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TABLE OF CONTENTS

TABLE OF CONTENTS

Cultivating Psycological Safety: Cornerstone of Resident Wellbeing

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Medical residency is a critical phase in the professional development of young physicians. It is during this period that residents acquire the necessary skills, knowledge, and confidence to become independent practitioners. The concept of psychological safety often underappreciated is crucial in fostering a supportive and nurturing environment for these young professionals. It refers to an environment where individuals feel safe to express themselves without fear of retribution, embarrassment, or judgment. It is characterized by creating a culture where residents feel free to seek guidance, admit mistakes and voice uncertainties without worrying about jeopardizing their careers.[1] It is a critical component of any healthcare team or organization to promote the free flow of ideas, innovations, and difficult conversations.[2] In the context of medical residents, psychological safety plays a pivotal role in creating an atmosphere that encourages learning, collaboration, and personal growth.

Medical residency is very stressful job dealing with life and death of human beings. That is the time to start a family as well, female residents have to go through tougher times of pregnancy, breastfeeding and have great challenge of work life balance. The residents in our country are unhappy with their work place and have low job satisfaction.[3] There are multiple reasons including long working hours, intense emotional environment, financial instability, poor career guidance and poor research facilities which lead to burnout among residents. Lack of support and mentorship, unclear expectations, inadequate feedback by mentors and lack of autonomy are other crucial factors.

Burn out during residency has gained significant attention as it impacts work performance and patient safety. It is known to compromise patient care due to poor professionalism and results in low satisfaction of patients.[4,5] Psychological safety reduces the burnout by encouraging residents to ask questions, seek feedback, and engage in open dialogue with their mentors and colleagues. When residents feel safe to admit their knowledge gaps or mistakes, they can actively participate in their learning process and address areas that require improvement. The researchers found that residents who perceived a higher level of psychological safety in their learning environment demonstrated greater confidence, improved communication, better overall performance and lesser burnout.[6,7] A systematic review examined the relationship between psychological safety and learning outcomes among healthcare professionals. The review concluded that psychological safety was positively associated with increased engagement, active learning, and knowledge acquisition.[8]

However, achieving and sustaining psychological safety requires a collective effort from hospital leadership, supervisors and the residents themselves. Here are few ways to cultivate culture of psychological safety:

- Cultivating a **culture of respect and non-judgment,** where feedback is constructive and supportive.
- Encouraging **open communication** and active listening among residents, attending physicians, and other members of the healthcare team.
- Promotes **Mentorship and Guidance** for providing regular opportunities for feedback, allowing residents to express concerns, seek guidance, and learn from experienced professionals.
- Recognizing and **Addressing power dynamics**

within the medical hierarchy to ensure that residents feel empowered to voice their opinions and contribute to decision-making.

- Offering **resources and support services** to promote resident well-being and mental health, such as counseling, peer support groups, and work-life balance initiatives.
- Residents **Engagement** are more likely to actively involve them in their educational journey, seek out new experiences, and embrace opportunities for growth and improvement.
- Arranging **workshops and training sessions** related to stress management, team work and communication.
- Making residents **part of various committees** can help them voice their concerns and help improve patient care.

Ensuring psychological safety for medical residents should be a top priority for medical education and healthcare institutions. By fostering an environment where residents feel safe, supported, and empowered, we can cultivate resilient, engaged, and empathetic physicians who will provide the highest quality of care to their patients while maintaining their own well-being.

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Inculcating Systems Thinking in Public Health – A Dire Need of Time

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There has been a growing interest in the application of systems thinking to public health over the last decade. Systems thinking and science is a broad category of analytical methodologies aimed at exploring the behavior of complex systems.[1] It is an approach to problem-solving places more emphasis on understanding complex systems and their interrelationships, rather than just focusing on individual components. In general, a systems thinking perspective requires curiosity, clarity, compassion, choice, and courage.

In public health and health promotion, systems thinking is a fundamental ability that aids professionals in developing policies and initiatives that are conscious of and prepared for unintended consequences when complex systems of factors interact to affect health outcomes. Understanding broader health variables including social and economic factors is made easier by this. The social determinants of health are a group of variables that can have a significant impact on health outcomes. These variables include income, education, housing, and social support. Understanding these components' interactions with one another and with other systems, such as the healthcare system or the environment, is facilitated by systems thinking.[2]

By applying systems thinking approach in design and implementation of public health programs provide assistance in recognizing the potential unintended consequences or areas where the program may need to be strengthened or modified. One example of the importance of systems thinking in public health is the study of infectious diseases; a complex interaction of environmental, social, and biological factors underlies the development of many infectious diseases. For instance, factors like poverty, social inequality, a lack of access to healthcare, and poor public health systems have an impact on the development of diseases like HIV and tuberculosis.[3]

Same stands true for chronic diseases and as a developing nation we are facing double burden of diseases. In Diabetes and Breast cancer Pakistan is at the edge of volcano. These diseases are complex problems that requires collaboration among various stakeholders, including healthcare providers, public health officials, policymakers, and the community. Systems thinking encourages a collaborative approach, bringing together diverse perspective and expertise from policy makers to practitioners working to prevent chronic disease and inform their decision making about how to intervene; systems thinking and systems change are prioritized as core elements of preventive research.[4]

Understanding these complex interactions is essential for developing effective public health interventions as the world experienced recently in Covid-19 Pandemic.[5] This comprehensive and multidisciplinary systems approach relies on these four key components: (1) rapid and massive data collection from wide variety of sources; (2) rapid communication to a broad array of sources; (3) transdisciplinary science, to understand and analyze data from various sources; and (4) modeling of the complex relationships among the components in the system. These four elements are necessary for precise predictions and recommendations that can be used by policymakers to protect the health of the public.[6]

In conclusion, systems thinking is a powerful tool for understanding the complex systems that shape public health outcomes. Public health professionals need to recognize that it is a lifelong practice. By applying a systems thinking approach, public health professionals can better understand the interplay of

various factors and design more effective interventions to improve health outcomes for populations.

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Comparison of Clinical, Hematological and Biochemical Characteristics of Patients Suffering from Delta and Non-Delta Variant of COVID-19

Omair Farooq,[1] Waqas Sami,[2] Alia Waheed,[3] Asim Mumtaz,[4] ZainabYousaf,[5] Eazaz Ali Khan,[6] Atiqa Arshad[7]

Abstract

Objective: To compare the clinical, hematological and biochemical characteristics of patients suffering from delta and non-delta variants of COVID-19.

Method: This cross-sectional study was conducted at Farooq Hospital Westwood Lahore during 1st March 2022 to 31st August 2022. After obtaining informed written consent, nasopharyngeal swabs and 5 ml of blood samples in both EDTA and clotted vacutainers of eighty two infected patients with COVID-19, who were admitted in COVID-19 unit, were collected. The viral nucleic acid was isolated from nasopharyngeal swabs by using a Qiagen nucleic acid extraction kit. RT-PCR was performed to detect the delta variant in COVID-19 infected patients by using SARS-CoV-2 Variant B.1.617 identification kit. Further hematological and biochemical parameters were performed.

Results: We did a comparative analysis of clinical and laboratory characteristic of delta and non-delta COVID-19 patients admitted in Farooq Hospital Westwood, confirmed by RT-PCR and found that patients presented with delta variant had more severe disease with significantly more cough, fever, shortness of breath and lower SpO2 at the presentation. The hematological and biochemical markers showed more lymphopenia, greater CRP, Interleukin 6, LDH and ferritin. Hospital stay of delta variants of COVID-19 patients had longer duration as compared to the non-delta COVID-19 patients.

Conclusion: Delta COVID-19 had more severe disease with more dyspnea, hypoxia, hematological and biochemical parameters abnormalities compared to the non-delta COVID-19 patients. Patients suffering from delta variant of COVID-19 had greater length of hospital stay as compared to the non-delta variant of COVID-19 with more oxygen requirement and more mortality rate.

Keywords: Severe acute respiratory syndrome Coronavirus 2, coronavirus disease 2019, delta variant, non-delta variant

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Introduction

Millions of people have lost their lives as a result of the ongoing pandemic of the coronavirus disease 2019 (COVID-19), which has a significant impact not only on the global economy but also on public health. It is believed that severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) emerged from bats as the natural source of various coronavirus (CoV) strains, including SARS-CoV and SARS-CoV-2.1 SARS-CoV-2 is another name for this contributing agent. As a result of SARS-CoV-2 infections during this ongoing pande-

mic, new variants have emerged that are more robust and have a significant impact on public health. This has provided space and opportunities for evolution and mutation.[2]

The SARS-CoV-2 variants of concern (VOC): Alpha, Beta, Gamma, and Delta have an impact on public health due to their high transmission rates; the probability of an effect on the seriousness of Coronavirus; and the effect of public health measures, treatments, diagnosis, and vaccines that work well.[3-5] Pakistan's COVID-19 infectivity rate appears to be continuing to rise worldwide due to the SARS-CoV-2 Delta variant (B.1.617.2).[6-8] From March to May 2021, the third wave took place in Pakistan, shortly thereafter, in July the fourth wave began. There has been an estimated 1,039,695 cases in the country, with 23,462 deaths.[9-11]

The delta variant transmits approximately twice as much as the preceding variants.[11] One of the reasons for mutations in the spike (S) area, such as P681R and L452R is the higher transmission rate of the delta variant.[12,13] At the moment, the delta variant is the most widely distributed variant worldwide. Notably, the delta variant has been linked to a higher mortality rate than other variants, showing higher risk of serious outcomes, ICU admission, and hospitalization.[14-16] The COVID-19 disease has been linked to numerous prognostic factors. However, our understanding of the delta variant's impact on COVID-19 outcomes is limited.[17,18] In this study, we did the com-parative analysis of clinical, hematological and bioche-mical parameters of patients admitted in Covid-19 unit of Farooq Hospital Westwood Lahore and suffering from delta and non-delta variants of COVID-19.

Material and Method

This cross-sectional study was conducted at Farooq Hospital Westwood Lahore during 1st March 2022 to 31st August 2022 and approved by the ethical & review board of Farooq Hospital. After obtaining informed written consent, samples were collected. The demographics and clinical characteristics were recorded on the predesigned proforma. About 05 ml of blood samples in both EDTA and clotted vacutainers of eighty two COVID-19 infected patients were collected, who were admitted in the said duration. Nasopharyngeal samples were collected with cotton swabs and a viral transport medium (VTM). The VTM was stored at 2-8°C till further procedure.

The nucleic acid was extracted within 24 hours after the sample collection. The viral nucleic acid was isolated from nasopharyngeal swabs by using a Qiagen nucleic acid extraction kit. In the manual nucleic acid extraction procedure, different steps were followed. Briefly, we added 25µL qiagen proteinase, 200µL sample, 200µL lysis buffer, 250µL absolute ethanol, 500µL wash buffer 1, 500µL wash buffer 2, 500µL absolute ethanol, and elution buffer. The viral nucleic acid of each sample was eluted with 60µL elution buffer.

The extracted viral nucleic acids were immediately subjected to a one-step RT-PCR reaction. The remaining nucleic acids were stored at -70°C. After the nucleic acid extraction, RT-PCR was performed to detect the delta variant in COVID-19 infected patients by using SARS-CoV-2 Variant B.1.617 Identification Kit. It detected the three mutations (P681R, E484Q, and L452R) in patient samples. The master mix was prepared as per instructions (add (n+1)×19.0µL of RT-PCR Mix and (n+1)×1.0µL of Enzyme Mix into a 1.5mL centrifuge tube). After that, 20µl mastermix was added in a 0.2mL PCR reaction tube. 5µl extracted nucleic acid was added. Positive and negative controls were run with the test batch. All the tubes were placed in a thermocycler (Rotar Gene-Q 5plex). Denaturation was performed at 95°C for 3 minutes and again for 15 seconds. Annealing was performed at 50°C for 45 seconds and 50 cycles were used. The last step of the extension was done at 60°C for 60 seconds and 50 cycles were used. The results were considered positive for delta variant when P681R and L452R sites were detected mutated, while the E484Q site was not. From EDTA and clotted samples, hematological and biochemical parameters were performed.

Results

This study was planned to determine and compare levels of clinical and laboratory parameters in delta and non-delta variant of COVID-19 positive patients. A total of 82 COVID-19 patients were enrolled in this study. The patients were divided in two groups on the basis of the delta variant presence and absence i.e. COVID-19 positive patients with delta variant positive and non-delta variant patients. From total 82 COVID-19 patients, 30 patients were having delta variant while 52 were non-delta strain. The median age of the patients was 63 years in which the youngest patient aged 20 years and the oldest patient aged 90 years of age. Out of 82 patients, 46 patients were males and 36 patients were females. The demographic features of these patients in the two groups are given in table 1. Also, the table represents the association of these parameters with the

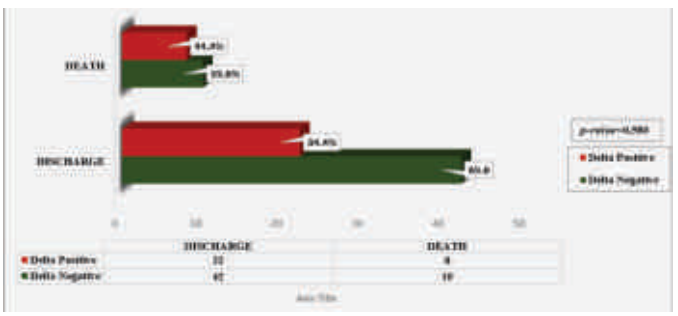
Table 1: *Frequency of demographic features and comparison in the two groups*

Variables	Delta Variant		P-value
	Negative	Positive	
	Median ± IQR	Median ± IQR	
Age	63.00 ± 18	64.50 ± 23	0.482
Variable	**n(%)**	**n(%)**	
Gender			
Female	25 (48.1%)	11 (36.7%)	0.499
Male	27 (51.9%)	19 (63.3%)	
Vaccination Status			
No	28 (53.8%)	17 (56.7%)	1.000
Yes	24 (46.2%)	13 (43.3%)	
Comorbidities			
None	19 (36.5%)	8 (26.7%)	0.970
Hypertension	6 (11.5%)	4 (13.3%)	
Diabetes mellitus	4 (7.7%)	3 (10.0%)	
Ischemic heart disease	1 (1.9%)	1 (3.3%)	
Multiple	22 (42.3%)	14 (46.7%)	
Oxygen Demand			
Room Air	20 (39.2%)	12 (38.7%)	0.977
5 Liter	11 (21.6%)	6 (19.4%)	
10 Liter	7 (13.7%)	4 (12.9%)	
15 Liter	6 (11.8%)	3 (9.7%)	
High Flow	7 (13.7%)	6 (19.4%)	

P value of <0.05 considered significant

groups.

The laboratory parameters were also analyzed in the two groups. The normality of these parameters was determined by Shapiro-Wilk test and it showed that all of these parameters were not normally distributed. Mann-Whitney U test was applied to determine the differences of these parameters in the two COVID-19 patients. C-reactive protein (CRP), ferritin and procalcitonin (PCT) showed statistically significant differences in the groups with p-value 0.026, 0.012 and 0.026 respectively. CRP, ferritin and PCT levels were statistically higher in the group with delta strain positive. The median



with IQR of these laboratory parameters in the two groups and the association is shown in the table 2.

Table 2: *Clinical and laboratory parameters with delta variant status of patients*

Variables	Delta Variant		P-value
	Negative	Positive	
	Median ± IQR	Median ± IQR	
Oxygen saturation	88.00±11.0	89.50±10.0	0.197
Hemoglobin	13.00±3.0	12.45±2.8	0.698
Total leukocyte count	9.2±8.5	10.85±5.6	0.622
Lymphocytes	11.0±8.0	10.0±6.0	0.567
Neutrophils	84.0±11.0	85.0±7.0	0.521
Platelets	223.5±10.0	205.50±81.0	0.509
Alanine aminotransferase (ALT)	37.5±29.0	44.50±42.0	0.275
Aspartate aminotransferase (AST)	38.50±21	40.0±34.0	0.890
Total protein	6.0±1.0	7.0±1.0	0.069
Albumin	4.0±1.0	4.0±0.0	0.129
Urea	42.0±23.0	40.50±36	0.698
Creatinine	1.0±0.1	1.0±0.1	0.565
Sodium	135.0±8.0	137.0±5.0	0.065
Potassium	4.0±0.0	4.0±1.0	0.158
CRP	56.0±42.0	73.5±41.0	0.026*
Ferritin	456.0±772.0	1059.5±962.0	0.012*
D-Dimer	0.69±0.54	0.67±0.53	0.491
Interleukin-6	40.5±67.3	35.0±56.0	0.609
Vitamin D	24.0±16.3	27.0±20.7	0.241
PCT	0.095±0.22	0.23±0.38	0.026*
Hospital stay	6.0±4.0	6.5±5.0	0.258

**Statistically significant association between the laboratory parameters and the delta variant status of the patient*
IQR= Inter quartile ranges
P value of <0.05 considered significant

Fig- 1: *Outcome of treatment among the delta negative and delta positive COVID-19 patients*

The outcome of the COVID-19 patients was also evaluated if they were discharged or died after the treatment. Almost 77% patients got discharged after the treatment and 21% patient died. The outcome status of the patient after treatment among the delta positive and negative patients is given in the figure 1.

Discussion

The delta variant is a globally growing dominant variant. The delta variant of SARS-CoV-2 disease was spread all the more pervasively, prompting considerable more infected cases unlike low transmission and high mortality of MERS-CoV and SARS-CoV disease that happened a few years prior. The symptoms of the delta variant are different from other variants in terms of severity. One of the reasons for the speedy transmission of the

delta variant was that the people did not wear face masks and stopped following necessary guidelines designed for SARS-CoV.19,20 The comparative analysis of clinical and laboratory parameters of delta and non-delta SARS-CoV-2 patients admitted in Covid-19 unit of Farooq Hospital Westwood was done. Patients presented with delta variant had lower oxygen saturation at the time of presentation. Delta variant patients had a longer hospital stay than non-delta COVID-19 patients. The prevalence of delta variant in vaccinated and unvaccinated patients was not different. A study is consistent with the present study that also showed that the prevalence of delta variant was not affected by vaccination.[21]

Patients with several other comorbidities like hypertension, diabetes mellitus, and ischemic heart disease are associated with severity and mortality.[22] In this study, comorbidities were not found to be significant with the delta variant. But they are still related to the high death ratio and needed admissions to the hospital's ICU. The hematological parameters were found to be not associated with the delta variant. In other words, the complete blood count parameters were less changed and not helpful in diagnosis and treatment outcome of this disease. Another important finding in the present study was that serum CRP, PCT and ferritin were quite deranged in delta variant patients. In COVID-19 these biochemical parameters were also found associated with the disease progression and severity.[23-25] This association represents the similarity in pathogenesis of delta variant and non-delta variant diseases.

Conclusion

In this study, we found a higher rate of hospital admissions and emergency care of patients with COVID-19 patients infected with the delta variant as compared with the non delta variant. The consequence of this study shows that the person with young age can also develop the delta variant infection. The patients with delta variant had more serious illness with lower oxygen saturation. Biochemical markers showed higher levels of CRP, PCT and ferritin. Delta positive patients also had longer hospital stay with high mortality rate than non-delta COVID-19 patients.

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Authors Contribution

AM: Conceptualization of Project
EAK, AA: Data Collection
OF: Literature Search
WS: Statistical Analysis
ZY: Drafting, Revision
AW: Writing of Manuscript

Frequency and Association of Gamble Variables of Impaired Glucose Tolerance Among Medical Students

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Abstract

Objective: To find out the frequency and association of gamble variables of impaired glucose tolerance among medical students.

Method: This cross-sectional study was conducted at Quaid-e-Azam Medical College Bahawalpur in month of March 2022 to assess the frequency of impaired glucose tolerance and the factors predisposing to the same. After necessary permissions, participants giving written informed consent were interviewed and participants were subjected to an oral glucose tolerance test (OGTT) and their heights, weights were measured.

Results: None of the participants had increased fasting blood glucose but 60 min after OGTT serum glucose levels were increased in 79(49.37%) subjects and 120 min after OGTT serum glucose was increased in 15 (9.3%) subjects. There was association of age, male gender, increased BMI, positive family history of diabetes, lack of physical activity, junk food intake and smoking with impaired glucose tolerance in medical students.

Conclusions: Impaired glucose tolerance was found in a substantial number of non-diabetic medical students and had a statistically significant association with gamble variables high BMI, family foundation of diabetes middle financial class, scarce physical activity, high junk food intake and smoking.

Keywords: Diabetes Mellitus, Prediabetes, Gamble Variables, Impaired fasting glucose (IFG), Impaired Glucose Tolerance (IGT).

