caused by recurrent typhoid fever in the past. In another study reported by Ahmed D et al²⁵ from Dhaka, 88% of resistant cases to ciprofloxacin were found have used ciprofloxacin in the past.

CONCLUSION

As in many other parts of the world, salmonella resistance to ciprofloxacin is highly prevalent in our society. Prior use of ciprofloxacin and recurrent typhoid fever are the main culprits responsible for such resistance in our population. We recommend further research work over the similar objective with more comprehensive and variety of risk factors and also recommend changes in policy especially with regards to better control of endemic typhoid fever and on counter availability of antibiotics.

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

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Frequency of Hypothyroidism in HCV Positive Patients at Chandka Medical College Teaching Hospital Larkana

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ABSTRACT

Objective: To determine the frequency of hypothyroidism in hepatitis C patients presenting to tertiary care Hospital.

Study Design: Case Series study

Place and Duration of Study: This study was conducted at the Medical Unit-I Chandka Medical, Larkana from January 2019 to July 2019.

Materials and Methods: The study was conducted on patients following inclusion and exclusion criteria and ethical approval and informed consent. The blood samples for TSH, T3 and T4 levels were sent to the laboratory of Larkana Institute of Nuclear Medicine and Radiotherapy (LINAR).

Results: Our results have shown that some 4 (4.9%) patients were diagnosed as hypothyroid patients, being more common in females and younger age.

Conclusion: We propose a massive epidemiological study not only to gather the relevant data but also focusing on some of the factors and reasons for co existence of hypothyroidism and HCV. HCV patients should also provided information regarding side effects of its treatment, among which is most commonest is hypothyroidism.

Key Words: Hepatitis C, Hypothyroidism, Epidemiology, Association.

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INTRODUCTION

Hypothyroidism is a endocrine disorder due to decrease production of thyroid hormones. It has a preponderance to age, sex and race. Hepatitis C virus (HCV) is a small enveloped positive strand RNA virus classified in the Hepacivirus genus within the Flaviviridae family.⁰¹ Chronic hepatitis C virus (HCV) infection can lead to both hepatic and extrahepatic dysfunction and endocrine dysfunction is also one of the extrahepatic feature.² With chronic hepatitis C infection around 80% of infected patients leads to chronic liver disease, and hepatocellular carcinoma. Infected blood or blood products are common route for Hepatitis C spread from person to person. One of the speculated mechanism with association of chronic HCV infection with endocrine diseases is through a type 1 T-helper-cell mediated immune response.³

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In one of the case control study the HEP C infected controls had higher thyroid stimulating hormone (TSH) and lower free T3 and free T4 levels, than did uninfected controls.⁴ In another study HCV-infected patients had hypothyroidism secondary to autoantibodies like anti-thyroid peroxidase or anti-thyroglobulin autoantibodies of (13%) than controls (3-5%).² With chronic HCV infection a high prevalence of hypothyroidism was observed with higher prevalent autoimmunity.^{5,6} Another evidence of immune thyroid disease due to HCV virus infection was observed due to production of anti-thyroid autoantibodies.^{1,2} A study from India conducted on pregnant women who were anti-HCV antibody positive some 16.7% had abnormal thyroid-stimulating hormone (TSH) and (13%) with overt thyroid disease 5% sub-clinical thyroid disease.⁷ Type 1 T-helper cell pattern of cytokine expression and activation via interferon-gamma provides the clue towards association of autoimmune thyroid disease secondary to Hepatitis C. Chronic hepatitis C includes all type of thyroid dysfunction i.e. hypothyroidism, hyperthyroidism, Hashimoto's disease and isolated increases in anti-thyroid autoantibodies.² As compared to hepatitis B or hepatitis D, chronic hepatitis C had higher prevalence of thyroid disorders and thyroid autoantibodies than in control series.² Considering the all above evidences of associations, very few studies have been conducted in Pakistan and little international data available. Considering the prevalence of hepatitis C in Pakistan especially villages the importance of our

study increased many folds. It is of utmost importance to conduct a massive prevalence studies in the area so that the required data can be gathered to solve these two combined issues. In our study hypothyroidism was observed in 13% of the HCV positive patients. So anti HCV positive patients should be periodically screened for thyroid dysfunction.

MATERIALS AND METHODS

The study was conducted in Department of Medicine Medical Unit-I and Endocrine ward, Chandka Medical College after fulfilling the criteria for inclusion and exclusion. After clearance from ethical review committee, a written informed consent was obtained from patients respectively. The blood samples were drawn for serum TSH, T3 and T4 levels and were sent to the laboratory of Larkana Institute of Nuclear Medicine and Radiotherapy (LINAR). Using kit IMMUNOTECH by Beckman Coulter company by immuno radiometric assay (IRMA) and radio immunometric assay (RIA) for TSH, T3 and T4 respectively by. A proforma was designed and filled with these variables along with demographic information and results of the blood tests for hypothyroidism.

Data Analysis: Version 17 of SPSS was used to enter the data. Descriptive statistics was used to summarize the categorical and continuous data. Frequencies and percentages was computed for the gender, hypothyroidism in hepatitis C. The mean \pm S.D was calculated from continuous data. Age, duration of diseases and gender stratification done to see impact of these variables on outcome.

Operational Definition:

Hepatitis C Patients: Patients were labeled Hepatitis C positive, who had anti HCV anti bodies detected by ELISA.

Hypothyroidism: Patients were labeled hypothyroid, who had serum TSH >7.1 mIU/ml (normal 0.4 mIU/ml to 7.1 mIU/ml), decrease T3 < 2.5 pmol/l (normal 2.5 pmol/l – 5.8 pmol/l) and T4 < 11.5 pmol/l (normal 11.5 pmol/l to 23 pmol/l) levels in serum.

Inclusion Criteria: All the patients of age more than 12 years of either sex having anti HCV anti body positive, detected by second generation ELISA method.

Exclusion Criteria: All patients fulfilling the below criteria were excluded from study.

1. Patients treated for Hepatitis C with interferon and ribavirin
2. Iodine deficiency
3. Post partum thyroiditis
4. History of thyroidectomy
5. Iatrogenic (radioactive iodine therapy for hyperthyroidism)

Patients taking drugs like amiodarone, thalidomide and lithium were also excluded from the study.

RESULTS

In this study a total number of 103 patients were enrolled after fulfilling the inclusion criteria. The mean age of the patients were 37.43 ± 9.04 years with age range between 19 to 58 years. The proportion of males were higher of 73 (70.9%) as compare to the proportion of female that was 30 (29.1%). The maximum number of patients were thirty six (35.0%) falling in age between 31 to 40 years of age. Fifty one (49.5%) patients had duration of anti HCV antibody positive between 6 to 12 months while 28 (27.2%) patients were duration of anti HCV antibody positive more than 12 months. Hypothyroidism was observed in 5 (4.9%) patients who were positive for Anti HCV antibody. When compared the gender with duration of HCV more male 37 (50.7%) patients was observed with duration of HCV 6 to 12 months. Similarly female 4 (13.3%) patients with hypothyroidism compared with male 1 (1.4%) patients. When age is compared with duration of age we found 19 (52.8%) patients between 6 to 12 months, two (5.6%) patients were found less than 6 months and eight (22.2%) patients more than 12 months. 3 (9.4%) patients were found with hypothyroidism between the age group of 21 – 30 years.

Table No.1: Age, mean \pm ST-Deviation

	N	Minimum	Maximum	Mean	Std. Deviation
Age	103	19	58	37.43	9.035

Table No.2: Age distribution

Age group	Frequency	Percent
<21 years	1	1.0
21-30 years	32	31.1
31-40 years	36	35.0
41-50 years	24	23.3
>50 years	10	9.7
Total	103	100.0

Table No.3: Distribution of duration of HCV

Duration of HCV	Frequency	Percent
Not Known	21	20.4
< 6 Months	3	2.9
6-12 Months	51	49.5
> 12 Months	28	27.2
Total	103	100.0

Table No.4: Frequency of Hypothyroidism

Hypothyroidism	Frequency	Percent
Present	5	4.9
Absent	98	95.1
Total	103	100.0

Table No.5: Comparison of gender according to Anti HCV Antibody Positivity

Sex	Since Anti HCV Antibody Positivity Duration				Total
	Not Known	< 6 Months	6-12 Months	> 12 Months	
Male	11 (15.1%)	2 (2.7%)	37 (50.7%)	23 (31.5%)	73 (100.0%)
Female	10 (33.3%)	1 (3.3%)	14 (46.7%)	5 (16.7%)	30 (100.0%)
Total	21 (20.4%)	3 (2.9%)	51 (49.5%)	28 (27.2%)	103 (100.0%)

Table No.6: Comparison of gender according to Hypothyroidism

Sex	Hypothyroidism		Total
	Present	Absent	
Male	1 (1.4%)	72 (98.6%)	73 (100.0%)
Female	4 (13.3%)	26 (86.7%)	30 (100.0%)
Total	5 (4.9%)	98 (95.1%)	103 (100.0%)

Table No.7: Comparison of Age According to Duration of Anti HCV Antibody Positivity

Age group	Duration since Anti HCV Antibody Positivity				Total
	Not Known	< 6 Months	6-12 Months	> 12 Months	
<21 years	0 (0%)	0 (0%)	1 (100.0%)	0 (0%)	1 (100.0%)
21-30 years	7 (21.9%)	0 (0%)	17 (53.1%)	8 (25.0%)	32 (100.0%)
31-40 years	7 (19.4%)	2 (5.6%)	19 (52.8%)	8 (22.2%)	36 (100.0%)
41-50 years	3 (12.5%)	1 (4.2%)	10 (41.7%)	10 (41.7%)	24 (100.0%)
>50 years	4 (40.0%)	0 (0%)	4 (40.0%)	2 (20.0%)	10 (100.0%)
Total	21 (20.4%)	3 (2.9%)	51 (49.5%)	28 (27.2%)	103 (100.0%)