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Introduction

Diabetes mellitus is an ongoing illness. As per the According to the International Diabetes Federation (IDF), the current burden of diabetes worldwide is approximately 415 million and is projected to rise to 642 million by 2040.[1] Death rates for individuals with diabetes are 2-3 overlay higher than non-diabetics; with cardiovascular and renal illnesses as the main source of death.[1] Albeit the commonness of both sort 1 and 2 Diabetes Mellitus is expanding around the world, the pervasiveness of sort 2 Diabetes Mellitus is rising significantly quickly, apparently due to expanding stoutness, diminished movement levels as nations have become more motorized, and the maturing of the populace. Similarly, there is a growing trend towards the development of type 2 diabetes mellitus at a much younger age than in the past.[5] The unusual glucose homeostasis in prediabetes leads to impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Various way of life changes and pharmacologic specialists forestall or postpone the beginning of DM.4 Early detection and treatment are crucial in reducing morbidity and mortality associated with type 2 diabetes mellitus. Screening for diabetes and pre-diabetes should be considered in males, especially those with a BMI greater than 25 kg/m², by a healthcare professional within the healthcare setting.[1] Gamble variables also include family foundation of

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diabetes, wealth index, junk food intake ,smoking and many more. The oral glucose resistance test (OGTT) is as of now the highest quality level for the conclusion of populace with prediabetes.[2]

Material and Methods

This cross sectional study was study was conducted at was conducted at Quaid-e-Azam Medical College Bahawalpur during the month of March 2022 to assess the prevalence of impaired glucose tolerance among medical students and the factors leaning toward something almost identical among them. Ensuing to getting assents from the Ethical review Board ERB and trained professionals. for coordinating the survey, individuals thru convenient sampling, giving created informed consent (n=160) after excluding 5 who had fasting serum sugar of >120 mg per dl, were talked with the aid of a predesigned and pretested survey sheet. Height of every member was estimated by a typical estimating tape upward lifted on an upward wall and the weight was estimated by a spring type pre-adjusted balance. Members were asked to fast for 8 hours and then exposed to an Oral Glucose tolerance Test. 75 gm of glucose dissolved in 100ml of water was given for ingestion and blood glucose was estimated utilizing a pre-adjusted hand held glucometer gadget before the glucose challenge I e. after 8 hours fasting and then after the glucose challenge at 60 min, and 120 min stretches. The got information was analysed through SPSS version 24. Simple frequencies and percentages were calculated and presented in the form of tables and figures. Chi square test was used as test of significance as the variables are qualitative in nature. P-value <0.05 was considered significant. Diabetes is defined as fasting serum glucose of >7.0 m mol per litre (126 mg per dl). Prediabetes is a condition characterized by fasting serum glucose levels ranging from 6.1 to 6.9 mmol/L. (110-125 mg per dl) and impaired glucose tolerance is defined as a serum glucose level >140 mg per dl after 120 min of 75 gms of oral glucose tolerance test.

It is a determinant or a factor which is associated with an increased risk of any disease or infection.

BMI :

calculated by weight in kg divided by height in meter square .WHO classification for BMI was used.

Underweight	18.5
Normal	18.5-24.9
Overweight- preobese	25-29.9
Obese	>30

Financial Status was based on income of the family in a month (in rupees)

Priveleged class	>100000
Working class	50000-100000
Lower class	<50000

Results

The circulation of study members as per age and gender shows that 88 (55%) of the members were women, while 72 (44%) were men. 80(50%) of all the members were between 21-23 years age bunch. Segment profile of the members is portrayed in (Table 1). Oral Glucose tolerance test OGTT: This study concluded that after 60min of OGTT, Out of 88 females,44(50%) had serum sugar 140-200 mg per dl while out of 72 males, 32 (44.44 %) had serum sugar 140-200 mg per dl. Only 3% of all had serum sugar >200 mg per dl after 60 min of glucose tolerance test. Out of total 160 study participants, 15(9.3%) had impaired glucose tolerance (serum Sugar >140 mg per dl).Out of 88 females,8(7.95%) and out of 72 males,7 (11.11%) had impaired glucose tolerance being slightly higher frequency in male medical students (Table 2) Association of Gamble variables with Impaired glucose tolerance: This study concluded that there was higher frequency of Impaired glucose tolerance in Male (11.11%) as compared to female (7.95%) medical students of Quaid-e-Azam medical college but this difference was statistically insignificant p= 0.891587 (Table 3). Regarding Association of financial status with Impaired glucose tolerance, this study proved that there is more frequency (66.5%) of impaired glucose tolerance in working class as compared to privileged and lower class and this difference is statistically significant. P= 0.010768 (Table 3) This study also concluded that Out of 15 (9.3%) medical students having impaired glucose tolerance 08(53.33%) had family history of paternal or maternal diabetes compared to 23(15.86%) out of 145 with normal glucose levels after 120 min of OGTT and this difference being statistically significant (p=.000473) proving an association of family foundation of diabetes with impaired glucose tolerance among medical students (Table 4) It was demonstrated in this cross sectional study that most 8(53.33%) out of 15 participants with impaired glucose tolerance were Obese as compared to normal and overweight in the study and this variation with high statistical significance. (p= .000104). Regarding history of surgery or trauma in study participants, it was observed that 05 (33.33%)

out of 15 with impaired glucose tests had history of surgery or trauma showing an insignificant (p=0.229472) association with it. (Table 4) This became evident in this study that daily Exercise and physical activity is an important gamble variable of impaired glucose tolerance in young adults as 08 (53.33%) out of 15 with impaired glucose resistance did no exercise as compared to those who do exercise daily proving a significant (p= 0.027794) association of lack of physical activity with Impaired glucose tolerance among medical students. (Table 4) As far as consumption of junk food is concerned, majority 7(46.66%) out of 15 suffering from impaired glucose tolerance consumed junk food on daily basis as compared to those who less oftenly ate junk food showing a statistically significant (p= .004849) relation between junk food consumption and impaired glucose tolerance. (Table 4) This was elucidated in this study that there was high frequency of smoking 10(66.66%) among those who had impaired tolerance to glucose hence showing a statistically significant (p= 0.026791)

Table 1: *Age and gender distribution of study participants*

Age	Women (%)	Men (%)	Total
18-20	40(45.45%)	18(25.0%)	58
21-23	40(45.45)	40(55.55%)	80
24-26	8(9.0%)	14(19.44%)	22
Total	88	72	160

Table 2: *Oral Glucose Tolerance test*

	Levels mg/dl	Women	Men
Serum glucose 60 in after OGTT	<100	1(1.13X)	2 (2.7%)
	101-140	42 (47.72%)	36 (50%)
	140-200	44 50%)	32 (44.44%)
	>200	1 (1.13%)	2 (2.7%)
Serum glucose 120 minimum After OGTT	< 140	80 (92.04%)	65 (88.88%)
	> 140	8 (7.95%)	7 (11.11%)
		88	72

Table 3: *Association Socio-Economic variable with impaired Glucose tolerance test*

Association of Gender with Impaired Glucose Tolerance	Impaired Glucose Tolerance	No. Impaired Glucose Tolerance	Total	Chi Squire test P Value
Male	07	65	72	X^2=0.018
Female	08	80	88	P value= 0.891587
Total	15	145	160	Insignificant
Association of Socio-Economic status	Impaired Glucose Tolerance	No. Impaired Glucose Tolerance	Total	Chi Squire test P Value
Privileged class	07	25	32	X^2 = 9.0623
Working class	05	101	106	P value = .010768
Lower Class	03	19	22	Significant
Total	15	145	160	

Table 4: *Association Personal Characteristics with impaired Glucose tolerance test*

Characteristics	Impaired Glucose Tolerance No. Impaired Glucose Tolerance		Total	Chi Squire test P Value
Family History of Diabetes	08	23	31	X^2= 12.2187
No Family History of Diabetes	07	122	129	P value = .000473 Significant
Total	15	145	160	
(BMI) Normal	05	78	82	X^2 = 18.3387
Over Weight	03	52	55	
Obese	08	15	23	P value = .000104 Significant
Total	15	145	160	
History of Surgery Or trauma	05	29	34	X^2 = 1.4441
No History of Surgery Or trauma	10	116	126	P value = .229472 Insignificant
Total	15	145	160	
(Exercise/ Physical activity)	08	32	40	
No Exercise/ Physical activity				X^2 = 7.1659
Physical Activity up to 02 hours	04	72	76	P value = 0.027794 Significant
Physical Activity > 02 hours	3	41	44	
Total	15	145	160	
(Junk food intake) Daily	07	20	27	X^2 = 10.6579
2-3 times per week	06	103	109	
Once a week	02	22	24	P value = 0.004849
Total	15	145	160	Significant
Smoking	10	54	64	X^2 = 4.9042
No Smoking	05	91	96	P value = 0.026791
Total	15	145	160	Significant

relation between smoking and impaired glucose tolerance. (Table 4)

Discussion

There is increasing prevalence of diabetes as well as prediabetes in younger populace in the world, therefore this cross sectional study to assess frequency and association of various gamble variables proved that Most of the subjects in this study were between 18-23 years, and a frequency of 9.3% having impaired glucose tolerance very similar to a study conducted in Swaziland where prevalence of prediabetes was 6.5 % in young adults[2] and also close to a study in England where impaired glucose tolerance was detected in 23% of 55 obese children (4 to 10 years) and 21% of the 112 overweight adolescents(11 to 18 years) Silent type 2 diabetes was observed in 4% of the fat adolescents.[6]

Our study concluded a statistically insignificant (p= 0.891) association of gender with impaired glucose tolerance among medical students of Quaid-e-Azam Medical College, Bahawalpur which is contrasting to a study on young adults in Swaziland where there was significant relation between male gender and Impaired tolerance to glucose and prediabetes[2] probably because of differences in sociocultural patterns and life styles.

This study also elucidated a strong association between working or middle financial class with impaired glucose tolerance which was statistically proven (p= 0.010768) and found to be similar to a study in the region of Augsburg KORA where a significant association was found between high socioeconomic class and impaired glucose tolerance as well as raised HbA1c.[21]

This study formed a source of a statistically significant (p= 0.0004) association between family foundation of diabetes and impaired glucose tolerance among young medical students and consequently enhancing the importance of regular screening and monitoring of progression from prediabetes to frank diabetes which was indistinguishable from results of a study on Hispanic population in United States, which also proved significance of the relation between family history and occurrence of diabetes[7] and this similarity might be due to biological and genetic predisposition to develop prediabetes and ultimately overt diabetes at much younger age group than expected.

In this current review, a strong statistically proven (p= 0.000104) relation was found between BMI and impaired glucose resilience. Correspondingly a study in Kerala found a positive relationship among BMI and a gamble of sort 2 diabetes mellitus.[8] In another concentrate, fundamentally high glucose levels were likewise tracked down in ladies with, high BMI and, low wellness and quick weight gain[9]. Also these results were in line with study of Swaziland[2]. where abnormal BMI was statistically related to prediabetes. However ,in a study conducted in Australia,[10] weight record, the level of muscle versus fat and similar midriff to hip ratio in a marginal glucose resistant populace were nearly same as our study results hence emphasizing on weight control strategies and programmes for addressing the diabetes epidemic situation in young adults contributing to renal and cardiometabolic morbidity and mortality.

This study concluded the role of scarce exercise and diminished activity levels in impaired glucose tolerance by proving a statistically significant (p= 0.027794) association between them, similar to a study in Uk, where ladies who participated in actual activity something like one each week had an age changed relative gamble (RR) of type 2 diabetes in contrast to ladies who did not practice showing that active work levels might be a promising way to reduce the burden of prediabetes and ultimately Diabetes in the young adults.[11]

In this current review, a statistically significant (p= 0.026) relation was found between junk food intake and development of impaired glucose tolerance matching to another study of America[22] where significant association was observed between unhealthy diets and frequency of diabetes type 2, featuring the significance of diet control at earliest stage of impaired glucose tolerance to hinder the progression of prediabetes to overt Diabetes. Assessment of prediabetes through hindered glucose tolerance is an important tool for prevention of compli-cations of diabetes in younger age bunch similar to esti-mates of study in China[13] which used post prandial glucose levels as an assessing gadget in contrast to A1c in overall population but another study suggested that 120min post OGTT to determine impaired glucose tolerance should have an increased threshhold level ie >200 mg per dl.[14] In another review among 300 students from college of Kansas,Lawrance.[15] the prevalence of hindered glucose was 9% showing the dangers associa-ted with it.This again proves the significance of addi-tional concentrated tests for early recognition of prediabetes and chance of diabetes in future.

Conclusion

A considerable number of non-diabetic medical students exhibited impaired glucose tolerance despite having normal fasting glucose levels. This was particularly observed in males and those who were severely overweight. These individuals with impaired glucose tolerance were likely to develop diabetes in the future. The presence of impaired glucose tolerance was positively associated with factors such as age, gender, socioeconomic status, BMI, physical activity, unhealthy dietary habits, and smoking. Consequently, the higher prevalence of pre-diabetes among these young medical students emphasizes the importance of implementing primary and secondary prevention strategies tailored to this specific population segment in order to enhance their quality of life.

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Authors Contribution

SH: Conceptualization of Project
STJ: Data Collection
SH, MTJ, MHJ: Literature Search
MTJ, MHJ: Statistical Analysis
SH, MTJ, MHJ: Drafting, Revision
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Bacterial Isolates and their Antimicrobial Susceptibility Pattern from Tracheal Secretions and Sputum of Admitted and Outdoor Patients

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Abstract

Objective: The purpose of study was to determine the frequent pathogens in tracheal secretions and sputum specimens along with the antimicrobial susceptibility pattern.

Methods: This descriptive study was conducted in the department of Pathology and Microbiology, Farooq Hospital Lahore, Pakistan and data included was taken from 1st August 2022 to 31st December 2022. The specimens were inoculated on blood agar and MacConkey agar and incubated for 24 hours at 37 0^0C. The Kirby Bauer disc diffusion method was employed to find out the antimicrobial susceptibility pattern. The SPSS was used to assess the data.

Results: From the total 102 positive culture growths, Klebsiella species (35.2%) was frequently *isolated* followed by Pseudomonas species (25.4%), Acinetobacter species (23.5%), *Escherichia coli* (9.8%), *Staphylococcus aureus* (3.9%), Citrobacter species (0.9%), and Proteus species (0.9%). The doxycycline and linezolid were completely effective (100%) against the gram positive cocci. The Klebsiella species, Pseudomonas species, Acinetobacter species, and *Escherichia coli*, showed maximum sensitivity to tigecycline.

Conclusion: The most commonly isolated gram negative rod was Klebsiella species and tigecycline was found to be the most effective antibiotic against it. Multidrug resistance among respiratory pathogens is the major issue so it is necessary to administer antibiotic therapy in a limited and objective manner.

Keywords: Antibiotic sensitivity pattern, gram negative rods, gram positive cocci, sputum specimens, tracheal secretions.

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Introduction

Tracheobronchial secretions are produced by the tracheobronchial tree's mucous glands and goblet cells. In addition to facilitating the interchange of heat and water during breathing, these secretions also serve to protect the respiratory tract. High morbidity and mortality rates are related to respiratory infections, particularly in critically ill patients.[1] An acute lung infection in a patient that develops outside of a hospital setting without recent hospitalization is referred to as "community-acquired pneumonia" (CAP). Since the advent of antibiotics, the etiology of CAP has undergone significant evolution. The CAP etiology and its clinical manifestations are complex and vary with age, region and current exposure.[2]

Hospital-acquired pneumonia is one of the most prevalent issue in health care associated infections. Previous literature reports that chronic respiratory diseases, multiple organ disorders, aspiration, intubation and mechanical ventilation are some of the risk factors.[3] Ventilator-associated pneumonia (VAP) accounts for approximately 15% of all hospital-acquired infections with the highest morbidity and mortality, ranking second in frequency. A patient who develops pneumonia after 48 hours of

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intubation and mechanical ventilation is known as VAP.[4-5]

VAP has decreased in high-income nations through a combination of surveillance, education, prevention and intervention.[6] There is a lack of data on VAP rates, the most common associated pathogens, and their antibiotic susceptibility profiles in Asia. The orderly survey and meta-analysis[7] of VAP occurrence, microbiological etiology, and cost sums up this information by country pay level, intervention guidelines and further research in the region.

One of the life-saving techniques for intensive care unit (ICU) admitted patients are mechanical ventilation, although this technique carries a greater risk of causing respiratory diseases. Multidrug-resistant infections in hospitals are always more likely to affect critically ill ICU patients. This occurs as a result of their prolonged hospitalization, immune-compromised profile, severe illness, and use of catheters and antibiotics.[8] The incessant and unselective use of wide range of antibiotics without promoting microbiological cultures and awareness prompts the advancement of these multidrug safe pathogens in the realm of microbial science and complicates the treatment of ICU patients.[9] The invasion of multidrug-resistant strains of microorganisms is increasing the morbidity of these patients. Pneumonia-associated pathogens include Klebsiella species, Pseudomonas species, *Staphylococcus aureus (S. aureus),* and Acinetobacter species.[10]

The diagnosis of VAP necessitates a high degree of clinical suspicion, physical and radiological examination along with microbiological investigation of respiratory secretions. The Centers for Disease Control and Prevention's criteria recommend bronchoalveolar lavage, lung biopsy, and tracheal aspirate as the three diagnostic options for VAP. The collection of tracheal aspirate specimens is the simplest and potentially the safest of the three; however, tracheal aspirate specimens have low diagnostic specificity for VAP and rarely differentiate between infection and colonization.[11]

A significant information gap in the prevention and treatment of especially VAP is being caused by the absence of recent national studies, and therefore is resulting in suboptimal outcomes for such patients in the ICU. The objective of this study was to determine the common pathogens and their antimicrobial sensitivity and resistance pattern in tracheal secretions and sputum specimens which can provide guidelines to physicians for appropriate empirical antibiotic treatment.

Materials and Methods

It was a descriptive study carried out in the Department of Pathology and Microbiology, Farooq Hospital Lahore, Pakistan. The data was taken from 1st August 2022 to 31st December 2022. All ethical considerations were addressed and the study was conducted after approval from the ethical review committee (IRB No. 0198). This study comprised all patients with tracheal secretions and sputum specimens that were examined throughout the specified time. Patients with other respiratory tract infections and immuno-compromised patients were excluded. The convenient sampling technique was used to choose the total 126 specimens which were independent of age and gender.

These specimens were collected from the outdoors and admitted patients of the ICU, private rooms, dental ward, medical ward, and pediatric ward. The patient collected the sputum specimen in a sterilized container. The endotracheal tube and a suction catheter tip were used to obtain the tracheal secretions from the patients who were unable to provide the sputum. The tracheal secretions and sputum specimens were applied on blood and MacConkey agars, which were then incubated for 24 hours at 37°C. The cultures were checked for any positive or negative growth after 24 hours. The bacteria were primarily identified on the basis of their colonial morphology, fermenter or non-fermenter, and presence or absence of hemolysis on blood agar. Gram staining, bench and biochemical tests were additionally used to detect the gram positive cocci and gram negative rods.[12]

The Kirby Bauer disc diffusion method was used to evaluate the antimicrobial susceptibility testing on Mueller-Hinton agar and these agar plates were incubated at 37°C for 24 hours. The results were analyzed in accordance with Clinical and Laboratory Standards Institute (CLSI) recommendations. The gram negative rods were tested with amikacin (30 µg), amoxicillin-clavulanic acid (30 µg), ampicillin (10µg), cefoperazone-sulbactam (105 µg), cefepime (30 µg), cefotaxime (30 µg), ceftazidime (30 µg), ceftriaxone (30µg), ciprofloxacin (5µg), fosfomycin (200µg), gentamicin (10µg), imipenem (10 µg), levofloxacin (5 µg), meropenem (10 µg), piperacillin-tazobactam (110µg), tigecycline (15µg), tobramycin (10µg), and trimethoprim-sulphamethoxazole (25 µg) antibiotic discs. For gram positive bacteria, amikacin (30µg), amoxicillin-clavulanic acid (30µg), ampicillin (10µg), azithromycin (15µg), chloramphenicol (30 µg), ciprofloxacin (5 µg), doxycycline (30 µg), erythromycin (15 µg), gentamicin (10 µg),

levofloxacin (5 µg), linezolid (30 µg), penicillin (10 µg), trimethoprim-sulphamethoxazole (25µg), tigecycline (15 µg), and vancomycin (30 µg) antibiotic discs were used. Cefoxitin (30 µg) was used for the identification of methicillin-resistant Staphylococcus species.[13] Statistical Package for the Social Sciences (SPSS) v.25.0 was used to assess the data. To determine the percentages and frequencies, descriptive statistics were applied.

Results

A total of 126 specimens including 60 (47.6%) tracheal secretions and 66 (52.4%) sputum specimens were taken from 69(54.7%) males and 57(45.3%) females. The mean age of study participants was 59.65±20.36. Three age groups were targeted in this study: children (<14 years), adults (15 years to 64 years), and elders (>65 years). Children constituted 11(8.7%) of the patient population whereas, 62(49.3%), and 53(42.0%), belonged to adults and elderly age groups, respectively. The outdoor patients were 06 (4.7%) while 120 (95.3%) patients were admitted to the hospital. Of admitted patients, 80 (63.4%), 18 (14.2%), 11 (8.7%), 08 (6.3%), and 03 (2.3%) were in ICU, medical ward, private rooms, pediatrics ward, and dental ward, respectively.

From 126 specimens, no growth was observed in 46 (36.5%) specimens while positive growth was observed in 80(63.5%) specimens. The gram negative rods were responsible for the majority of the isolates. From total of 80 positive growth specimens, 22(27.5%) specimens have double growth of organism. Specimens 76 (95.0%) were gram negative rods while the remaining 04 (5.0%) were gram positive cocci.

From 102 positive growth cultures, Klebsiella species (n=36; 35.2%) was most prevalent subsequently followed by Pseudomonas species (n=26; 25.4%), Acinetobacter species (n = 24; 23.5%), *Escherichia coli ([E. coli];* n = 10; 9.8%), *S. aureus* (n = 04; 3.9%), Citrobacter species (n = 01; 0.9%), and Proteus species (n = 01; 0.9%). All isolated *S. aureus* were resistant to the surrogate marker (cefoxitin) hence, identified as methicillin resistant S.

Table 1: *: Bacterial isolation with respect to gender, age, category and departments of patients, and specimens*

	No growth N (%)	*Klebsiella species* N (%)	*Pseudomonas species* N (%)	*Acinetobacter species* N (%)	*E. coli* N (%)	*S. aureus* N (%)	*Citrobacter species* N (%)	*Proteus species* N (%)
Genders								
Females	24/46 (52.1%)	16/36 (44.5%)	12/26 (46.2%)	11/24 (45.8%)	3/10 (30%)	1/4 (25%)	0/1 (0%)	0/1 (0%)
Males	22/46 (47.9%)	20/36 (55.5%)	14/26 (53.8%)	13/24 (54.2%)	7/10(70.0%)	3/4 (75%)	1/1 (100%)	1/1(100%)
Age groups								
Children	3/46 (6.5%)	6/36 (16.7%)	6/26 (23.1%)	1/24 (4.1%)	0/10 (0%)	0/4 (0%)	0/1 (0%)	0/0 (0%)
Adults	25/46 (54.3%)	14/36 (38.8%)	15/26 (57.6%)	15/24 (62.5%)	4/10 (40%)	0/4 (0%)	0/1 (0%)	1/1(100%)
Elders	18/46 (39.2%)	16/36 (44.5%)	5/26 (19.3%)	8/24 (33.4%)	6/10 (60%)	4/4 (100%)	1/1 (100%)	0/0 (0%)
Category of patient								
Outdoor	4/46 (8.6%)	1/36 (2.7%)	1/26 (3.8%)	0/24 (0%)	0/10 (0%)	0/4 (0%)	0/1 (0%)	0/1 (0%)
Admitted	42/46 (91.4%)	35/36 (97.3%)	25/26 (96.2%)	24/24 (100%)	10/10(100%)	4/4 (100%)	1/1 (100%)	1/1(100%)
Admitted patient departments								
ICU	26/46 (56.5%)	25/36 (69.4%)	12/26 (46.1%)	19/24 (79.1%)	8/10(80.0%)	4/4 (100%)	1/1 (100%)	0/1 (0%)
Medical ward	7/46 (15.2%)	5/36 (13.8%)	5/26 (19.2%)	1/24 (4.1%)	2/10 (20%)	0/4 (0%)	0/1 (0%)	1/1 (100%)
Private rooms	7/46 (15.2%)	1/36 (2.7%)	2/26 (7.6%)	1/24 (4.1%)	0/10(0%)	0/4 (0%)	0/1 (0.0%)	0/1 (0%)
Pediatrics ward	4/46 (8.6%)	3/36 (8.3%)	5/26 (19.2%)	2/24 (8.3%)	0/10(0%)	0/4 (0%)	0/1 (0%)	0/1 (0%)
Dental ward	2/46 (4.3%)	2/36 (5.5%)	2/26 (7.6%)	1/24 (4.1%)	0/10(0%)	0/4 (0%)	0/1 (0%)	0/1 (0%)
Specimens								
Tracheal secretion	13/46 (28.2%)	24/36 (66.6%)	12/26 (46.1%)	21/24 (87.5%)	8/10 (80%)	2/4 (50%)	1/1 (100%)	1/1(100%)
Sputum	33/46 (71.8%)	12/36 (33.4%)	14/26 (53.9%)	3/24 (12.5%)	2/10 (20%)	2/4 (50%)	0/1 (0%)	0/1 (0%)

aureus (MRSA). Klebsiella species was the most prominent bacterial isolate while Proteus species was the least common (Figure 1).

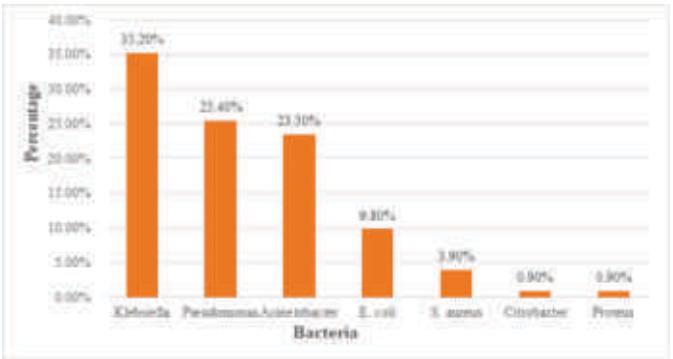
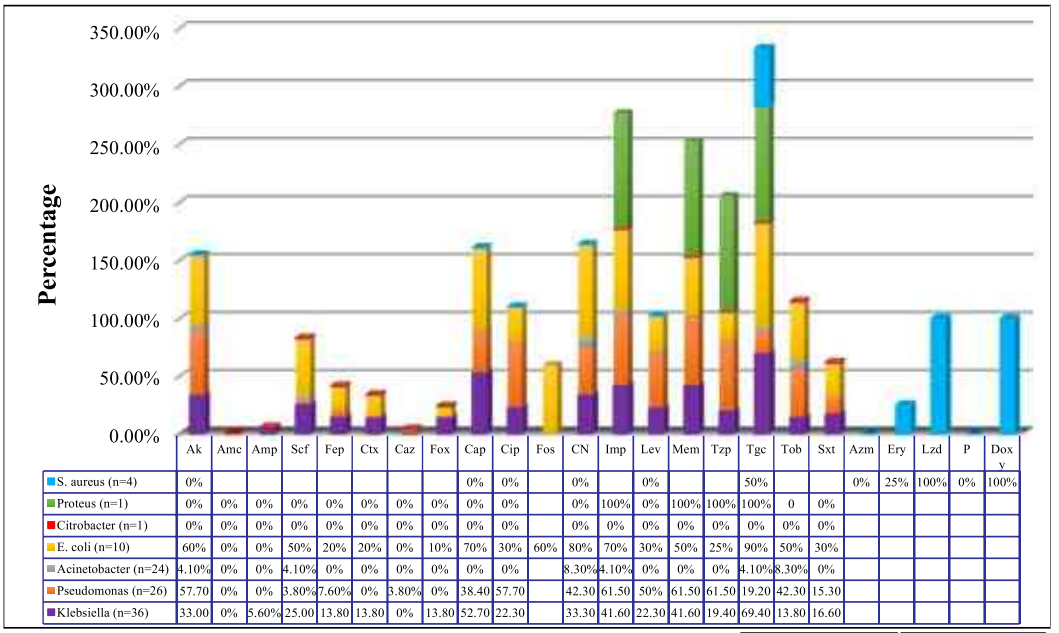


Figure 1: *Bacterial growth in tracheal secretions and sputum*

In females, Pseudomonas species (46.2%) was the most common isolate while in males Citrobacter species (100.0%), Proteus species (100.0%), and E. coli (70.0%) were the common isolates. In total, 23.1% of children developed an infection of Pseudomonas species which represented the commonest bacterial growth as compared to other bacterial growths. In the adult age group, Proteus species (100.0%), and Acinetobacter species (62.5%) were common while in the elder age group S. aureus (100.0 %), Citrobacter species (100.0%), and *E.coli* (60.0%) were common isolates. The majority of bacterial growths were observed in admitted patients and many of them were in the ICU department. The tracheal secretions had highest number of bacterial growth. The frequency and percentages of descriptive characteristics with respect to no growth and bacterial growth were also observed (Table 1).

The doxycycline and linezolid were 1(100%) sensitive to gram positive cocci. The Proteus 1(100%), *E. coli* 9(90%) and Klebsiella species 25(69.4%) showed maximum sensitivity to tigecycline. Similarly, the sensitivity of Proteus species was maximum for carbapenems 1(100%) and piperacillin-tazobactam 1(100%). In addition, the aminoglycosides performed better in the case of Acinetobacter species. However, a worrisome trend was observed for Citrobacter species which tested completely resistant to all applied antibiotics. In addition, the sensitivity of carbapenems was less for *E. coli,* Pseudomonas and Klebsiella species. The majority of the bacteria were completely resistant to ampicillin and amoxicillin-clavulanate except ampicillin 2(5.6%) was sensitive in the case of Klebsiella species. All antibiotic sensitivity results have been summarized in Figure 2.



	Ak	Amc	Amp	Scf	Fep	Ctx	Caz	Fox	Cap	Cip	Fos	CN	Imp	Lev	Mem	Tzp	Tgc	Tob	Sxt	Azm	Ery	Lzd	P	Dox y
S. aureus (n=4)	0%								0%	0%		0%		0%			50%			0%	25%	100%	0%	100%
Proteus (n=1)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%		0%	100%	0%	100%	100%	100%	0	0%					
Citrobacter (n=1)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%		0%	0%	0%	0%	0%	0%	0%	0%					
E. coli (n=10)	60%	0%	0%	50%	20%	20%	0%	10%	70%	30%	60%	80%	70%	30%	50%	25%	90%	50%	30%					
Acinetobacter (n=24)	4.10%	0%	0%	4.10%	0%	0%	0%	0%	0%	0%		8.30%	4.10%	0%	0%	0%	4.10%	8.30%	0%					
Pseudomonas (n=26)	57.70	0%	0%	3.80%	7.60%	0%	3.80%	0%	38.40	57.70		42.30	61.50	50%	61.50	61.50	19.20	42.30	15.30					
Klebsiella (n=36)	33.00	0%	5.60%	25.00	13.80	13.80	0%	13.80	52.70	22.30		33.30	41.60	22.30	41.60	19.40	69.40	13.80	16.60					

Figure 2: *Antimicrobial sensitivity of gram negative rods and S. aureus from tracheal secretions and sputum specimens*

Discussion

In clinical and non-clinical settings, bacteria are becoming more and more resistant to conventional antibiotics.[14] Due to excessively invasive procedures, such as the use of artificial ventilator support, the rate of nosocomial infection in patients admitted to the ICU is also gradually rising.[15] This emerging resistance is a serious issue, with the proper use of antibiotics and improvement in hospital settings can stop the bacteria from showing more resistance. In the present study, 63.5% of the samples showed positive bacterial growth. Gupta et al. conducted a study in which, the positive growth rate was 53%.[16] Chandra et al. conducted another study, in which 72.3% of the samples were positive.[17] Malik et al. conducted a research project in Pakistan; the percentage of positive cultures was 83%.[18] The improved infection control measures in our hospital's ICU setup are to blame for the significant drop in our study. However, the decreased proportion of positive growth may be limited by our study's convenient sampling technique.

The gram negative rods were the frequent source of infection, outnumbering gram-positive cocci, which caused only 4% of all positive culture growths in our research study. This was in accordance with Chandra et al. findings. In Gupta et al. studies, gram negative rods accounted for 85% of the bacterial growth, where 86% of the specimens contained gram negative rods.[16,17] The majority of the gram negative bacteria in the isolates of patients belonged to the Klebsiella, Acinetobacter, and Pseudomonas species according to Deepti et al. study.[17] The bulk of gram negative infections are contracted in hospitals which are more tenacious and challenging to treat. Strenuous measures should be taken to prevent the spread of gram negative rods, particularly in the ICU.

The most prevalent isolate in the present study was a Klebsiella species (35.2%). A study conducted in Lahore, Pakistan revealed Klebsiella pneumoniae as the most frequently isolated bacterium from tracheal secretions (35.4%).[18] Chandra et al. reported the most prevalent isolate was also Klebsiella (32.35%).[13] In George et al. study, Acinetobacter (37.5%), Pseudomonas (21.8%), and Klebsiella (15.6%) were the most prevalent isolates.[19] The considerable rise of multidrug-resistant isolates can be credited with the rise in Klebsiella species found in this study, particularly in the ICU department.

This study showed Klebsiella species was highly sensitive to tigecycline (73.5%) and chloramphenicol (54.3%). Pseudomonas species exhibited 62.5% sensitivity to tigecycline. Klebsiella was 62% sensitive to sulzone, while Pseudomonas showed maximum sensitivity to pipercillin-tazobactam (73%).[20] The sensitivity to drugs of Klebsiella species and Pseudomonas species gradually decreased. Cross-infections and the improper use of antibiotics, may be blamed for this increasing prevalence of multidrug resistant gram-negative bacteria[21]. The remaining gram-negative rods were most resistant to fluoroquinolones, cephalosporins, and antibiotics like ceftazidime, ceftriaxone, ciprofloxacin, and cefepime. This was almost in agreement with the trend described by Gupta et al. and Malik et al. studies.[16,20]

The time duration of the study was one of the limitations. Additionally, this research study was performed in a single tertiary care facility, making it impossible to apply the findings to the entire population.

Conclusion

Klebsiella species was the most frequently isolated species of gram-negative rods in tracheal secretions and sputum specimens. Moreover, this study concludes that Tigecycline is highly effective against gram negative rods in vitro. According to the new guidelines that have been updated in light of such research, it is necessary to administer antibiotic therapy in a limited and objective manner.

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Authors Contribution

OF: Conceptualization of Project
SR: Data Collection
MA: Literature Search
ZY: Statistical Analysis
ZY, AM: Drafting, Revision
NW: Writing of Manuscript

Reversible Effects of Ribavirin on the Testicular Weight of Albino Rats

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Abstract

Introduction: Ribavirin because of its genotoxic quality causes adverse effects on the gonads in a temporary way that has been studied on the testicular tissues of various experimental animals.

Objectives: To study the changes in mean testes weight of albino rats after treatment with Ribavirin in different doses at different time points.

Methods: The research lab and the animal house of the Anatomy Department of Postgraduate Medical Institute, Lahore was the place of this experimental study where 72 adult male albino rats were divided into 4 groups: A, B, C and D; with 18 rats each. Intraperitoneal injections of distilled water were given to control group A and Ribavirin in the doses of 20mg, 100mg and 200mg/kg body weight, as a single dose for 5 days was administered to experimental groups B, C and D. Every group was further split up into 3 subgroups according to the sacrificial days 20th, 40th and 60th since after administration of the last dose of the drug. On each sacrificial day, 6 rats were randomly selected from a group and sacrificed. Their testes were dissected out and weighed after the removal of the epididymis. The mean testes weight was also calculated.

Results: In comparison with the control groups on the 20th and 40th sacrificial days all experimental groups showed a decrease in the values of mean testes weight (MTW) which was more in medium and high-dose treated groups due to the toxic effects of Ribavirin on rat's testes. On the 60th sacrificial day, only low-dose treated groups showed the values of MTW very close to that of controls due to the reversibility of changes induced by Ribavirin on rat's testes. On the same time point medium and high dose treated groups still had reduced values of MTW in comparison with controls due to the late recovery.

Conclusion: A patient on Ribavirin therapy must be informed by a physician regarding its toxic effects on his reproductive health and the reversibility of its gonadotoxicity after discontinuation of this drug.

Key words: Ribavirin, Testicular toxicity, Mean testes weight.

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Introduction

Hepatitis is a huge community health issue in the world which is linked with the loss of many lives due to liver ailments.[1] The Hepatitis C virus (HCV) was detected in 1989 and disseminated through contact with infected blood. 60 to 80 percent of long-standing infections bring about liver cirrhosis and hepatic cancer.[2] Ribavirin (RBV) orally and injectable Interferon alpha is an adjuvant therapy that has proved to be a powerful treatment for chronic Hepatitis C. RBV, an antiviral drug was produced in 1970 and its wide-ranging activity against viruses was spotlighted in 1972.[1]

Ribavirin is a broad-spectrum antiviral drug active against many RNA and DNA viruses. Ribavirin along with interferon-alpha is very effective to control hepatitis C virus infection. It is also used in the treatment of chro-

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nic hepatitis E virus infection, respiratory syncytial virus infection and various hemorrhagic fevers. This drug is being considered for the treatment of cancers on the basis of some studies. Ribavirin intracellularly changes into Mono-, Di- and Triphosphates and gets active. Ribavirin triphosphate concentration is found high inside the cells that stop the replication of viruses. Its mode of action is to decrease the guanosine triphosphate GTP level in the cell by inhibition of inosine monophosphate dehydrogenase IMDH resulting in stoppage of viral mRNA capping and sometimes may cause modification of the immune response of the host cell. Another mechanism of action is viral mutagenesis.[3]

Ribavirin is harmful to the developing baby if any one of the parents is taking ribavirin. That's why both parents should adopt useful contraceptive measures during ribavirin therapy and even six months after its last dose.[4] RBV is not suitable for either sex during six months prior to conception and its use is also prohibited during pregnancy due to its teratogenicity. The pregnancy registry of RBV was initiated in 2003 for documentation of its most probable harmful effects on embryos.[5]

In the light of the results of various studies done on Ribavirin, it is known for causing deleterious effects on the morphology and physiology of different tissues like bone marrow, liver, epididymis and testis of laboratory animals.[6,7,8,9]

Ribavirin exerts its cytotoxicity by causing cell death due to the stoppage of cell division.[6]

Due to its metabolites, Ribavirin was proved reversibly genotoxic in patients of Crimean-Congo hemorrhagic fever taking this drug in the doses advised by their physicians.[7]

Chromosomal aberrations were noted in patients with long-standing infection of hepatitis C, taking adjunctive medication containing Pegylated interferons and Ribavirin.[8]

The cytotoxicity of RBV has been noted in seminiferous tubules and sperms of testes in previous studies. The current research was undertaken to observe the effects of different doses of Ribavirin on the mean testes weight of rats at three sacrificial times and reversibility of these changes was noted at these time points after discontinuation of this drug.

Materials & Methods

This randomized controlled experimental study was conducted at the Research lab and animal house of Postgraduate Medical Institute, Lahore, and approved by the review board of the University of Health Sciences, Lahore. 72 adult male albino rats weighing in the range of 180 - 200gms were obtained from the National Institute of Health, Islamabad. The rats were kept at 24±2°C and a 12hrs light and dark cycle was maintained. All animals were fed a normal diet and were given water ad libitum. After adaptation of a week rats were split up into 4 groups A, B, C and D with 18 rats in each group by using a computer-generated random numbers table. Ribavirin used was purchased from Getz Pharma Company, Karachi, Pakistan. Scientific balance (Sartorius precision balance®, Germany) was used to measure doses of Ribavirin. The intervention done was as follows:

Control group A: Intraperitoneal injection of 0.75ml/kg body weight (b.w) of distilled water was given to the rats once daily at 24 hrs. intervals for 5 days.

Subgroups according to schedule of sacrifice:

A1,20th day

A2, 40th day

A3, 60th day

Experimental group B: Intraperitoneal injection of Ribavirin 20mg/kg b.w dissolved in 0.75ml of distilled water was given to the rats once daily at 24 hrs. intervals for 5 days.

Subgroups according to schedule of sacrifice:

B1, 20th day

B2, 40th day

B3, 60th day

Experimental group C: Intraperitoneal injection of Ribavirin 100mg/kg b.w dissolved in 0.75ml of distilled water was given to the rats once daily at 24 hrs. intervals for 5 days.

Subgroups according to schedule of sacrifice:

C1, 20th day

C2, 40th day

C3, 60th day

Experimental group D: Intraperitoneal injection of Ribavirin 200mg/kg b.w dissolved in 0.75ml of distilled water was given to the rats once daily at 24 hrs. intervals for 5 days. .

Subgroups according to schedule of sacrifice:

D1, 20th day

D2, 40th day

D3, 60th day

3 sacrificial days 20th, 40th and 60th from the last dose were selected and 3 subgroups of every group were made in accordance with these sacrificial times forming 12 subgroups in total. From each study group, six randomly selected rats were sacrificed on each sacrificial day. Their testes were dissected out and weighed after the removal of the epididymis. The weight of each testis was recorded and the mean testes weight of all study groups was calculated. The data was entered in Table-1 at various sacrificial times and dose-related changes in mean testes weight were studied in comparison with the controls.

Statistical Package for Social Sciences (SPSS), version 23 was used to analyze the data. For quantitative variables Mean (± SD) was calculated. Analysis of variance (ANOVA) was applied to show the statistical difference in the mean of all groups. Post-hoc Tukey test was applied to evaluate the difference of means between the groups at 5% level of significance ($p < 0.05$).

Results

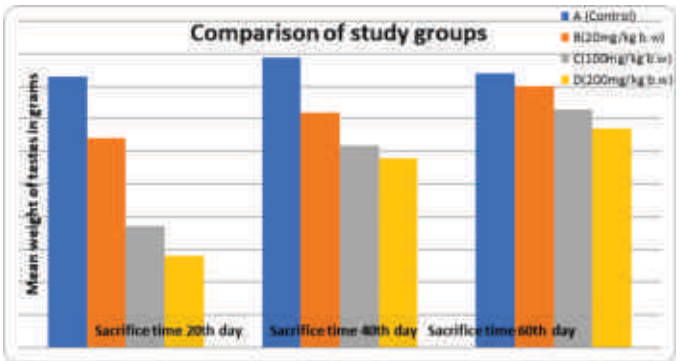
In comparison with the controls mean values of testes weight (MTW) showed a reduction in all experimental groups though it was more marked in medium and high-dose treated groups, on the 20th and 40th days from the last treatment (Fig 1). This decrease in values was more pronounced on the day 20th. By applying ANOVA comparison was made and an overall reduction in the values was found significant with p-value<0.001. A statistically significant difference between all study groups in all possible combinations was found when the Post Hoc test was applied. (Table 1). Between C2 and D2 groups significant difference was not found (Table 1). On the 60th day from the last dose of the drug in comparison with control groups, a reduction in the values of mean testes weight was noticed but it was not as noticeable as was observed on days 20th and 40th. The values of the low-dose group were very close to the controls in comparison with the medium and high-dose

Table 1: *Comparison of mean values of testes weight (MTW) in grams among study groups at different sacrifice times*

Taaimes	Groups	n	MTW	ANOVA	Post Hoc Test	
			Mean ±SD	p-value	Comparison groups	MTW p-value
20th day	A1 (Control group)	6	0.83 ±0.089	<0.001**	A1 - B1	<0.001**
	B1(RBV20mg/kg b.w)	6	0.64 ±0.04		A1 - C1	<0.001**
	C1(RBV100mg/kg b.w)	6	0.37 ±0.01		A1 - D1	<0.001**
	D1(RBV200mg/kg b.w)	6	0.28 ±0.01		B1 - C1	<0.001**
					B1 - D1	<0.001**
					C1 - D1	0.026*
40th day	A2 (Control)	6	0.89 ± 0.05	<0.001**	A2 - B2	<0.001**
	B2(RBV20mg/kg b.w)	6	0.72 ± 0.10		A2 - C2	<0.001**
	C2(RBV100mg/kg b.w)	6	0.62 ±0.008		A2 - D2	<0.001**
	D2(RBV200mg/kg b.w)	6	0.58 ± 0.01		B2 - C2	0.034*
					B2 - D2	0.002*
					C2- D2	0.576
60th day	A3 (Control)	6	0.84 ± 0.03	<0.001**	A3 - B3	0.56
	B3(RBV20mg/kg b.w)	6	0.80 ± 0.08		A3 - C3	0.004*
	C3(RBV100mg/kg b.w)	6	0.73 ± 0.02		A3 - D3	<0.001**
	D3(RBV200mg/kg b.w)	6	0.67 ± 0.03		B3 - C3	0.074
					B3 - D3	0.001*
					C3 - D3	0.164

*-p-value≤ 0.05 statistically significant change
**-p-value< 0.005 highly significant change
n= Number of rats in each group

groups (Fig 1). This reduction in the values was compared by applying ANOVA, which was significant with a p-value<0.001. Post Hoc test showed a statistically significant difference between A3 and C3, A3 and D3, and B3 and D3 groups. No significant difference



between A3 and B3, B3 and C3, C3 and D3 groups was found (Table 1).