Table No.8: Comparison of Age According Hypothyroidism

Age group	Hypothyroidism		Total
	Present	Absent	
<21 years	0(0%)	1 (100.0%)	1(100.0%)
21-30 years	3(9.4%)	29(90.6%)	32(100.0%)
31-40 years	1 (2.8%)	35 (97.2%)	36 (100.0%)
41-50 years	1 (4.2%)	23 (95.8%)	24 (100.0%)
>50 years	0 (0%)	10(100.0%)	10(100.0%)
Total	5 (4.9%)	98 (95.1%)	103(100.0%)

DISCUSSION

Hypothyroidism is a endocrine disorder resulting from decreased production of thyroid hormones. Autoimmune hypothyroidism is linked with chronic hepatitis C infection. Our results have shown that the some 14 patients (11.1%) found to be hypothyroid, out of which 9 (9.6%) hypothyroid were male and 5 hypothyroid (15.6%) were female.

Like our study, many conducted studies have shown the nearly same association of hypothyroidism and hepatitis

C of 15.3% which is 1% higher than our study. An Indian study conducted for determination of the incidence of thyroid abnormality in pregnant women with hepatitis C virus (HCV) infection, found 13 women (16.7%) had abnormal thyroid-stimulating hormone (TSH) of >5 mIU/L in hypothyroid group.⁵

A retrospective study from Peshawar (Pakistan) of 9054 patients with thyroid problems, showed 4% and 5.4% of hypothyroid and subclinical hypothyroid frequency in adult group which is slightly different from our study showing more in old age group and women.¹⁰ A comparative study was done in 630 patients with hepatitis C to determine its association of with thyroid disorders, which included a control group of 389 and 268 subjects from an iodine-deficient area and iodine sufficient area, and third group of 86 subjects with chronic hepatitis B. The results found that chronic hepatitis C patients 13% patients had hypothyroid 38% patient had thyroid antibodies than rest of the groups.³

A study from Greece showing the incidence and features of thyroid disease, and to identify its outcome in treated and untreated chronic hepatitis C patients. Out of some 94 patients with chronic hepatitis C 11 found to be hypothyroid and 2 hyperthyroid, which subsequently landed to hypothyroidism.⁶

As compared to study conducted in Sindh Pakistan for determining the frequency of thyroid abnormalities with interferon and ribavirin treatment of chronic hepatitis C, 84.6% patients out of 100 had hypothyroidism and 15.3% pts had hyperthyroidism⁷ which is inferior to our study in relation to define cause and outcome where interferon treated patients are in exclusion criteria.⁸

A study from Italy on auto immune thyroid abnormalities in a cohort of untreated children with vertically acquired, chronic, HCV infection, showed that 11.1% HCV-infected children suffered subclinical hypothyroidism.⁹

A study from Poland for frequency determination of thyroid abnormality (TD) during antiviral treatment of chronic hepatitis C (CHC).Thyroid dysfunction occurred in 40 patients (33.3%), more often in women than in men, which is similar to our study 156 % female and 96% male,¹¹ though its age statics showed no differences where as our study showed positive findings in old age group. The range of thyroid antibodies was 4.6 to 15% in chronic Hepatitis C infection.¹²

A retrospective performed on 94 patients with Chronic Hepatitis C by Vezali et al.¹³ to evaluate thyroid function for the development of autoimmune thyroid diseases. The sum 33 patients were in control group as compare to 61 patients in treatment group who received had treatment with PEG-IFN- plus ribavirin. After the follow up of 80.1 and 39.4 months duration, 13 (21.3%) patients on PEG-IFN- plus ribavirin had 13 patients developed thyroid disorder out of which 11 had hypothyroidism.¹²

A UK based study showed higher frequency of

antibodies against chronic hepatitis C from France in autoimmune thyroid patients. A 16 patients comes out to be anti HCV antibody positive in 46 autoimmune thyroid disease.¹⁴

Our study results have shown in line prevalence of hypothyroidism in HCV than the international world. This is due to the proposed factors are not related to socio cultural and underdeveloped and ill developed facilities and institutions have no role on this association.

The results of our study would provide a strong rationale where from other studies could built their hypothesis and massive epidemiological studies. Our study results would also provide the health policy makers and decision bodies to pursue this as an issue in our country. So that this combined epidemic could be controlled.

CONCLUSION

The study concluded that in the sample of HCV patients some patients were diagnosed as hypothyroid, being more common in female and at younger age. The prevalence of hypothyroidism is in line with other studies conducted internationally. Also international studies has shown similar predisposition for females like our study. On the basis of our findings we would propose a massive epidemiological study not only to gather the relevant data but also focusing on some of the factors and reasons for co existence of hypothyroidism and HCV. We also propose that HCV patients should also provided information regarding side effects of its treatment, among which is most commonest is hypothyroidism.

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