Figure 1: *Bar Graph Showing a Comparison of Mean Testes Weight (MTW) Among Study Groups at different Times of Sacrifice.*

Discussion

Regarding the effects of ribavirin on the mean weight of testes on the 20th and 40th days, it was noted that there was a significant decrease in mean testes weight in all experimental groups (p- value<0.001) (Table 1) (Fig 1). Reduction in values is suggestive of the presence of degenerative changes inside the seminiferous tubules of the testes. The reduction in values was more marked in high-dose groups due to more severity of the toxic effects. Because of the diminishing effects of Ribavirin reduction in MTW became less marked on the 60th days of sacrifice due to the beginning of regenerative changes as signs of recovery in the low dose group only. While high-dose groups still showed a more marked reduction in values probably due to late recovery. These findings are in accordance with a study by Narayana et al., (2005) that investigated the harmful effects of Ribavirin on body weight, testes weight, epididymis weight and many other reproductive parameters of albino rats. He observed that ribavirin is toxic to the reproductive parameters of rats in a transient way. This drug caused the vacuolization and sloughing of seminiferous epithelium that resulted in the reduction of body weight and organ weights in rats especially in high-dose groups in comparison with controls.[9]

Rao et al., (2005) studied the cytotoxicity of Ribavirin in mice testes and found that Ribavirin induced a reduction in testes weight due to decreased spermatogenesis and structural damage of germ cell chromosomes. Abnormal sperms formation due to point mutations was also noted in this study.[10]

Almasry et al., (2017) observed the effects of Ribavirin on the thickness of peritubular sheaths around seminiferous tubules of testes and testicular function in rats. He noticed that after 4 weeks of Ribavirin treatment, there was a significant reduction in the body weight of rats and a significant decrease in testes weight. He found that significantly increased thickness of peritubular sheath and sloughing of germinal epithelium caused shrinkage of tubules due to cell loss. After 4 weeks of Ribavirin administration decrease in Testosterone level was also found. Diminution in the values of body weight is due to side effects of this drug and testicular weight lessening is probably due to testicular damage and apoptosis in experimental groups.[11]

El-Kholy et al., (2019) noted that Sofosbuvir and Ribavirin administration caused harmful effects on the reproductive system and fertility of adult male rats as shown by a decrease in the level of serum testosterone. It had degenerative effects on the histology of the testes such as an increase in collagen deposits, an increased number of caspase-3 positive cells and DNA fragmentation. That's why the cytotoxic effects of these drugs must be kept in mind by physicians when advising them to patients. In order to find out the reversibility of their toxic effects, studies can be done and some agent that is protective against their gonadotoxicity must be explored.[12]

The present study highlighted the reversible cytotoxic effects of Ribavirin on the mean testes weight of albino rats that are dose-dependent and time-dependent.

Conclusion

Ribavirin administered to rats produced a reduction in testicular weight because of its harmful effects on testicular tissue but these effects were found reversible after discontinuation of the said drug. The low-dose group was the only one that exhibited more recovery as compared to the high-dose, which revealed less healing finally. Its probable toxicity on the fertility of a patient must be kept in mind while prescribing this medicine. The patient who is taking this medicine should be guided regarding the reversibility of its reproductive toxicity and the usage of effective contraceptives while taking ribavirin therapy.

Conflict of Interest *None*

Funding source *None*

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Author's Contribution

AB: Conceptualization of Project

FB: Data Collection

GPW: Revision

MF: Literature Search

FF: Wwriting of the Manuscript

Frequency of Hypertension in Patients Diagnosed with Sensorineural Hearing Loss At a Tertiary Care Hospital

Faisal Rafiq,[1] Mazhar Iftikhar,[2] Jawad Ahmad,[3] Sana Nadeem,[4] Azam Khan,[5] Ghulam Murtaza[6]

Abstract

Objective: To determine frequency of hypertension in adult patients diagnosed with sensorineural hearing loss and to determine which hearing frequencies & degrees are more affected with respect to grades of hypertension.

Method: This is a Cross sectional study which was conducted in the ENT Department UNIT-I, Services Institute of Medical Sciences, Lahore / Services Hospital, Lahore. Duration of this study was One year from May 2020 to April2021.100 patients who met the inclusion criteria were enrolled for the study. Then history of patient for hypertension was taken and blood pressure was also checked on the spot and hypertension was labelled accordingly. Hearing thresholds were assessed via pure tone audiometry by delivering pure tones at frequencies of 125-8000hz at the intensities from 0 dB to 120 dB in 5 dB steps to check for both air and bone conduction by using Garson Stadler audiometer & categorized according to WHO criteria of normal hearing <25dB, mild 26-40dB, moderate 41-60 dB, severe 6180dB, profound > 80 dB hearing loss.

Results: Patients' mean age was 47.70±9.04 years, 67(67%) patients were male. The hypertension was found in 55(55%) patients in which grade I severity of hypertension was noted in 42(76.4 %) patients and grade II severity of hypertension was noted in 13(23.6%) patients.

Conclusion: According to this study the frequency of hypertension was 55% in adult patients with sensorineural hearing loss in which 76.4% had grade I and 23.6% had grade II hypertension

Keywords: Sensorineural Hearing Loss, Hypertension.

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Introduction

Hearing loss affects 360 million people globally, making it the sixth most common reason for years spent with a disability.[1] A person's ability to carry on daily conversations, locate sounds and interpret speech, remember things, operate cognitively, and maintain their psychosocial well-being are all significantly impacted by hearing loss. Various congenital and acquired factors, including aging, noise exposure, ototoxic medications, genetic changes, and systemic disorders, can cause hearing loss.[1] Hypertension is a major global health burden. Systolic Blood Pressure of at least 110 to 115 mm Hg was estimated in 3.5 billion adults and Systolic Blood Pressure of 140 mm Hg or higher was estimated in 874 million adults worldwide.[2] Among all community groups around the world, hypertension is a major risk factor for cardiovascular illnesses. Variations in blood pressure have been associated with mortality, end-organ damage, and cardiovascular events according to several studies.[1] Vascular disease and mortality are significantly increased by arterial hypertension. It is connected to vascular disease, renal disease, heart disease, and stroke.[3] Heart and blood vessels structural changes are likely to result from hypertension[4]. Hyper-

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tension induced microangiopathy leads to atrophy in cranial nerve VIll, blood vessels and spiral ganglion.[5] Cochlea is mainly supplied by end arteries. Hypertension induced blood pressure variation makes the ears more susceptible to damage.[6] The most significant contributor to cochlear damage brought on by hypertension appears to be stria vascularis dysfunction. Additionally, the most common cause of internal ear bleeding through the cochlear, anterior vestibular, and anterior inferior cerebellar arteries is hypertension in the vascular system. This, in turn, is likely to cause progressive or sudden hearing loss.[7] Hearing loss, tinnitus, and vertigo is associated with smoking, hypertension, diabetes mellitus, lifestyle, age, family history of illness, leisure activities, and occupational noise exposure. The incidence of auditory symptoms also appears to be correlated with noise exposure over the course of a person's lifetime.[8] Data showed that 4.6% of people between the ages of 18 and 44 have hearing loss. In comparison, 54 percent of people over 65 years old and 14% of people between the ages of 45 and 64 encounter hearing. Joss is affected by a number of factors, including repeated exposure to loud noise, breathing poisonous materials, ingesting ototoxic drugs and pollutants, injuries, and genetic predisposition.[9] Literature showed that chances of hypertension were high among patients of sensorineural hearing loss. According to a study done in Nigeria, 16 percent of hypertensive participants experienced mild to severe sensorineural hearing loss, particularly in the higher frequencies, as a result of inner ear microangiopathy, cochlear nerve neuropathy and reduced blood flow to the stria vascularis. Patients with hypertension have been found to have vasoconstriction leading to decreased blood flow to stria vascularis.[10] A large study conducted in china showed increased hearing thresholds among hypertensive patients.[7] Another study published in Brazil in 2017, showed that prevalence of bilateral high frequency mild sensorineural hearing loss in hypertensive individuals above 60 years of age was 66.26% who underwent audiometric assessment.[6] According to one study, people with sensorineural hearing loss had a significant frequency of hypertension, or 46.8% of cases.[11] Such a study has not yet been conducted in Pakistan, and no local data is found which could help us to determine the prevalence of hypertension in patients of sensorineural hearing Joss. This study aims to get local magnitudes which will be helpful for us to implement the screening of hypertensive patients to prevent sensorineural hearing loss in adults. One early disability prevention strategy may be the early referral of hypertensive individuals for audiometric testing.

Materials and Methods

This was a Cross sectional study, carried out Department of ENT Unit-I, Services Institute of Medical Sciences, Lahore / Services Hospital, Lahore. and duration of study was one year from May 2020 to April 2021. Sampling technique was Non-probability consecutive sampling and a Sample size of 100 patients was calculated with 95% confidence level, 10% margin of error and taking expected percentage of hypertension i .e. 46.8% patients with sensorineural hearing loss.[11] Patients with sensorineural hearing loss (as per operational criteria) between the ages of 35 and 65, of either gender were included in the study. Patients other than essential hypertension & >65 years of age, patients with history of conductive or mixed type of hearing loss, ear infections, previous ear surgery, head injuries, history of ototoxic drugs, noise trauma, acoustic neuroma as assessed by history, ear examination & previous medical record. Patients with kidney diseases, diabetes, history of cerebral stroke, degenerative diseases of the central nervous system, coagulopathies, dyslipidemias as assessed by history & previous medical record were excluded from study. Data collection procedure: Through the outpatient department of ENT Unit-I, Services Hospital, Lahore, 100 patients who met the inclusion criteria were enrolled. Consent was obtained in writing and informed. Demographic information (name, age, sex) and presenting complaints were noted on the given Performa. Hearing thresholds were assessed via pure tone audiometry by delivering pure tones at frequencies of 125-8000Hz at the intensities from 0dB to 120dB in 5 dB steps to check for both air and bone conduction by using Garson Stadler audiometer and hearing loss was labeled according to the WHO criteria, which classify hearing loss into four categories: mild (normal hearing is 25 dB), moderate (41-60 dB), severe (61-80 dB), and profound (>80 dB). Patients with sensorineural hearing loss were assessed for hypertension. History of these patients was checked for hypertension (>10 years) and BP was also checked on the spot and hypertension was labeled (according to operational definition). Patients were then treated in accordance with hospital practice. Performa contains a record of all of this data (attached). Data analysis: In order to evaluate the collected data, SPSS version 20 was used. Age and blood pressure were provided as quantitative

variables with a mean and standard deviation. The frequency and percentage of qualitative characteristics including gender, smoking, and hypertension were shown. Age, gender, and smoking status were stratified in the data. Chi-square test was used post-stratification to compare hypertension in stratified groups. P value 0.05 was taken as significant.

Results

The patients ranged in age from 35 to 63 years old, with a mean age of 47.70± 9.04 years. 33 patients (33%) were female and 67 (67%) were male patients. The patients' male to female ratio was 2.03 Table-1. In this study most of the 81(81%) patients presented with bilaterally decreased hearing followed by itchy ears, occasional tinnitus and rest of the patients reported other complaints. Fig-1 According to this study the most common severity of hearing loss was bilateral mild to moderate Sensorineural hearing loss noted in 26(26%) patients followed by bilateral moderate degree of Sensorineural hearing loss and rest of the patients belonged to other severity of hearing loss. The hypertension was found in 55(55%) patients. Fig-2 In this study the mean systolic blood pressure of the patients was 136.50± 10.48 mmHg and the mean diastolic blood pressure of the patients was 88.41±7.05 mmHg. Of 55 patients, grade I severity of hypertension was noted in 42(76.4%) patients and grade II severity of hypertension was noted in 13(23.6%) patients. (Table 2). Patients age ≤ 50 years the hypertension was found in 17(28.3%) patients and in patients having age >50 years the hypertension was found in 38(95%) patients (p value=<0.001). In male patients the hypertension was found in 41(61.2%) patients and in female patients the hypertension was found in 14(42.4%) patients (p-value=0.076). Similarly in patients with H/O smoking the hypertension was found in 20(74.1%) patients and in patients without H/O smoking the hypertension was found in 35(47.9%) patients (p-value=O .02) .Table 3

Table 1: *Summary statistics of age (years) and Sex.*

	N	**100**
Age (Years)	Mean	47.70
	Standard Deviation	9.04
	Minimum	35.00
	Maximum	63.00
Sex	Male	67
	Female	33

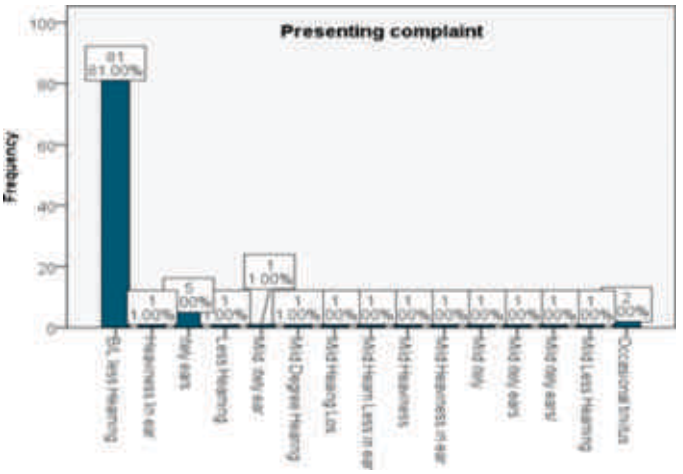

Fig-1: *Distribution of Presenting Complaint*

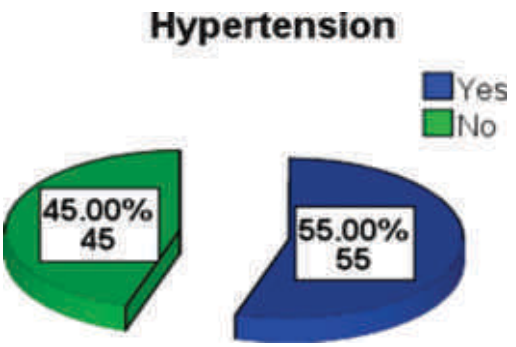

Fig-2: *Hypertension*

Table 2: *Distribution of severity of hypertension (n=55)*

		Frequency	**Percent**
Grade	I	42	76.4
	II	13	23.6
	Total	55	100.0

Table 3: *Comparison of hypertension between age groups, gender and H/O smoking*

		Hypertension		**Total**	**p-value**
		Yes	No		
Age groups	≤ 50	17	43	60	<0.001
		28.3%	71.7%	100.0%	
	>50	38	2	40	
		95.0%	5.0%	100.0%	
Gender	Male	41	26	67	0.076
		61.2%	38.8%	100.0%	
	Female	14	19	33	
		42.4%	57.6%	100.0%	
H/O Smoking	Yes	20	7	27	0.020
		74.1%	25.9%	100.0%	
	No	35	38	73	
		47.9%	52.1%	100.0%	

Discussion

The onset of cognitive decline in older persons has been linked to midlife increases in sensory neurological deficits in hearing, vision, and olfaction.[12] Untreated hearing loss increases the likelihood of cognitive decline, falls, hospitalization, and other adverse effects.[13] Age, sex, race, and genetics are a few of the risk factors that cannot be changed, but other lifestyle-related factors can. Their research is essential.[14] For adults, hearing is traditionally evaluated using pure-tone Audiometry.[15] Regardless of the severity, hearing loss is a problem that lowers quality of life. When hearing loss is developed in adulthood, it develops gradually and may make oral language comprehension challenging. Studies on the adult population have shown that hearing loss begins around the age of 30 and worsens over time. Men experience the effects sooner and more strongly than women. Despite similarities in the audiologic configuration. A hearing system issue could have negative psychosocial effects on a person's quality of life, including low self-esteem, loneliness, unhappiness, and impatience. Furthermore, it is well recognized that adult metabolic changes, such as systemic arterial hypertension (SAH), are widespread and may be made worse by the presence of hearing loss or the reverse.[16]

In this study, hypertension was found in 55(55%) patients. Of 55 patients grade I severity was noted in 42(76.4%) patients and grade II severity of hypertension was noted in 13(23.6%) patients. Some of the studies are discussed below showing their results as. Both prospective investigations by Agrawal et al.[16] and Lin et al[17]. found correlations between hypertension and the likelihood of hearing impairment. However, they found that a higher percentage of their individuals had hypertension (27% in the study by Agrawal et al.[12] and 30.8% in the study by Lin. et al.[17]

Starck et al[18] further supported these conclusions in their investigation, where reported that hearing impairment was influenced by diastolic blood pressure. Agarwal et al.[16] discovered that individuals with grade I hypertension had a prevalence of hearing loss of 36.7% in their case-control study of hearing loss in hypertensives, which included both hypertensives and a control group. With an increase in the severity of hypertension, they saw an increasing prevalence of hearing loss. According to a study done in Nigeria, 16% of hypertensive participants experienced mild to moderate sensorineural hearing loss, especially at higher frequencies because of inner ear microangiopathy and cochlear nerve neuropathy. The blood flow to the stria vascularis has been found to be decreased in hypertension patients as a result of vasoconstriction.[10] According to Saurabh Agarwal et al.[16], there may be a connection between hypertension and an increase in hearing threshold. Patients with hypertension exhibit a greater increase in hearing threshold compared to those without hypertension. Those with grade 3 hypertension showed the most noticeable increase in hearing threshold, especially at higher frequencies. 50 hypertension individuals over the age of 45 in Brazil were examined audio metrically by Brohem et al.[19]; 62% of them showed sensorineural hearing loss. A large study conducted in china showed increased hearing thre-shold among hypertensive patients.[7] Another study pub-lished in Brazil in 2017, showed prevalence of bilaterally high frequency mild sensorineural hearing loss in hyper-tensive individuals above 60 years of age was (66.26%) who underwent audiometric assessment.[6] One study showed the frequency of hypertension was high in patients with sensorineural hearing loss i.e. 46.8 % cases.[11] According to a study by Boshen Wang et al[9], persons with hypertension have much more hearing loss than patients without the condition. A noticeable increase in hearing loss was observed in patients with grade 2 hypertension. The risk of hearing loss will be reduced by effective and doable techniques for reducing the risk of hypertension and work-related noise expo-sure. In light of this study the results showed that grade 1 hypertension, grades 2 and 3, and isolated systolic hypertension all had a clear effect on hearing impairment. ($P<0.05$).[9] According to Rosen et al,[20] there is a connection between high blood pressure and hearing loss in the high frequencies, according to a study conducted with hypertension patients in the USA. After examining the hearing symptoms of 50 hypertensive patients, Markova,[21] in the Check Republic, concluded that arterial hypertension is a significant risk factor for hearing loss. On the other hand, in a retrospective investigation carried out in Denmark utilizing the records of 342 patients assessed between 1945 and 1961 sequentially, Hansen et al[22] did not connect arterial hypertension to hearing loss in this cohort. Contrary to what had been reported in earlier investigations, Sharorodsky et al[23] and other studies also revealed no association between high blood pressure and the chance of hearing loss .[24,25]

Conclusion

The prevalence of hypertension in adult patients with sensorineural hearing loss was 55 percent, with 76.4% having grade I and 23.6% having grade II

hypertension.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

FR: Conceptualization of Project
MI: Data Collection
JA: Literature Search
SN: Statistical Analysis
AK: Drafting, Revision
GM: Writing of Manuscript

Factors Influencing the Acceptability of Intra-Articular Corticosteroid Injections among Pakistani Patients with Arthritis

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Abstract

Objective: To assess patients' awareness and attitude towards intra-articular therapy. To determine the frequency of refusal among patients who were offered intra-articular steroid injections and to identify the various reasons for this refusal.

Method: This was a cross-sectional study done at the Rheumatology CMH Lahore outpatient clinic from 1st June to 31st July 2022. A total of 204 patients 16 years or above who were potential candidates for intra-articular corticosteroids (IACS) or who had received injections in the past were asked about their knowledge, beliefs, and consent for intra-articular injections as per pre-defined questionnaire.

Results: Out of the total 204 patients, 34% refused to get the intra-articular injection. Their major concern was fear of injection, dependence, and only temporary pain relief. Consent was directly correlated with disease severity as determined by pain visual analogue score (VAS) and affected activities of daily living (ADLs), and physician guidance (p=0.001). A negative review from a relative or a personal bad experience leads to rejection of IACS (p=0.001). Those who did not have prior knowledge of IACS, and its response variability agreed more (p=0.01).

Conclusion: The patients' fear of dependency, partial effectiveness, and pain were major concerns that lead to the refusal of IACS in almost one-third of the patients. Information gathered from different sources apart from doctors misleads the patients.

Keywords: Intra-articular injections, osteoarthritis, total knee replacement

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Introduction

The word arthritis refers to the inflammation of one or more joints and it encompasses a wide range of conditions, some of which have systemic manifestations. The effects of arthritis range from intermittent bouts of joint pain to chronic persistent pain ultimately resulting in reduced mobility and ability to perform day-to-day activities. The debilitating outcomes of arthritis have resulted in major socioeconomic and psychological setbacks.[1]

More than 350 million people are living with arthritis, mostly females, affecting all age groups as three in five people with arthritis are below 65 years of age.[2] In the United States, almost every 1 in 5 people suffer from arthritis and the projected prevalence by the year 2030 is likely to exceed more than 67 million.[3] In Pakistan alone, the prevalence of osteoarthritis (OA) was found to be 26.67 per 1,000 people. However, statistics for various types of arthritis are widely undetermined in Pakistan due to insufficient records of increasing disease burden.[4] Management of arthritis can be surgical and non-surgical. Non-surgical options include topical ointments, oral tablets, and

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intra-articular therapy (IAT) which directly deliver pharmacological substances into the joint space. IACS has somewhat proven effective if there isn't any significant improvement via conservative management (such as exercise, physiotherapy, and medication).[5]

Intra-articular procedures are widely performed by rheumatologists, orthopaedics as well as rehabilitation specialists around the world. IACS not only treat osteoarthritis, inflammatory arthritis, and seronegative spondyloarthropathies but is also used in joint synovitis and effusion.[6-7] Mainly three products are used in OA via IAT; which includes corticosteroids, hyaluronic acid, and blood-derived products (PRP).[8] Despite their tested efficacy and safety in clinical trials, when it comes to daily practice, a multitude of factors may affect the results of IATs, including the type of arthritis, size and location of the joint, procedure along with post-procedure care. The potential risks such as septic arthritis, skin pigmentation, and cartilage damage can be avoided by proper injection techniques and guidance.[9]

It is a common observation that there is a disparity between the requirement and patient choice for IACS, an effective, fast, and economical treatment option to relieve severe pain. Many patients are reluctant to opt for them as they have inadequate information regarding their indications. A preceding negative experience from the remote past or indirect bad experiences through some relatives and the understanding that it is a normal aging process discourage the patients from seeking professional help. [10]

As IAT is introducing a new era of improved lifestyle, especially for those not opting for surgery, more emphasis should be given to this treatment option. IACS are used frequently yet we don't know about the patient's concerns. Our research projects the patient's perspective which can help us modify our clinical practices and eradicate misconceptions about IACS.

Materials and Methods

The study was carried out at CMH Lahore rheumatology clinic 2 months after approval from the ethical committee (Case#.693/ERC/CMH/LMC). Patients aged > 16 years who were potential candidates for IACS or had previously had intra-articular injections were selected using convenience sampling. The sample size was decided by taking the frequency of IAT as 26%.[11] Indications included having Grade 2 or 3 Osteoarthritis (OA) (The Kellgren Lawrence Classification) or Inflammatory arthritis or Adhesive Capsulitis. Patients having Grade 4 OA or any contra-indications for IACS (bleeding disorder, septic arthritis, cellulitis, uncontrolled diabetes, or recent febrile illness) were excluded. Written consent was obtained, and a questionnaire was filled out using open-ended questions. Participants were asked about the severity and duration of the disease, prior treatment experience, and pain relief after it. The participant's knowledge and general perceptions (beliefs and expectations) regarding these injections, their source of information, and the decision-making process of getting IACS were also recorded. Statistical Analysis was done using SPSS-26. Age and disease duration were presented as mean+ SD. Qualitative variables like gender, diagnosis, and perceptions about IACS were shown as frequency and percentage. Chi-square was used to find any association between gender, disease duration, disease severity/disability, previous treatment experience of own or relatives with the willingness to get intra-arcticular injections.

Results

The mean disease duration was 3.08+3.18 years and

Table 1: *Baseline Characteristics of Patients*

Baseline characteristics	N (%)
Age, median (range) years	55 (21-76)
Gender	
Female	151 (74)
Male	53 (26)
Profession	
Working	61 (30)
Retired	143 (70)
Living	
Urban	160 (78.4)
Rural	44 (21.6)
Diagnosis	
OA	101 (49.5)
RA	71 (34.8)
FROZEN SHOULDER	16 (7.8)
GOUT	7 (3.4)
AS/REACTIVE	6 (2.9)
Disease duration	
<6months	34 (16.7)
1-3years	87 (42.6)
>3years	83 (40.7)
Number of prior IACS injections	
0	132 (64.7)
1-3	66 (32.4)
>3	6 (2.9)

the mean duration of attending a rheumatology clinic was 1.17+0.97 years. (Table-1)

Almost half of the patient bulk had OA as the primary diagnosis followed by rheumatoid arthritis. ADLs were affected in 66% of our patients. IACS was already received by approximately 35% of the patients. Among them 14% had only mild benefits lasting for a few days, 35% had moderate efficacy lasting up to 1 month and 51% had months of pain relief with IACS. Of those who received IAT, 40% had no prior physician guidance regarding the procedure and its complications. The decision-making of patients is greatly influenced by proper guidance and severity of pain as most patients who opted for wanted rapid pain relief. The previous treatment experience with IACS also directly decides the next IACS. (Table-2). Similarly, previous bad experiences

Table 2: *Correlation of Physician Guidance, Pain Severity, and Previous Experience of Iacs with Injection Decision*

		Physician guidance		Total	p-value
		No	Yes		
Injection decision	Yes	39 (47.6%)	96 (78.7%)	135 (66.2%)	0.001

		Pain rating (10-point scale)			Total	p-value
		1-3	4-6	≥7		
Injection decision	Yes	2 (20%)	27 (38.6%)	106 (85.5%)	135 (66.2%)	0.001

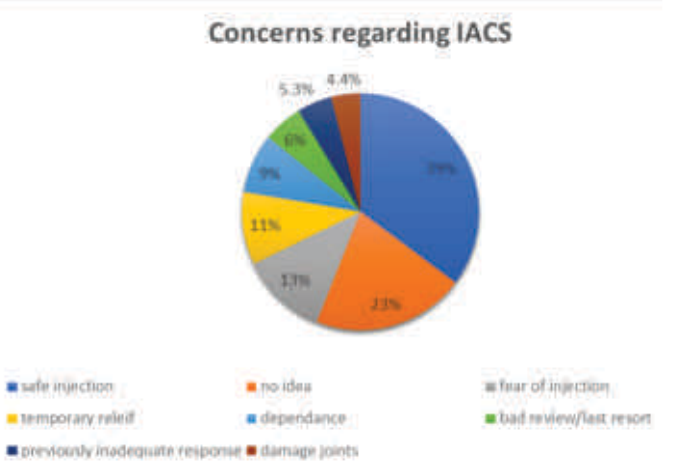
		Duration of the pain relief				Total	p-value
		0 (no effect)	1 (1 week)	2 (1 month)	3 (>1 month)		
Injection decision	Yes	1 (33.3%)	4 (44.4%)	19 (65.5%)	30 (96.8%)	54 (75%)	0.001

of a relative strongly influence the decision-making with 100% rejecting this option. (P=0.001)

Only 60% were aware of the variability in response to IACS. If known only 54% showed a willingness to expect uncertain benefits while 84% who consented had no awareness about it. (p=0.01)

When advised for IACS 135/204 (66%) agreed to it while 69/204-(34%) opted for other treatments. Among those who received the first treatment, 53/71 patients (-74.6%) agreed to the second treatment. Consent was frequently given by male patients compared to female patients (p=0.046). The major concerns regarding the choice of this option are shown in Fig-1.

Most knew about this therapy through physicians (67.5%), while 22.5% got information from peers. Decision-making was shared by only 68.6% while the other 64 (31.3%) patients relied on their physicians to decide for them as they trusted their physician or didn't have



enough knowledge to decide on their own.

Discussion

Osteoarthritis is the most frequently occurring joint disease worldwide, with increase in life expectancy and obesity its prevalence is further rising. The knee which is the most commonly affected joint accounts for 83% of the total disability load of OA.[12] Out of the various treatment options available for its management, IACS, and hyaluronic acid are currently United States Food and Drug Administration (US FDA) or European Medicines Agency (EMA) approved. The treatment plan must be individualized and regularly reviewed depending on the patient's needs and expectations. The treatment decision is largely based on the contraindications for surgery, NSAIDs, and the presence of comorbidities.[13] In one local study done on patients with chronic knee osteoarthritis comparing IACS injection and ultrasound therapy there was statistically significant reduction in pain score and range of motion in the IACS group (p-value<0.001).[14]

It has been observed that the baseline conservative treatment modalities are inadequately utilized before referral to secondary care in most of the patients. In a study done on patients with large joint OA, 81% of the patients did not have adequate exposure to conservative treatment modalities in the past.[15] In another study done on patients who had TKR, only 29% utilized IACS a year before having knee surgery. Although those injected < 3 months before surgery had a 19% increased rate of infection.[16] On the other hand a study done in Karachi found out a

different treatment trend where oral medication was the mainstay of treatment either used alone or in combination with IACS and/or physiotherapy.[17] In fact another study documented that out of 2000 patients with knee osteoarthritis, 98.7% were symptom free by conservative measures and only 1.3% needed surgery.[18] In our study, 35% of the patients had IACS secondary to failure or contraindication for oral drugs.

According to a survey including 200 rheumatic patients, 27% were kept unaware of the pros and cons of IACS. The main joints injected were the knee (66%), and shoulder (42%) with corticosteroids most used (83%). Consent was taken by 82 (41%). Ultrasound (US)-guided technique was used in 35% of the cases. Only half of them got benefitted from IAT lasting from one week to years. Some patients experienced an increase in pain, difficulty walking, or swelling (20%) after the injection.[19]

As per our survey of IACS, 51% had very good results. Regarding the procedure and its complications, 40% reported no prior physician guidance. The procedure was performed blindly in >90% of our patients.

In another European survey conducted from 26 different countries, it was reported that intra-articular procedures are performed on daily basis by rheumatologists (97%) and orthopedics (89%) for inflammatory arthritis (76%), degenerative arthritis (74%), and crystal arthritis (71%) in the knee (78%) and shoulder (70%). Around 30 to 69% of doctors considered it safe to inject IACS in the presence of co-morbidities or before surgery, while almost none of them use it in the case of prosthetic or septic joints. Most (65%) agreed that a maximum of 2-3 IACS could be given safely in the same joint. Patients were informed about the procedure by most doctors (72%) with 10% taking written and 56% using verbal consent.[20]

In our study, the most frequent indication for IACS was OA followed by inflammatory arthritis. The most injected joint was the knee (80%) followed by the shoulder (50%). Patients reported only verbal consent taken from them, also in 60%.

The refusal rate for IACS in our study was 34% as patient-centred outcomes are not given importance in clinical practice. Torre reported that patient preferences, concerns, procedure cost, and post-procedure care were considered by only 63% of health professionals before doing procedures.[21] IAT is an important procedure used for more than 70 years now. To improve the quality of care one must consider the safety and cost-effectiveness of IATs with better randomized controlled trials. Using ultrasound for diagnosis and guidance can also lead to better outcomes.[22]

Decision-making was shared in 68.6% of patients with most patients relying upon the recommendation of their doctor. Patients considered a lot of factors including the impact of arthritis on their living, fear of injections, its side effects, effectiveness, cost, doctors' guidance, and experiences shared by the relatives before deciding.[23] We also found that disability, failure of conservative treatments along with a willingness to get fast relief while avoiding surgery were the major deciding factors for IAT.

According to Selton, the major concerns for patients deciding on IAT were effectiveness and possible side effects.[24] In our study, 11% were concerned about its effectiveness, and 13.4% about dependence and damage to the cartilage. Also, uncertainty about results was the main deciding factor going for IAT (p=0.01).

The patient-physician relationship is of utmost importance in increasing acceptability and compliance. Patients think that their priorities are not given importance while physicians find it difficult to explain all treatments.[25] Our results show that detailed physician guidance is directly related to the consent for IACS (p=0.001).

This study has pointed out various gaps in the practice of IACS, especially a need for more comprehensible information as reluctance is more particularly seen due to insufficient information given by physicians resulting in several questions being left unanswered from the patient's end. Therefore, physicians should spend more time clearing the misconceptions of patients before injecting so that they feel more secure and confident in deci-ding and show more cooperation with their physicians.

Suggestions for improvement could also be possible with wider availability, better local anesthesia, minimal side effects, greater efficacy, better accuracy, and more expertise. Also, a straight diagnosis beforehand with informed shared decision-making and a proper follow-up improves outcomes. IACS should only be used when patients feel severe symptoms but not be given on a scheduled basis. Also, they should not be used again if previous injections fail to provide considerable benefit.

Conclusion

Although patients consider IAT as a reasonably safe

but painful technique, they fear its dependency and short-term effectiveness. There is a higher degree of agreement for IACS with proper physician guidance in patients who suffer increasing pain and dependency, while a previous bad experience and uncertainty about results lead to refusal.

Conflict of Interest *None*

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Authors Contribution

SS,SSR: Conceptualization of Project

SS,NK,NFC: Data Collection

SS,SSR: Literature Search

Diagnostic Role of Anti-Mullerian hormone in Polycystic Ovarian Syndrome

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Abstract

Objective: To evaluate if the elevated levels of Anti-Mullerian hormone (AMH) could serve as an indicator of polycystic ovarian syndrome (PCOS) in patients presenting with infertility.

Method: The present study was conducted at Institute of Molecular Biology and Biotechnology, The University of Lahore and Australian Concept Infertility Medical Center (ACIMC), Lahore. It was a case control study. A total of 101 females aged between 20-40 years presenting with infertility were included in this study. Among study participants, 51 infertile females had PCOS and 50 were non-PCOS infertile subjects. After taking informed consent, medical history and anthropometric indices were recorded on standardized proforma. Transvaginal ultrasound was done to assess ovarian morphology. Serum AMH, follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH) and prolactin levels were measured by commercially available ELISA kits. Serum AMH levels were measured in 10 healthy, fertile females having normal menstrual cycle as normal reference values in our population.

Results: Mean AMH levels were significantly higher (9.9±1.1ng/ml) in females with polycystic ovarian syndrome as compared to subjects without this syndrome (1.0± 0.3ng/ml). Mean FSH levels were significantly lower in females with PCOS (p value 0.001) but LH: FSH ratio, serum luteinizing hormone and prolactin level were not significantly different in two groups.

Conclusion: The study provides evidence that raised serum levels of AMH are associated with the presence of PCOS and therefore can serve as useful marker in diagnosis of PCOS.

Keywords: PCOS, AMH, infertility

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Introduction

Polycystic ovarian syndrome (PCOS), one of the common diseases effecting females of reproductive age, was for the first time, described by Stein and Leventhal in 1935.[1] It is a multisystem disease which is characterized by increased levels of androgens, irregular menstrual periods, hirsutism and cyst formation in the ovaries.[2] The delayed sequels of this condition include diabetes mellitus, obesity and cardiovascular disease.[3] Over the years, a number of screening procedures, imaging techniques and biochemical markers have been used for diagnosis of polycystic ovarian disease. The gold standard for diagnosing the PCOS is Rotterdam criteria (2003). According to this criterion, the diagnosis of PCOS is made if any two of the following three are present: Oligo/anovulation, clinical or biochemical hyperandrogenism, polycystic ovaries on ultrasound (≥12 follicles with a diameter of 2-9mm or/and ovarian volume >10ml).[4] The Rotterdam criteria relies on findings of ultrasound as cornerstone for diagnosis of PCOS.[5] Although high resolution sonographic techniques are developed, yet there is still a deal of observer variability regarding ovarian morphology and technical difficulties in performing ultrasound.[5] Another reason for avoiding ultrasound for diagnosis of PCOS is that majority of ultrasounds are made trans-abdominally not trans-

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vaginally affecting the accuracy of findings.[6] Abnormal FSH and LH secretion has also been observed in patients having PCOS resulting in altered FSH/LH ratio but studies have shown that these values do not significantly differ between PCOS and non-effected group.[7]

Anti-Mullerian hormone which is produced by granulosa cell correlates with number of antral follicles which are 2-9mm in size.[4] Studies have shown that anti-mullerian hormone levels show a significant increase in females having PCOS due to excessive accumulation of preantral and small antral follicles as result of impaired folliculogenesis.[5,8] It has also been suggested that increased levels of AMH may also be associated with ovarian hyperandrogenism.[5] It is a less invasive and stable parameter during menstrual cycle.[9] The present study was conducted to find out whether serum AMH can be used as biomarker to diagnose PCOS in females of reproductive age group in our population presenting with infertility.

Material and Methods

The present study was conducted at Institute of Molecular Biology and Biotechnology and The University of Lahore and Australian Concept Infertility Medical Center (ACIMC), Lahore. The present study was conducted at Institute of Molecular Biology and Biotechnology, The University of Lahore and Australian Concept Infertility Medical Center (ACIMC), Lahore. Study population and sample size, consisted of 111 females between age of 20-40 years. The females diagnosed for PCOS according to Rotterdam criteria were included as study subjects.[4] An equal number of age-matched non-PCOS infertility subjects were included as control group in the present study. Exclusion criteria was the patients with other systemic or chronic diseases, congenital adrenal hyperplasia, Cushing syndrome and androgen secreting tumors. The subjects who used hormonal drugs within three months before beginning of the study were also excluded. It was a case control study. The subjects were divided into two age-matched groups as Group-1 (cases), consisted of infertile patients diagnosed to have PCOS on the basis of Rotterdam criteria. (n=51) Group-2 (controls) consisted of patients without PCOS but presenting with infertility due to other factors. (n= 50). In addition, a group of 10 healthy fertile women were included for reference level of AMH. Physical characteristics and history of the subjects were recorded on Preforma. Body weight and height were recorded using Camry weight scale. Body mass index (BMI) was calculated according to following equation: BMI= Body Weight (kg)/Height (m^2). BMI of 18.5-24.9 kg/m^2 was taken as normal. Physical examination for evaluation of hirsutism was based on modified Ferriman-Gallwey Score. To determine the biochemical markers, 5 ml of blood sample was collected from each participant under aseptic techniques on third day of menstrual cycle. Blood sample was transferred to evacuated serum tubes. Serum was separated by allowing the blood to clot and centrifuged at 3000 rmp for 10 minutes. Serum AMH, FSH, LH, Prolactin and TSH were determined by enzyme-linked immune-sorbent assay using commercially available kits, AMH (Beckman Coulter, Inc. Brea, USA), FSH (Cloud-Clone Corp, Housten, TX, USA), LH and TSH (Cayman Chemical, Ann Arbor, MI, USA), Prolactin (Abcam, Cambridge, MA, USA). All determinations were made in duplicate. Data was analyzed using SPSS version 20. Quantitative variables were described using means and standard deviations. Qualitative variables were described using percentages. The significance of differences between two groups were determined by student's t-test. The p value of <0.05 was considered significant.

Results

The general characteristics of the subjects are given in table I. The medical history of the subjects and controls is given in table II. Table 3 shows mean ± SEM of the FSH, LH, Prolactin, AMH and TSH. The p value shows significantly increased levels of AMH in subjects with PCO as compared to control group.

Discussion

Table 1: *Physical characteristics of subjects (n=111)*

Characteristics	Subjects with PCOS n=51 mean ± SEM	Subjects without PCOS n=50 mean ± SEM
Age (Years)	33.3±0.4	33±0.4
BMI	26.6±0.6	27.0±0.6

Table 2: *Medical history of subjects (n= 111)*

Medical History	Subjects with PCOS (n= 51)	Subjects without PCOS (n=50)
Age at menarche (mean± SEM)	13.4± 0.1	13.1±0.2
Primary infertility (%)	78	68
Irregular menstrual cycle (%)	24	12
Dysmenorrhea (%)	20	4
Heavy bleeding (%)	26	6

Table 3: *Levels of biochemical markers*

Biochemical marker	Subjects with PCOS n=51	Subjects without PCOS n= 50	p-value
AMH[a] (ng/ml)	9.9±1.1	2.1±0.4	0.001*
FSH (m IU/ml)	6.4±0.3	10.1±0.9	0.001*
LH (m IU/ml)	6.9±0.6	7.8±1.2	0.18
Prolactin	15.6±0.9	17.1±1.0	0.6
TSH (µIU/ml)	3.5±1.5	1.4±0.1	0.095

a-Mean AMH level in healthy fertile women (n=10);1.8± 1.0ng/ml
p-value less than 0.05 is considered significant

The current study was carried out to find out the association between PCOS and AMH levels in infertile patients in our settings. In this study, significantly high levels of AMH were seen in patients diagnosed with PCOS as compared to those without PCOS. Previous studies have shown that secretion of AMH by granulosa cells in polycystic ovaries increases several folds as compared to normal ovaries. Christina et al conducted a study to determine the effectiveness of AMH in detection and diagnosis of polycystic ovaries. On the basis of the results, he concluded that AMH levels were significantly high in patients with PCOS and that serum AMH levels have a sensitivity and specificity as in screening of PCOS[10]. In another study conducted by Nada et all, high serum AMH levels were correlated with PCOS. They found that AMH can be a promising marker in diagnosis of PCOS especially if evaluation of ovarian morphology was complicated[11]. Similar results were also found in a study conducted for hormonal profiling for diagnosis of polycystic ovarian syndrome by Henri et al[12]. Muhammad Salman et al also recommended that elevated AMH serum levels can be used as a strong predictor to reflect the certainty of PCOS diagnosis among women of reproductive age13. Studies have demonstrated that AMH level do not change with menstrual cycle as FSH, LH and inhibin do. In present study, FSH level were significantly lower in patients with PCOS but LH/FSH ratio was normal in majority of the patients. Similar results were also reported in a study conducted by Li Wei Cho et al. They found that LH /FSH ratio was not significantly different between PCOS and normal subjects.[7] The stability in levels of AMH regard-less of menstrual cycle further favors the use of AMH as biomarker for diagnosis of AMH.[14]

Conclusion

Raised AMH level have significant association with PCOS.

Conflict of Interest *None*

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Authors Contribution

MUQ: Conceptualization of Project
SK: Data Collection
FS: Literature Search
SQA: Statistical Analysis
YA: Drafting, Revision
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Neutrophil to Lymphocyte Ratio As A Predictor of Endoscopic Damage in Caustic Injuries

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Abstract

Objective: To assess the ingestion of caustic substances is a medical emergency and esophagogastroduodenoscopy (EGD) is helpful in diagnosis, prognostication and management. Here, we investigated the NLR of patients, to assess the correlation of neutrophil lymphocyte ratio (NLR) with degree of caustic injury and to evaluate whether NLR can predict the degree of caustic endoscopic injury.

Method: This cross sectional study was carried out on 180 patients in gastroenterology department of DHQ teaching hospital, Gujranwala from 1st Jan 2021 to 31 Dec 2021. The endoscopy was performed and CBC was sent for analysis of NLR. The esophageal and stomach mucosal injury was graded by Zargar's classification and divided into low grade and high grade. Independent sample t test was used for comparison between mean NLR versus low and high grade injury.

Results: Patients with high grade damage has remarkably higher values of NLR as compared to low grade. For prediction of grade of damage, ROC analysis was used and AUC (area under curve) value was 0.838 (95% CI (0.783-0.894, p<0.001) and if we take NLR cut-off value as 3.5, the sensitivity will be 96.0% and specificity 63.3%, if we take cut-off value as 4.5, the sensitivity will be 93.1% and specificity 48.1% and if we take cut-off value as 5.5, the sensitivity will be 75.2% and specificity 35.4%.

Conclusion: Neutrophil to lymphocyte ratio can predict degree of gastroesophageal injury in patients with caustic ingestion.

Keywords: Caustic injury, NLR, Zargar classification

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Introduction

The ingestion of caustic substances is a medical emergency causing serious injuries to gastrointestinal tract[1]. Caustic substances ingestion (CSI) is usually accidental in children while intentionally in adults, and injuries tend to be severe.[1,3] Most of caustic ingestions are seen in female gender and younger age group.[11] Caustic substances with high and low pH are responsible for most of gastroesophageal injuries including mucosal swelling, exudates, redness, ulcerations and visceral perforation in acute setting.[2,3] Late sequelae include strictures in the esophagus and stomach, pyloric channel deformities and narrowing, mucosal metaplasia and carcinoma.[3] The depth of damage depends on many factors like socioeconomic status, intend of intake, physical consistency, concentration of the substance, ingested volume, contact time, and pH.[4-6] Endoscopy is used for assessment of gastroesophageal mucosal damage.[6-8] Endoscopy has role not only in diagnosis of mucosal damage due to corrosive but also helpful in making plan for management and prognostication[6]. In general, EGD

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is performed as early as possible usually with 1 to 2 days after corrosive ingestion[9] and Zargar's classification (annexure attached) is routinely used to grade gastroesophageal injury.[6] EGD is usually avoided in patients with unstable hemodynamic status, respiratory distress, and suspected visceral perforation.[3] Patients with low grade corrosive injury 0, I and IIA usually have no long term complication while patients with high grade injury IIB and III may develop strictures, fistulas and carcinoma.[10,12] Increase in morbidity, mortality, systemic complications and death was seen with every increase in grade of caustic injury.[3]

Patients with corrosive ingestion when present in medical emergency, initial management start with securing of airway and stabilization of hemodynamic status and surgical evaluation.[6] Blood tests and X-rays are done to assess any complication. Patients are treated with an injectable acid suppressive therapy (proton pump inhibitors) and are kept nil per oral till their condition is stabilized and endoscopy done and their extent of injury is graded.[14-16] Complicated patient with corrosive ingestion are transferred to intensive care unit (ICU) for further management.[6]

Negative endoscopy rate is 60 to 80 % in patients with corrosive substance ingestion[10,13] and yet many studies have been done for prediction of gastroesophageal damage in patients with corrosive ingestion at admission. EGD is inevitable for determination of gastroesophageal damage in patients with corrosive ingestion, because of questionable reliability of history obtained from patients and attendants.

The complete blood count (CBC) is cost effective, easily available and widely used blood test.[13] Routine blood test like CBC is used for assistance in diagnosis of different anemia, infections and blood disorders, it has been recently investigated that NLR which is easily available from routine CBC is a marker of inflammation and high value is associated with bad prognosis[19] and increased illness in different diseases.[17] Normal NLR values in an adult health population are between 0.78 and 3.53.[20]

In a study conducted by Seyit Uyar and Mehmet Kok on relationship of NLR and endoscopic damage in corrosive ingestion has found that patients with gastroesophageal injuries induced by corrosive has higher NLR value ($p<0.001$) and found cut off value of NLR higher than 8.71 has acceptable diagnostic value with sensitivity of 90% and specificity of 91.7% for the discrimination of low and high grade damage (grade 0, 1, 2A vs. 2B 3, 4).[18]

The objective of this article was to determine significance of NLR values of patients in predicting severity of caustic gastroesophageal injury.

Material and Methods

The study was designed as cross sectional with non-probability convenience sampling and conducted in Gastroenterology Department of DHQ hospital Gujranwala for 12 months last year.

The sample size of 180 was calculated by using 'WHO software for Sample Size Determination in Health Studies' considering 95% confidence level with 5% margin of error and taking reported high grade injury rate as 86.4% in caustic ingestion cases.[10] Patients of either gender between ages of 15 to 60 years presenting with caustic intake and willing for endoscopy were included in this study. Patients with atherosclerotic cardiovascular disease, cerebrovascular disease, autoimmune disease, malignancy or active infection; and on drugs like antiplatelet, anticoagulant or immunosuppressive evaluated by history and physical examinations (investigations as required) were excluded from this study. Patients in which endoscopy were contraindicated due to instability of hemodynamic and respiratory status, and suspected perforations were excluded. Patients were also excluded if endoscopy cannot be done within first 24 hour and CBC cannot be done within first 24 hour. After an informed written consent a detailed history of presenting symptoms, past history, drug and personal history and physical examination and appropriate inves-tigations were taken and recorded on proforma. The CBC was done within first 24 hour for analysis of NLR. The endoscopy was performed and the esophageal and sto-mach mucosal injury was graded by Zargar's classifi-cation within first 24 hour.

The data was collected and interpreted through SPSS version 22. Quantitative variables like age, neutrophil to lymphocyte ratio were presented as mean±SD. Qualitative variables like gender, injured or non-injured, severity of caustic injury grade were presented in form of frequencies and percentages. Chi-square test was applied to ascertain correlation of grade of injury with gender, suicide attempt and corrosive substance used. Independent sample t-test was applied to compare the mean age and neutrophil to lymphocyte ratio between low and high grade damage. ROC analysis was applied to determine the area under curve and cut-off value for NLR for the prediction of the grade of damage. A p-

value ≤ 0.05 was considered significant.

Results

Total 180 patients were included, majority the patients were female (76.1%). High grade injury was observed in 101 (56.1%) patients. Suicidal attempt was present in 151(83.9%) patients. Acid substance was used by 144 (80.0%) patients. The mean age of the patients was 23.3 ± 7.1 with age range from 14 to 60 years. Chi-squares test revealed no significant association of gender and corrosive substance used with grade of injury while significant association was observed between suicidal attempt and grade of injury (Tab 1).

Table 1: *Relationship of grade of injury with gender, suicide attempt and corrosive substance used for suicide*

Variables	Category		Grade of injury		p-value
			Low	High	
Gender	Male	n	22	21	0.271
		%	27.8%	20.80%	
	Female	n	57	80	
		%	72.7%	79.2%	
Suicidal attempt	Yes	n	61	90	0.031*
		%	77.2%	89.1%	
	No	n	18	11	
		%	22.8%	10.9%	
Substance	Acid	n	59	85	0.115
		%	74.7%	84.2%	
	Alkali	n	20	16	
		%	25.3%	15.8%	

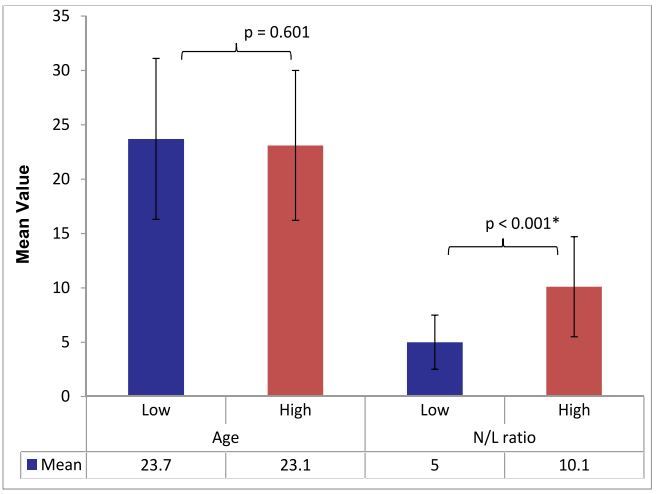

Figure 1: *Comparison of age and NLR between low and high grade injury*

Independent sample t test showed that there was no considerable variance in age between low and high grade injured patients. Significant difference was found in N/L ratio between low- and high-grade injuries. N/L ratio was higher in high grade injury as compared to low grade injury (fig 1).

If we take NLR cut-off value as 3.5, the sensitivity will be 96.0% and specificity 63.3%, if we take cut-off value as 4.5, the sensitivity will be 93.1% and specificity 48.1% and if we take cut-off value as 5.5, the sensitivity will be 75.2% and specificity 35.4%. ROC analysis was used for the anticipation of the grade of damages as low vs. high and AUC (area under curve) value was 0.838 (95% CI (0.783-0.894, p<0.001) (Tab 2)

Table 2: *ROC analysis and sensitivity and specificity of NLR in prediction of grade of injury*

Area under curve	p-value	95% Confidence Interval	
		Lower	Upper
0.838	< 0.001	0.783	0.894
Grade	**Cut-off value**	**Sensitivity**	**Specificity**
Low vs. High	3.5	96.0%	63.3%
	4.5	93.1%	48.1%
	5.5	75.2%	35.4%

Discussion

Corrosive substances ingestion can lead to irreversible devastating complications. Endoscopy is recommended for evaluation of degree of injury by corrosive ingestions and usually done in the first 1 to 2 days after ingestion. Zargar classification is used to grade injury, patients with low grade of injury (I and IIA) usually don't develop complications and are discharged on same day while patients with high grade of injury (IIB and III) usually develop complications and stay longer in hospital. In this study, total 180 patients were included and high grade injury was observed in 101 (56.1%) patients.

Studies on inflammatory markers like neutrophil to lymphocyte ratio have done in different diseases such as atherosclerotic cardiovascular diseases, inflammatory diseases and tumors[17,19,21], but are limited in corrosive substances injuries. In this study, NLR values of patients with low and high grade injury were studied and significant difference was found in NLR values between low- and high-grade injuries. NLR was higher in high grade injury as compared to low grade injury. High levels of NLR indicate severe caustic damage, extensive involvement, and the likelihood of developing complications with high sensitivity. A low NLR may be directive in

deciding a hospital discharge.

Sung Jan et al have conducted a study on NLR values of patients with nonmetastatic head and neck cancer and found that high NLR values were associated with poor survival[21].

Jing et al have conducted a study on prognostic value of NLR in patients with lung cancer and found that elevated NLR values were associated with poor survival[22].

Uyar S and Kok M have made a retrospective evaluation of 190 patients presented in University of Health Sciences Antalya Training and Research Hospital, Turkey with diagnosis of caustic ingestions. The purpose of this article was to establish the link between degree of corrosive damage and inflammatory markers such as white blood cells (WBC), C-reactive protein (CRP) and NLR and to evaluate predictability of NLR for severity of injuries. NLR was remarkably high in patients with mucosal damage than patients without it (p=0.010), whereas WBC and CRP not. NLR was also remarkably high in patients with both esophagus and gastric injuries compared to patients without organ damage (p<0.001). NLR, WBC and CRP were weakly correlated to the grade of involvement. Higher NLR value revealed higher degree of corrosive damage. NLR also appears to more definitive marker to distinguish between lower and higher degree of damage.[18]

Karalla et al have conducted a retrospective study in Turkey on 133 patients admitted due to corrosive ingestions , and revealed that patients in Group I have NLR and WBC values were statistically important and lower than patients in Group II (p<0,05). Patients with Zargar grade 0, 1 and 2A corrosive injury were included in Group1, whereas 2B, 3A and 3B corrosive injury included in Group 2.[10]

Ghonem and El Sharaby included 44 patients with corrosive ingestion presented in medical emergency, Tanta University. They used leucocyte parameters to assess acute complication due corrosive ingestions, and they found that NLR is good predictor of acute complications and cut off value >2.42 has 63.64% sensitivity and 100% specificity.[8]

Conclusion

Neutrophil to lymphocyte ratio can predict degree of gastroesophageal injury in patients with caustic ingestion.

Annexure I

Zargar classification and its corresponding endoscopic description

Zargar classification	Description
Grade 0	Normal mucosa
Grade I	Edema and hyperemia of the mucosa
Grade IIA	Superficial ulcerations
Grade IIB	Deep or Circumferential ulcerations
Grade IIIA	Transmural ulcerations with focal necrosis
Grade IIIB	Transmural ulcerations with extensive necrosis
Grade IV	Perforation

Conflict of Interest *None*

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Authors Contribution

NA: Conceptualization of Project
NA: Data Collection
RKF: Literature Search
NA: Statistical Analysis
MM: Drafting, Revision
NA, MAN: Writing of Manuscript

Comparison of Mean Change in Frequency of Stool with Zinc Supplementation versus Placebo in Children with Acute Diarrhoea

Mohammed Abbas,[1] Zeemal Hayat,[2] Shazia Naz,[3] Abeer Qadir,[4] Hassan Abbas,[5] Mohammed Ali Khan[6]

Abstract

Objective: To determine the effect of zinc supplementation in children with watery diarrhoea. The objective was to compare the mean change in frequency of stool with zinc supplementation versus placebo in paediatric patients with acute diarrhoea in addition to standard treatment.

Method: It was a randomized controlled study done in Department of Paediatrics, Punjab Rangers Teaching Hospital, Lahore over 6 months. 68 children of both genders aged under 5 years who presented with acute diarrhoea were sub-divided into two equal groups; Group -A received oral zinc with standard management while those in Group-B received standard management alone. Frequency of stools was recorded after 72 hours, mean change calculated and then compared between the groups.

Results: Mean duration of acute diarrhoea was 3.81±1.56 days. The study groups were comparable with regards to mean frequency of stools at presentation (7.71±2.76 vs. 7.79±2.67; p-value=0.894). However, after 72 hours, the mean frequency of stools was significantly lower in children receiving additional zinc supplementation as compared to placebo (3.94±2.84 vs. 5.50±2.77; p-value=0.025). The mean change in the frequency of stools was considerably higher in the group on zinc supplementation as compared to placebo group (3.76±0.89 vs. 2.29±0.63; p-value<0.001).

Conclusion: In this study, zinc supplementation was found superior to conventional management of children presenting with acute diarrhoea evident from considerably greater reduction in the mean frequency of stools. The low cost, wide-spread availability and ease of administration advocate the preferred use of zinc in the management of such patients.

Key Words: Acute Diarrhoea, Zinc Supplementation, Loose Stools

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Introduction

Diarrheal diseases is one of the most common cause of morbidity around the world and is the second highest reason of deaths in children, aged one month and above, after pneumonia. Annually, it accounts for more than 1 million deaths, with most occurring in developing countries. Therefore, 25% of deaths in young children living in South-East Asia are attributed to acute watery diarrhoea.[1] In spite of improvements in standard of living, advancement in water purification, food hygiene and sanitation, diarrheal disease remains a significant economic burden.[2]

Zinc deficiency, which is a major part of malnutrition, is associated with growth restriction and increased incidence of diarrhoea and pneumonia, especially in children <5 years of age. Around the world, zinc deficiency is responsible for around 170,000 deaths from diarrhoea and 400,000 deaths from acute respiratory illnesses in the same age group, which accounts for 4% of mortality.[3-5] An Indian study by Sachdev et al. on a trial of zinc supplementation in children admitted to

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hospital with acute gastroenteritis, reported similar findings.[6]

Zinc is of considerable importance to public health, as it is necessary for strengthening of immune system and growth. It also plays a role in improving intestinal function and optimal development of brain.[7] There is an increased risk and severity of infectious diseases, such as, AGE (acute gastroenteritis) and ARI (Acute respiratory Infections) in children with under-nutrition and accounts for 35% mortality.[8]

Supplementation with zinc reduced fecal output in children with deficiency and many clinical trials confirmed an improvement with zinc supplements AGE. An analytical study conducted by Chirla S et al. came to the conclusion that, with zinc supplementation, there was a 15% lower probability of continuation of diarrhoea in acute cases and 24% lower probability in persistent cases (>14 days).[9] The large number of cases of diarrhoea in resource-limited countries is associated with lack of access to clean drinking water, improper sanitation, and poor health and nutrition.[10] In a study, children who received zinc reported 12.5% reduction in stool frequency, 15.5% shortening of diarrhoea duration, and 18.0% reducing diarrhoea.[11]

There are limited local studies on zinc supplementation in children with diarrhoea. If we are able to prove the role of zinc supplementation in children with diarrhoea, it will not only fill the knowledge gap but also will help in treating the dehydration in our children in better way and reduction in morbidity and mortality due to diarrhoea. Therefore, this study has been planned to determine the effect of zinc supplementation in children with watery diarrhoea. The objective was to compare the mean change in frequency of stool with zinc supplementation versus placebo in paediatric population with acute gastroenteritis in addition to standard treatment.

Material and Method

A randomized controlled study was performed at the Department of Paediatric Medicine, Punjab Ranger's Teaching Hospital Lahore over 6 months from 25/01/2021 to 24/07/2021. A total of 68 (34 in each group) patients were taken in this study, the sample size was estimated at 80% power of test and 95% confidence level and the mean change in stool frequency at 72 hours was expected as 3.74±0.17 with zinc supplementation and 2.09±2.7 with placebo, in children with acute diarrhoea.

Selection of patients was by consecutive, non-probability sampling. The inclusion criteria were all children, between 2 months to 5 years of age with acute watery diarrhoea. The definition of acute watery diarrhoea is the passage of 3 or more stools per day, of consistency grade III or more (grading given in annexure), of duration of no longer than 14 days. Children excluded from the study were those with 3rd degree malnutrition, severe dehydration, systemic infection, blood in stools and other comorbidities.

All information was recorded on a structured questionnaire. All selected cases were given a probiotic and oral rehydration solution. In addition, a light diet was given to children who were able to take solids. The lottery method was used to divide the sample into two groups.

The first group (n=34) was given zinc supplementation by a staff nurse in addition to the regime mentioned above; the second group did not receive additional zinc supplementation. Outcome was derived on the basis of assessment of improvement in the condition of the patient. For infants <6 months of age, 10 mg/day zinc was prescribed, and for >6 months group, 20 mg/day zinc was given. Documentation of age, gender, the duration of diarrhoeal symptoms and the type of milk feed (breast milk vs. formula) was taken. On Day-1, notes were taken on the number of diarrhoea episodes and stool consistency, then repeated on Day-3. Outcome was measured, as change in frequency of stool, at 72 hours, in terms of mean change in number of stools passed. Then number of stools were noted after 72 hours of giving zinc supplementation. The number of stools at admission and at 72 hours was subtracted for change.

Patients were followed up in wards. The data was analyzed through SPSS version 25.0.

Results

Selected cases ages were from 6 to 60 months with a mean of 25.3±14.7 months. Majority (n=30, 44.1%)

of the children were aged above 2 years (Fig 1.). There were 41 (60.3%) boys and 27 (39.7%) girls with boys to girls ratio of 1.5:1 (Fig 2) The number of days that acute diarrhoea remained ranged from 2 to 7 with a mean of 3.81±1.56 days.

Both the study groups were comparable in terms of mean age (p-value=0.954), mean duration of diarrhoea (p-value=0.700) and duration of diarrhoea (p-value= 0.806) as shown in Table 1.

The frequency of stools ranged from 3 to 12 at presentation with a mean of 7.75±2.70 while 0 to 11 after 72 hours of treatment with a mean of 4.72±2.89. The change in frequency of stools ranged from 1 to 5 with a mean of 3.03±1.07. Both groups were comparable in terms of mean frequency of stools at presentation (7.71±2.76 vs. 7.79±2.67; p-value=0.894). However, after 72 hours, the mean frequency of stools was significantly lower in children receiving additional zinc supplementation as compared to placebo (3.94±2.84 vs. 5.50±2.77; p-value=0.025). The mean change in the frequency of stools was significantly higher in the zinc group as compared to placebo group (3.76±0.89 vs. 2.29±0.63; p-value<0.001) (Table 2). A similar difference was noted in mean change in frequency of stools between the groups based on age, gender and duration of diarrhoea as shown in Table 3.

Table 1: *Baseline Characteristics of Study Groups n=68*

Characteristics	Zinc n=34	Placebo n=34	P-value
Age (months)	25.4±15.7	25.2±13.9	0.954
• ≤1 years	7 (20.6%)	6 (17.7%)	0.943
• **1-2 years**	12 (35.3%)	13 (38.2%)	
• **2-5 years**	15 (44.1%)	15 (44.1%)	
Gender			
• **Boys**	21 (61.8%)	20 (58.8%)	0.804
• **Girls**	13 (38.2%)	14 (41.2%)	
Duration of Diarrhoea (days)	3.74±1.68	3.88±1.45	0.700
• **2-4 days**	19 (55.9%)	20 (58.8%)	0.806
• **5-7 days**	15 (44.1%)	14 (41.2%)	

Chi-square test and independent sample t-test, observed difference was statistically insignificant

Discussion

Acute gastroenteritis remains a major source of ill-health and morbidity in children under 5 years in countries with limited resources. This massive burden accounts for 800,000 child deaths, annually, from diarrhoea in the preschool age group, which translates into more than 10% of total paediatric deaths.[2] Bringing down these numbers is vital to reduce the child mortality rate by two-thirds until 2025, as planned by UN's Millennium Development Goal 4.[1,2,12]

Zinc is a potent agent in the intestine by modulating ion transport, stimulating enterocyte growth and differentiation, decreasing intestinal permeability, and regulating oxidative stress and inflammation.[3] Intestinal loss in acute diarrhoea leads to zinc deficiency, and chronic zinc deficiency makes the child more vulnerable to diarrhoea, leading to a vicious cycle.[4] It has been seen in recent evidence that zinc supplementation has significant benefit on the clinical course of acute diarrhoea by redu-

Table 2: *Comparison of Means of Frequency of Stools before and after the Treatment as well as Mean Change between the Study Groups n=68*

Frequency of Stools per Day	Zinc n=34	Placebo n=34	P-value
At Presentation	7.71±2.76	7.79±2.67	0.894
After 72 hours	3.94±2.84	5.50±2.77	0.025*
Mean Change	3.76±0.89	2.29±0.63	<0.001*

Independent sample t-test, * observed difference was statistically significant

Table 3: *Comparison of Mean Change in the Frequency of Stools between the Study Groups n=68*

Subgroups	Mean Change in Frequency of Stools		P-value
	Zinc n=34	Placebo n=34	
Age			
• ≤1 years	3.71±0.76	2.33±0.52	0.003*
• 1-2 years	3.83±1.03	2.31±0.63	<0.001*
• 2-5 years	3.73±0.88	2.27±0.70	<0.001*
Gender			
• Boys	3.76±0.89	2.30±0.57	<0.001*
• Girls	3.77±0.93	2.29±0.73	<0.001*
Duration of Diarrhea			
• 2-4 days	3.79±0.98	2.35±0.67	<0.001*
• 5-7 days	3.73±0.80	2.21±0.58	<0.001*

Independent sample t-test, * observed difference was statistically significant

cing the frequency of stools and duration of stay in hospital.[13]

In the current study, we observed that the mean age of children with acute gastroenteritis was 25.3±14.7 months. Our observation matches with that of Laghari et al. (2019) who reported a similar value of 25.12±6.05 months among such children presenting at Liaquat University of Medical and Health Sciences in Jamshoro.[13] In another local study involving children with acute watery diarrhoea presenting at Combined Military Hospital (CMH) Peshawar, Ehsan et al. observed a mean age of 25.8±4.2 months.[14] This was again echoed in an Indian study, by Mujawar et al. reporting a mean age of 27.1±10.2 months.[15] Pickering et al. and Sarker et al. made a similar observation in Bangladesh and reported a comparable mean age of 29.3±16.7 months and 23.2 ± 3.2 months respectively in such children.[16,17] Sathiadas et al. reported a comparable mean age of 25.0±12.1 months in Sri Lankan children with acute diarrhoea.[18] Strand et al.reported a similar mean age of 25.9±7.2 months among Norwegian children presenting with diarrhoea,[19]while Dhingra et al. reported it to be 23.2± 15.3 months in Tanzania.[20]

In the present study, we observed a relative male predominance among such children with boys to girls ratio of 1.5:1. Similar findings were seen in Laghari et al. who observed a male predominance of 1.5:1 among such children presenting at Liaquat University of Medical and Health Sciences, Jamshoro.[13] Ehsan et al. observed similar male predominance (M:F; 1.6:1) among children with acute watery diarrhoea presenting at Combined Military Hospital (CMH) Peshawar[14] while Qureshi et al. reported it to be 2.3:1 at Aga Khan University Hospital, Karachi.21 Mujawar et al. and Patel et al. reported similar male predominance among Indian such children with male to female ratio of 1.5:1 and 1.3:1 respectively[15,22] while Palihawadana et al. reported it to be 1.5:1 in Sri Lanka.[23] Sobouti et al. observed similar male predominance in Iranian children with diarrhoea and reported it to be 1.6:1.[24]

It was observed that after 72 hours of oral zinc supplementation, the mean frequency of stools was significantly lower in children receiving additional zinc as compared to placebo (3.94±2.84 vs. 5.50±2.77; p-value = 0.025). Also, the mean change in the frequency of stools was significantly higher in the zinc group as compared to placebo group (3.76±0.89 vs. 2.29±0.63; p-value<0.001).

Our observation is in line with a similar previously published study where Laghari et al. evaluated the effect of zinc in the management of acute diarrhoea among children. They too reported that the mean frequency of stools after 72 hours of treatment was significantly lower in the experimental groups (2.40±0.81 4.28 ± 1.07; p-value<0.001) as compared to controls. They also observed a similar significantly greater reduction in the mean frequency of stools with zinc as compared to placebo (3.74±0.17 vs. 2.09±2.7; p-value <0.001).[13]

The addition of zinc was found superior to conventional management of children presenting with acute diarrhoea evident from considerably greater reduction in the mean frequency of stools regardless of child's age, gender and duration of diarrhoea which along with its low cost, wide-spread availability and ease of administration advocate the preferred use of zinc in the management of such children presenting in future paediatric practice so that the alarmingly high burden of diarrhoea and subsequent malnutrition in Pakistan can be reduced.

Conclusion

In the present study, addition of zinc was found superior to conventional management of children presenting with acute diarrhea evident from considerably greater reduction in the mean frequency of stools regardless of child's age, gender and duration of diarrhea which along with its low cost, wide-spread availability and ease of administration advocate the preferred use of zinc in the management of such children presenting in future pediatric practice.

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Authors Contribution

MA: Conceptualization of Project
HA: Data Collection
SN: Literature Search
AQ: Statistical Analysis
MAK: Drafting, Revision
ZH: Writing of Manuscript

Positive Predictive Value of Ultrasound in Predicting Non-Alcoholic Fatty Liver Disease taking Magnetic Resonance Imaging as Gold Standard

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Abstract

Objective: To determine the positive predictive value of ultrasound in predicting non-alcoholic fatty liver disease taking magnetic resonance imaging as gold standard.

Method: 84 patients of both sex groups with ages in the range of 18-60 years suspected to have NAFLD underwent ultrasound examination of the liver and kidney and the ratio of mean gray-scale intensity of the liver / renal cortex calculated. The NAFLD on ultrasound was labelled as per operational definition. The MRI was performed and areas under the water peak and fat peak were recorded. Liver fat content was calculated. The NAFLD on MRI was labelled as per operational definition. All the data was noted along with demographic details of the patient.

Results: The age of the patients ranged from 18 years to 60 years with a mean of 41.4years. Male to female ratio of 1:5 was found. The BMI of the patients ranged from 22.6 Kg/m2 to 34.8 Kg/m2 with a mean of 30.8 Kg/m2 and 71.4% patients were obese. 34.5% patients were diabetic. The diagnosis of NAFLD was confirmed in 96.4% cases on MRI. Taking MRI diagnosis of NAFLD as gold standard, it yielded a positive predictive value of 96.4% for ultrasound in predicting NAFLD.

Conclusion: Ultrasound showed a high positive predictive value in the diagnosis of non-alcoholic fatty liver disease irrespective of patient's age, gender, BMI and history of diabetes which advocate its preferred use in future medical practice.

Keywords: NAFLD, MRI, ultrasound, predictive value, diabetic

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is fat accumulation in liver which is not caused by excessive alcohol intake. NAFLD is the most common liver condition in the world with a prevalence of up to 30% and 10% in developed and developing countries respectively. NAFLD is found predominantly in obese and diabetic patients due to its pathogenesis being associated with insulin resistance. NAFLD has genetic and lifestyle risk factors, and it is recognized as a major indicator in deaths and diseases related to liver. With the growing obesity and metabolic syndrome epidemidcs, non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease worldwide and will become one of the leading causes of cirrhosis.[1-3] The non-invasive modalities to diagnose and evaluate NAFLD are ultrasound, elastography, CT scanning, MRI which employs various techniques including chemical shift and spectroscopy.[4] The sensitivity and specificity of MRI in detecting NAFLD is reported to be 100%.[5-7] Zhang, et al. in 2014 conducted a study and calculated the positive predictive value (PPV) of ultrasound in predicting NAFLD and found it to be

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94.2%.[8] The positive predictive value varies with the prevalence of the disease. In our community, a related study has not been published yet and thus there is a dire exigency to perform it so that ultrasound's PPV in predicting NAFLD, taking MRI as gold standard, in local population could be determined which up till now has been proven to be a silent disease; and this silent disease's incidence is progressively increasing. This study will help us to determine the PPV of ultrasound (which is readily available and is a cheap modality) in detecting NAFLD, which can help us in using this modality as screening tool among the local population, helping in early detection of NAFLD and reducing the mortality and morbidity associated with NAFLD caused by its progression to hepatic cirrhosis, hepatocellular carcinoma, and hepatic failure in very short period of time.

Materials and Methods

It was a cross-sectional survey. Research was conducted at Department of Diagnostic Radiology, Combined Military Hospital Lahore. Duration of study was 6 months from 11/09/2020 to 10/03/2021. Sample size of 84 cases was computed with 95% confidence level and 5% margin of error along with expected PPV of ultrasound abdomen predicting NAFLD to be 94.2%. Non-Probability, Consecutive Sampling was employed to select the subjects. Both gendered patients with a range of age between 18 years to 60 years, predicted to have NAFLD on ultrasound as per operational definition. Patients who signed written informed consent to participate in the study. Patients who were taking steroids (>3 doses in past 4 weeks), having hepatitis B or C as per ELISA method, or having any structural abnormality of kidney on ultrasound as per history/investigations and patients who had history of ingestion of alcohol for >7 days in past 8 weeks. After acceptance from institution's ethical review committee, 84 patients suspected to have NAFLD on routine abdominal ultrasound scan presenting in department of radiology as per operational definition and who satisfied the above-mentioned specifications were detailed about the study. Patients gave their coplete histories and written consent was taken. Patients underwent ultrasound examination of the liver and kidney and the gray-scale intensities of both the liver and the kidney were determined two times in a single patient and then the ratio was calculated by dividing mean gray-scale intensity of the liver / mean grayscale intensity of the renal cortex. The NAFLD on ultrasound was labelled as per operational definition. The MRI was performed by measuring the fat content in the right lobe of the liver only while patient was in a supine position. Areas under the water and fat peaks were registered. Liver fat content was determined by [liver fat content (%) = area under the fat peak / (area under the fat peak + area under the water peak) × 100]. The NAFLD on MRI was labelled as per operational definition. The proforma was filled using the patient's data and his/ her demographics. All the ultrasound examinations were performed by the same consultant of the radiology department on the same ultrasound machine and all the MRI fat contents were calculated on the same MRI machine to eliminate bias and confounding variables were controlled by exclusion.

Results

The age of the patients was in the range of 18-60 years with a mean of 41.4±11.7 years. 14 (16.7%) males and 70 (83.3%) females with a male: female totaling 1:5. The BMI of the patients spanned between 22.6 Kg/m^2 to 34.8 Kg/m^2 with a mean of 30.8±3.6 Kg/m^2 and 60 (71.4%) patients were obese. 29 (34.5%) patients were diabetic (Figure:1). The diagnosis of NAFLD was confirmed in 81 (96.4%) cases on MRI. Taking MRI diagnosis of NAFLD as gold standard, there were 81 (96.4%) true positive and 3(3.6%) false positive cases. It yielded a positive predictive value of 96.4% for ultrasound in predicting NAFLD taking MRI as gold standard as shown in Table-1

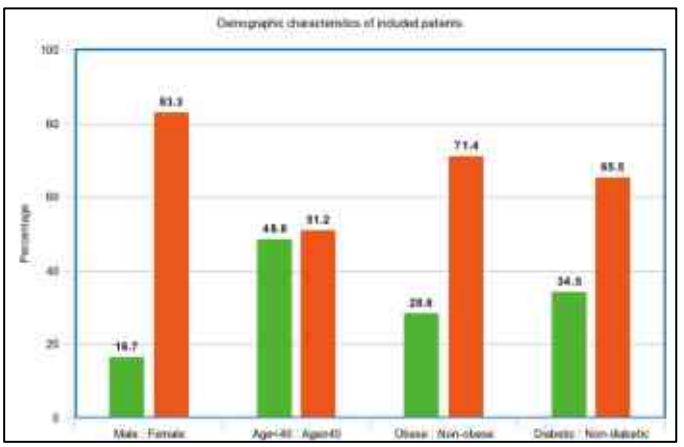

Fig-1: *Demographic Characteristics of study patients*

NAFLD on MRI	Frequency	Percent (%)
Yes (True Positive)	81	96.4%
No (False Positive)	3	3.6%
Total	84	100.0%

Positive Predictive Value = $\frac{81}{81+3} \times 100$

Positive Predictive Value = 96.4%

Table-1: *Frequency of NAFLD on MRI and Positive Predictive Value of Ultrasound*

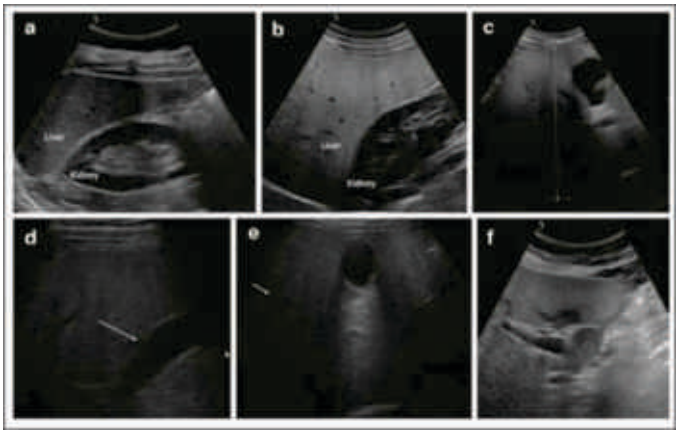

Fig-2: *Appearances of fatty change liver on ultrasonography*

Discussion

One of the foremost causes of liver disease in the world is nonalcoholic fatty liver disease (NAFLD) with increasing prevalence because of the epidemics of obesity and metabolic syndrome and has become the main referral reason to hepatologists.[9] NAFLD is fat buildup in liver more than 5% of the organ's weight, not being explicated by at risk alcohol intake which has a 30 g/ day threshold in males and 20 g/day threshold in females.[10,11] NAFLD carries both a clinical and an economic burden which will increase with population growth.[9] NAFLD is not considered benign as it can advance to hepatocellular carcinoma, liver transplantation, and ultimately death.[1] A subset of patients with NAFLD is usually asymptomatic and is incidentally detected during routine medical workup for some other problem[2]. Delay in the diagnosis adversely affects the prognosis of patient and necessitates accurate screening tests to timely identify patients with early changes at a stage when medical intervention is more effective and is associated with better outcome.[2-4] MRI is the current gold standard for the diagnosis of NAFLD with sensitivity and specificity of 100%.[5-7] However, it is a time consuming test and can't be performed in routine.[5] On ultrasonography fatty change liver appears as increased parenchymal echogenicity in comparison to kidneys. This change is easy to be noticed by ultrasonologist. Few recent studies reported good positive predictive value of ultrasound in the detection of NAFLD which along with its non-invasive nature and bedside availability favoured its use in future practice.[8,12]

However, the available evidence was limited while there was no regional publication which demanded the present study. A comparable mean age of 41.04±12.66 years was observed by Niaz et al. (2011) among patients presenting at PNS Shifa Hospital, Karachi.[13] Iqbal reported similar mean age of 40±12 years in patients presenting with NAFLD at Aga Khan University Hospital, Karachi.[14] A relatively higher mean age of 52.31±5.96 years has been reported by Afzal et al. among patients presenting at Shaikh Zayed Hospital, Lahore[15] while a much lower mean age of 30.26±9.[16] years was observed by Ahsan et al. at Jinnah Postgraduate Medical Centre, Karachi.[16] Kumar et al. observed similar mean age of 40.9±12.[8] years among Indian such patients.[17] We observed that there was a female predominance among patients with non-alcoholic fatty liver disease with male: female of 1:5. A similar female predominance among NAFLD patients has been reported previously by Ahsan et al. (1:6), Alavi et al. (1:2) and Afzal et al. (1:1.7) in local population and Kumar et al. (1:4.3) in Indian population,[15-18] while Taseer et al. reported nearly equal gender distribution among such patients at Nishtar Hospital Multan.[19] Kalra et al. on the other hand observed a male predominance (1.4:1) among such patients in Indian population.[20] We observed that ultrasound had a positive predictive value of 96.4% in predicting NAFLD taking MRI as gold standard. In a previous study, Zhang et al. (2014) reported the positive predictive value of ultrasound in predicting NAFLD to be 94.2% in line with the present study.[18] Our observation is also in line with that of Almeida et al. (2008) who reported the positive predictive value of ultrasound in diagnosing non-alcoholic fatty liver disease to be 98.4%.[12] This study is first of its kind in our native population. In the present study,

ultrasound was found to have a high positive predictive value of 96.4% in the diagnosis of non-alcoholic fatty liver disease irrespective of patient's age, gender, BMI and history of diabetes which along with its low cost, non-invasive and radiation free nature and widespread and bed-side availability advocate the preferred use of ultrasound in the diagnostic evaluation of patients suspected of NAFLD in future medical practice.

Conclusion

In the present study, ultrasound was found to have a high positive predictive value of 96.4% in the diagnosis of non-alcoholic fatty liver disease irrespective of patient's age, gender, BMI and history of diabetes which along with its low cost, non-invasive, radiation free nature, and bed-side availability advocate the preferred use of ultrasound in the diagnostic evaluation of patients suspected of NAFLD in future medical practice.

Conflict of Interest *None*

Funding source *None*

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TMM, MA: Drafting, Revision
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Perception and Willingness towards COVID-19 Vaccination in Pregnant Females in Jinnah Hospital, Lahore

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Abstract

Objective: To identify perceptions, concerns and barriers affecting willingness for COVID-19 vaccination among pregnant females.

Method: This was a cross-sectional study conducted on 356 pragnent women from Gynae outdoor department of Jinnah Hospital, Lahore from August 2021 to January 2022. It was a cross sectional study conducted on 365 pregnant women from gynae outdoor department of Jinnah Hospital, Lahore. After informed consent, data were collected with the help of a semi-structured questionnaire; entered, cleaned and analyzed using SPSS version 20.0. Chi Square was applied as a test of significance where p value is 0.05

Results: Among 365 females, only 58(15.9%) were vaccinated. About 6(10.4%) women received vaccination in the 1st trimester and 26(44.8%) each in the 2nd and 3rd trimester. Significant contributors for vaccination were vaccination center location, advice from health care provider, perception about vaccine safety and vaccine protection, supportive family attitude, previous history of COVID-19 infection and suspicious rumors.

Conclusion: Vaccine hesitancy and rejection can be minimized through a multipronged strategy to combat infodemic and to educate the public. Health care providers can play a vital role through their effect communication and counseling.

Keywords: COVID-19, Vaccine hesitancy, barriers, pregnancy, COVID-19 Vaccination

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Introduction

A bunch of atypical pneumonia cases were discovered in Wuhan, China in December 2019 which was named as COVID-19 caused by severe acute respiratory syndrome Coronavirus (SARS-COV-2). Symptoms were variable from asymptomatic disease or mild symptoms to severer acute respiratory distress which caused high mortality. It was declared as a pandemic by the World Health Organization (WHO). In Pakistan, It was first detected on 26th February 2020 in Karachi, Sindh and later spread to the whole county.[1,2]

During this time period, pregnant females were included in high risk group who were 70% more prone to getting infected and developing complications such as miscarriages, pre-eclampsia, postpartum hemorrhage in mother and premature deliveries followed by ICU admissions, ventilator support requirements and death in babies.[3] High mortality and restriction of social life due to lockdown resulted in increased mental health issues. Vaccination was the only escape in this dreadful condition. Numerous Medical and Research Institutes developed vaccines for COVID-19. Depending upon vaccine efficacy, approximately 60-90% vaccination coverage is required to contain this disease.[4] Despite the urgent need of vaccination to curb the pandemic, vaccine hesitancy was observed worldwide. About 31% vaccine

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hesitancy was observed globally. In the UK, 25%, in Canada 14% and in Australia 9% of the population surveyed, were reluctant for immunization.[5] Pakistan already has vaccine hesitancy and rejection issues in the past, especially observed in Polio vaccine. So, the same attitude was observed this time against COVID-19. Before the introduction of the vaccine, conspiracy theories were fabricated and people were reluctant due to fear of side effects. Social networks played a vital role in its spread.[6,7] As the vaccine was formulated in a short time, so the public had safety concerns. The compulsion to get vaccinated also added fuel to the fire.[8] Hence, this study was designed to identify perceptions, concerns and barriers affecting willingness for COVID-19 vaccination among pregnant females

Material and Methods

The cross-sectional study was conducted at Gynae outdoor department of Jinnah Hospital, Lahore from August 2021 to January 2022. The Institutional Ethical Review Committee granted ethical approval. Furthermore, prior to enrollment in the study, permission from the participants was obtained. All pregnant women of child bearing age (15–49 years) were included; however, divorced, widow, post-menopausal women were excluded from the study.

Following formula was used to calculate the sample size

$$n = \frac{z^2 1-\alpha/s\, P(1-P)}{d^2}$$

Where Confidence interval was 95%, margins of error 5 percent and the anticipated population was 0.614.[4] The estimated sample size was 365. After informed consent, data was collected through a pre-tested questionnaire. Observations were noted on a questionnaire. Data were entered, cleaned and analyzed using Statistical Package for Social Sciences (SPSS) version 20. Frequency tables were generated for all possible variables including age, education, occupation, family income, vaccination status, advice regarding vaccination, short term complications, advice by health care regarding vaccination, awareness about vaccination, vaccination center availability, perception regarding vaccination safety, suspicious rumors, effect of COVID-19 and family attitude. Means and other parameters of central tendency were calculated for continuous data. The comparison was done to find out the association of vaccination status with respect to baseline variables. Chi Square was applied and p-value of ≤ 0.05 was considered statistically significant.

Results

The study was conducted in Jinnah hospital in Gynae outpatient department and 365 pregnant females were assessed through questionnaire to estimate the frequency of their willingness for COVID-19 vaccination and associated concerns and perceptions. Among 365 females, only 58(15.9%) were vaccinated and 307 (84.1%) were not vaccinated. About 6(10.4%) women received vaccination in the 1st trimester and 26(44.8%) each in the 2nd and 3rd trimester. Literacy percentage for the participants was 74.2% and 248(67.9%) women were 18–30 years of age. A large proportion of 318(87.1%) were housewives while only 47(12.9%) were working women while the monthly household income of 356(97.5%) participants was more than 20,000. Only 102(27.9%) women received advice from a health care provider regarding vaccination. A Hundred percent of participants had awareness about vaccination, while only 30(8.2%) complained that the vaccination center is distant from their residence. As far as the perception of respondents regarding vaccination is concerned, more than half of respondents 195(53.4%) thought that COVID-19 vaccination is not safe. A major proportion of 339(92.9%) participants replied that vaccination can have side effects, only 5(1.4%) replied that it has no negative impact and 21(5.8%) described that COVID-19 does not exist. About two third of participants 21(66%) confirmed that they have heard suspicious rumors about vaccination. How-ever, 257 (78.6%) participants found support from the household regarding vaccination. Short Term Compli-cations after COVID-19 Vaccination in Pregnant Females (n=58) were described in the pie chart below.

Discussion

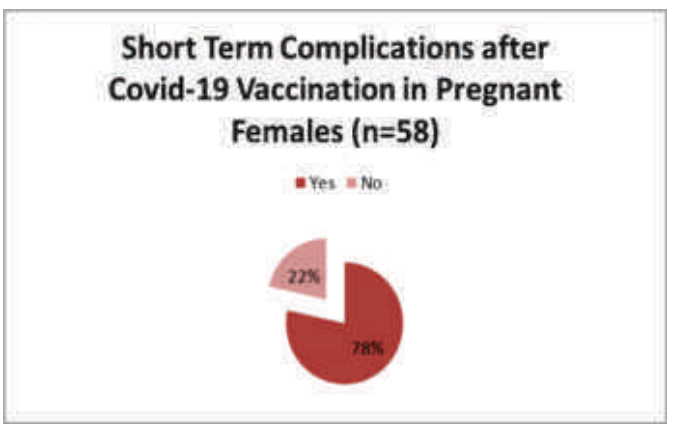

Table 1: *Inferential statistics regarding association of Vaccination Status with variables*

Characteristics	Vaccinated		Not Vaccinated		p-value
	n	%	n	%	
Near	57	17.0	278	83.0	0.050
Not Near	1	3.3	29	96.7	
Yes	37	36.3	65	63.7	<0.001
No	21	8.0	242	92.0	
Safe for both	55	32.4	115	67.6	<0.001
Not safe	3	1.5	192	98.5	
Supportive	57	19.9	230	80.1	<0.001
Non-Supportive	1	1.3	77	98.7	
Yes	9	45.0	11	55.0	<0.001
No	49	14.2	296	85.8	
Yes	58	33.9	113	66.1	<0.001
No	0	0.0	29	100.0	
To some extent	0	0.0	165	100.0	
Yes	17	7.1	22.4	92.9	<0.001
No	41	33.1	83	66.9	

P-value ≤0.05 significant.
Test Applied: Chi-square

The Covid infection has imposed a great threat on physical, mental and social health of the population. Pregnant women are under great vulnerability and in need to get vaccinated which can only be possible if their concerns and perceptions are identified which can affect their willingness to get vac-cinated. We pursued to determine perceptions and deter-minants related to COVID-19 vaccine hesitancy amid pregnant females in Lahore to monitor inoculation struggles in this at risk population.

This survey revealed low vaccination status (15.9%) among pregnant females, higher understanding about vaccine efficacy (93%) and high safety apprehensions relevant to complications on the fetus (46.8%). COVID-19 shot coverage in gravid women varied globally, from 77% in a study steered in China to 37% in a study executed in Turkey.[9,10] Vaccine approval related to safety and efficacy was on the higher side, but administration status in this population is quite low at 16%, which indicates a quest for an initiative to boost acceptance ultimately leading to sufficient vaccination in the population. Our decreased vaccine willingness is directly proportional to low supposed threat of infection due to decreased countrywide infection rates as per this study, enhanced infection risk perception was considerably associated with superior vaccine reception in expectant women in our study. Reduced vaccine reception has also been influenced by endorsements from the local Health Ministry during survey times.[11] It was observed that due to organizational support for vaccination regarding gravid and lactating females, vaccine approval was quite higher than in our study population (44-58% and 55% in gravid and lactating females correspondingly).[12]

In our study, suspicious rumors were reported by 66% of women, although 76% of the family was supportive in administration of COVID-19 vaccine. However, other studies reported concerns regarding vaccine willingness among gravid women as compared to non-gravid and lactating women.[13] A potential justification might be that expectant women may have been learned of the bigger hazard of severe ailment in infected gravid women, thus lessening their vaccine acceptance.

The healthcare providers were of the least concern to advise the pregnant ladies towards vaccination (27.9%). Although gravid women make more trips to health care centers due to ante-natal checkups, investigations and thus have a more chance to visit health care provider. It is the best time for physician to give a brief counseling regarding vaccine safety and to give answers to patients' questions and concerns. Many studies have indicated that due to certain concerns regarding developing fetus and her own wellbeing, pregnant women avoid vaccination.[12,13]

Deficient safety data is a major contributor towards vaccine avidity in this study population. Expectant women were more anxious due to possible current and future side effects of the vaccine on child's health. According to observational data from different countries, mRNA-based vaccines were proved safe for expectant and lactating mothers and no short or medium duration side effects were observed for them.[14] Appropriate dissemination of this data can play a vital role to enhance vaccine acceptance.

In this study, it was found that decreased education level and age were not significantly connected with higher vaccination numbers in pregnant women. This is dissimilar to other studies where greater education level and age were linked with greater inoculation administration.[15] It is quite evident that females who were highly educated and of younger age were better conversant about the inoculation administration. This can also clarify our finding of lowered vaccine numbers in pregnant women, as a smaller fraction of pregnant women had a graduate degree or higher (6.6% vs. 1.9%). Certainly more pregnant women will be ready to get a jab

after dissemination of safety data regarding vaccination.

Limitation of this study was the cross-sectional method and the short duration of study, i.e. 3 months. During study conduction, Government recommendations regarding vaccine safety were changed with more emphasis on its safety. However, the results of this study are still relevant and valid, as these results depict the need of educational approaches targeting women who are either unsure or unwilling to accept the inoculation. In addition, vaccine acceptance was measured via participant reply, and not based upon actual vaccination rates. Reported intent is not a true reflection of human behavior on vaccination. Moreover, discussion regarding side effects and safety issues can also lead to vaccination uptake.[16]

This study is targeting a special vulnerable group, i.e. pregnant women in whom chances of complications after COVID-19 are high. Through this study we are able to propose platforms, namely social media and mass media, to raise awareness about the safety of vaccine in pregnant women to promote vaccination coverage. Along with expansion of the vaccination program, education of the masses is also very important

Conclusion

The perceptions regarding vaccine safety and willingness to receive COVID-19 vaccination are strongly related to the trusted recommendations from health care providers. Health education should be delivered to enhance the willingness in females. The data shows only 15.9% of pregnant females are vaccinated against COVID-19, which is a potential threat and the government should take strong measures to overcome this issue.

Conflict of Interest *None*

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Authors Contribution

FG: Conceptualization of Project
KH: Data Collection
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FM, RH: Statistical Analysis
ZT: Drafting, Revision
SK: Writing of Manuscript

Occupational Health Risks among Pathologists and Pathology Trainees: An Analysis of Prevalence and Factors

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Abstract

Objective: To assess the prevalence of work-related hazards faced by Pathologists and residents in the Pathology laboratory in Pakistan.

Method: This cross-sectional study was conducted over a period of one month from January 2023 to February 2023. The research questionnaire was shared online amongst the Pathologists and Pathology residents. The collected data was analyzed using SPSS version 28. The qualitative data was described in terms of percentages or frequencies and analyzed using the Chi-square test. A P-value < 0.05 was considered statistically significant.

Results: Out of 172 participants, the majority (74.5%) were females. 51.6% of the participants had 31 to 45 hours working, with 26.7% spending 2-4 hours daily on the microscope. Musculoskeletal disorders were seen in 93.2% of the study population followed by visual strain (90.6%) and anxiety and stress in 90.1%. 35.4% reported that the pain was severe enough to take off from work, which involved a greater percentage of females (38%) than males (26%). Males were found to exercise more as compared to females (p-value= 0.044). A significant finding in our study was that psychological disturbances were experienced more in females as compared to males (p-value=0.00,0.00 & 0.00).

Conclusion: This study highlights the importance of workplace-based hazards faced by pathologists. Postural support, monitoring work hours, and taking small stretch breaks can play an important part in their professional well-being.

Keywords: Occupational hazards, safety, pathologists

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Introduction

Healthcare workers have always been at risk of exposure to hazardous substances, sometimes, the damage is acute even life-threatening like in the COVID pandemic while in other instances their sufferings are subtle, slowly compromising their health.[1,2]

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Pathologists working in the background and helping the clinicians in proper treatment of their patients, through the precise diagnosis of diseases are constantly exposed to infectious agents and hazardous chemicals in the laboratory.[3] In most low- and middle-income countries, the safety measures and standards to protect healthcare workers are not up to the mark.[4] Insufficient resources, poor data collection and ineffective enforcement of regulations all contribute to increasing occupational health hazards. Risk management is an important but neglected aspect of the medical field. This should be incorporated into everyday practices and people concerned must be aware of the risks and the remedies.[5] The prevalence of work-related hazards faced by Pathologists and residents working in pathology laboratories

varies worldwide but is consistently present throughout.[6] To the best of our knowledge, not much work has been done in the past to find out sufficient data from the Pathologist population of Pakistan. We find it important to do so, also making them aware of the potential risks and find out a solution in the form of safe conditions and a healthy working environment where they can practice their profession in better health. The association or prolonged use of a microscope and the development of chronic pain syndromes is a long-known problem however most pathologists are not very well informed about this hazard. They first realize it when they experience it. Musculoskeletal disorders are the most common work-related injuries noticed by pathologists worldwide followed by stress, burnout, depression, neuropathies, and respiratory problems.[6,7] Musculoskeletal disorders are strongly associated with continuous and long hours of using microscopes and computers. In the majority of cases, the damage and severity of symptoms are directly proportional to the time spent on these devices. Without conscious awareness, these professionals are attaining awkward postures which are very damaging for their neck, shoulder, and lower back leading to variable symptoms the most important indeed is the pain, which becomes responsible for their days off from work.[8] Multiple studies have highlighted that the microscopes commonly used are not optimized and do not provide a neutral sitting position, requiring the pathologist to bend forward giving them a posture called the so-called pathologist's hump.

The importance of following postural guidelines, monitoring work hours, taking small stretch breaks, and creating awareness about ergonomics can't be underestimated. More than 60% of pathologists reported relief of their musculoskeletal problems using an ergonomically optimized microscope.[8] Visual impairment is another common work-related problem in this occupational group.[6] Although, most pathologists have ametropia, even before joining this field many have noticed aggravation of symptoms in the form of deterioration of refractive errors during their work years in Pathology.

Formaldehyde is a hazardous chemical which is widely used in pathology laboratories worldwide. Its ability to penetrate the tissues deeply and its low cost makes it a preferred selection for tissue fixation and processing. This ability of the chemical, on the other hand, is a source of chronic health problems for the pathologists dealing with it.[7]

Studies have shown that exposure to formaldehyde leads to wheezing, (24%), %), burning eyes (25%), and cough (21.7%).[9-11] Certain malignancies including brain tumors, lympho-hemopoietic neoplasms, and nasopharyngeal and pancreatic cancers are being linked to formaldehyde exposure, although the relationship between cancer and formaldehyde is still not well established.[9-11] Its use in floor and equipment disinfection is another application in pathology laboratories. It is somewhat difficult to remove this chemical from the labs. But the concerning fact is that exposure level to this chemical is usually not monitored in our laboratories. It is much beyond the acceptable occupational exposure limits. This is found to be maximum amongst the residents and the technologist involved in the histopathology section of the Pathology lab, involved in tissue grossing and processing.[9-11]

Most of the above-mentioned problems can be mitigated by preventive measures and initiatives to reorganize the lab space, reposition gross stations and employ protective gear.

The chronic stress observed by Pathologists is itself a risk factor for multiple mental and physical health issues. A local study revealed that the anxiety score was the second highest among pathologists.[12] Many international studies document the increased risk of exposure to tuberculosis and transmission of blood-borne infections like HIV and HCV in healthcare workers of lower-middle-income countries.[2,13] Working close to infectious aerosols put the pathologist at high risk of getting these infections. Needle puncture and cutting injuries are other possible sources of infection. The prevalence of latex allergy symptoms is also quite high ranging from 16 to 18% reported in three different studies. The risk of developing allergic symptoms increases with an increased period of contact while wearing latex gloves for an extended duration. Two studies reported a prevalence of 4.2% and 4.4% of the latex-specific IgE antibody levels. Pathologists and pathology residents working for long hours on the grossing stations are continuously exposed to the effects of latex. It is reported that the use of powder-free latex and nitrile gloves in labs significantly reduces the risk of these allergic symptoms.[14-16] This study aimed to assess the prevalence of work-related hazards faced by Pathologists and residents in the Pathology laboratory in Pakistan, due to the lack of available data on the subject. The goal was to gather information on the types of hazards and their frequency to better understand the working conditions in the patho-

logy laboratory.

Materials and Methods

This was a cross-sectional study conducted over a period of one month from January 2023 to February 2023 after getting approval from the Ethical review board of CMH Lahore Medical College (IRB No: 737/ERC/CMHLMC). The research questionnaire constructed on Google Forms was disseminated via online social media platforms amongst the Pathologists and residents of Pathology working in any Pathology laboratory. Residents who have recently joined this field or spent less than two years in the environment of the Pathology laboratory were excluded. Informed consent was taken from the participating Pathologists and only those who show their willingness were included in the study. The sample size was calculated to be 161 using the formula $n= Z^2 P (1-P)/ E^2$. This questionnaire was adapted from previous literature (Fritzsche et al)[6], with some modifications taking into account the local conditions. It was reevaluated, and its validity and reliability were confirmed. Data was collected on a pre-designed, self-reported questionnaire with 6 sections comprising 43 questions related to demographics, occupational circumstances, working hours, and health issues like musculoskeletal disorders, visual problems, behaviour abnormalities, psychological disturbances, mental ailments, and other medical conditions. The collected data was analyzed using SPSS version 28. The qualitative data was described in terms of percentages or frequencies and analyzed using the Chi-square test. A P-value < 0.05 was considered statistically significant.

Results

The largest study population (38.5%) belonged to the 31 to 40 years age group followed by the group of 41 to 50 years (23.6). The majority (74.5%) of the participants were females. Consultants including both male and female pathologists constituted 62.7% of participants. Microbiologists constituted the largest group making 34.2% followed by histopathologists making 29.8% of the study population. 38.5% of the participants had been in their professional field for more than 10 years. 51.6% have 31 to 45 hours per week working hours. 26.7% reported that they spend 2-4 hours per day on the microscope and 41.6% spend two to four hours on computer screens. As most of the pathologists were working in institutions, they were following an individual signed out, however, 77.6% had a shared burden of responsibility regarding sign-outs in their department.

Regarding physical issues, musculoskeletal disorders were the most common seen in 93.2% of the study population followed by visual strain experienced by 90.6% and anxiety and stress in 90.1%. The frequency distribution of these disorders is shown in Table 1.

35.4% reported that the pain was severe enough to take off from work, which involved a greater percentage of females (38%) than males (26%). 47.2% required some medicine or physiotherapy to get pain relief. The work habits of participants are summarized in Table 2. Results show that those who follow recommended posture suffer less frequently from musculoskeletal problems (29.7%) as compared to 48.5% of those who did not follow the recommended posture. Regarding the practice of taking stretch breaks, more males were in a habit of taking stretch breaks during their work hours, however, the p-value was not found to be significant (p-value=0.11). However, males were found to exercise more as compared to females (p-value=0.044). Stress and anxiety were the second most common complaint experienced by 90.1% of pathologists, some feeling occasionally (67.1%) and others frequently (23%). Feeling depressed at various times in their professional life was admitted by 66.5%. Reasons for feeling stressed out are shown in Fig.2. A significant finding in our study was that psychological disturbances including stress/anxiety, depression and feeling of burnout were experienced more in females as compared to males (p-value=0.00,0.00 & 0.00).

Table 1: *Health issues faced by Pathologists*

	Occasional %	Frequent %	Never %	Total
Neck/ shoulder pain	55.3	37.9	6.8	100
Wrist pain	36.6	16.1	47.2	100
Lumbosacral pain	55.3	24.8	19.9	100
Eye fatigue	24.8	65.8	9.3	100
Work related anxiety/Stress	67.1	23	9.9	100
Sleep disturbances	59.6	18.6	21.7	100
Latex skin allergy	20.5	5	74.5	100
Splashes on mucous membranes	32.9		67.1	
Any type of cutting injury during work	37.9		62.1	
Needle stick injury	49.7		50.3	

Regarding visual problems, 60.9% suffered from visual aquity problems before joining their specialty however 55.3% noticed deterioration in their vision after joining

Table 2: *Awareness level of Pathologists/ Consultants regarding safety/preventive measures/protocols*

	YES	NO	Occasio-nally	Mostly
Stretch breaks during work hours	57.8	42.2		
Regular exercise /sports	33.5	66.5		
Follow recommended posture for Microscope/ computer	23	21.7	19.3	36
Familiar with the term Ergonomics	67.1	32.9		
Awareness about protocols to follow after work accidents/injuries	81.2	18.8		

Pathology as their field of specialty. Although 62.7% of the pathologist have been exposed to chemicals and

Table 3: *Availability of safety /preventive measures at the workplace (in percentages)*

	YES	NO	Occasio-nally	DON'T KNOW
Ergonomically designed lab	23	41		36
PPE availability	62.1	9.9	28	
Cut resistance gloves availability	2	69.6	23.6	4.8

infectious materials, less than 5% of the pathologist have been diagnosed with hepatitis B, C or HIV during their profession.

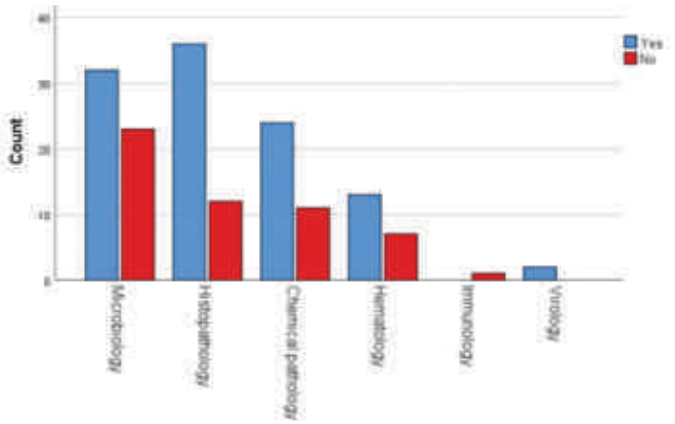

Fig. 1: *Profession Related Depression in different Sub-Specialities of Pathology*

Discussion

Working in the field of pathology has short-term and long-term consequences. Many of these problems can simply be ameliorated solely by creating awareness among pathologists. Timely reminders and interventions should be scheduled, and it should be emphasized over and over to pathologists to seek evaluation and treatment for work-related issues, even if the symptoms are mild. In our study population, 38.5% of subjects were in the age group of 31 to 40 years which is close to the results

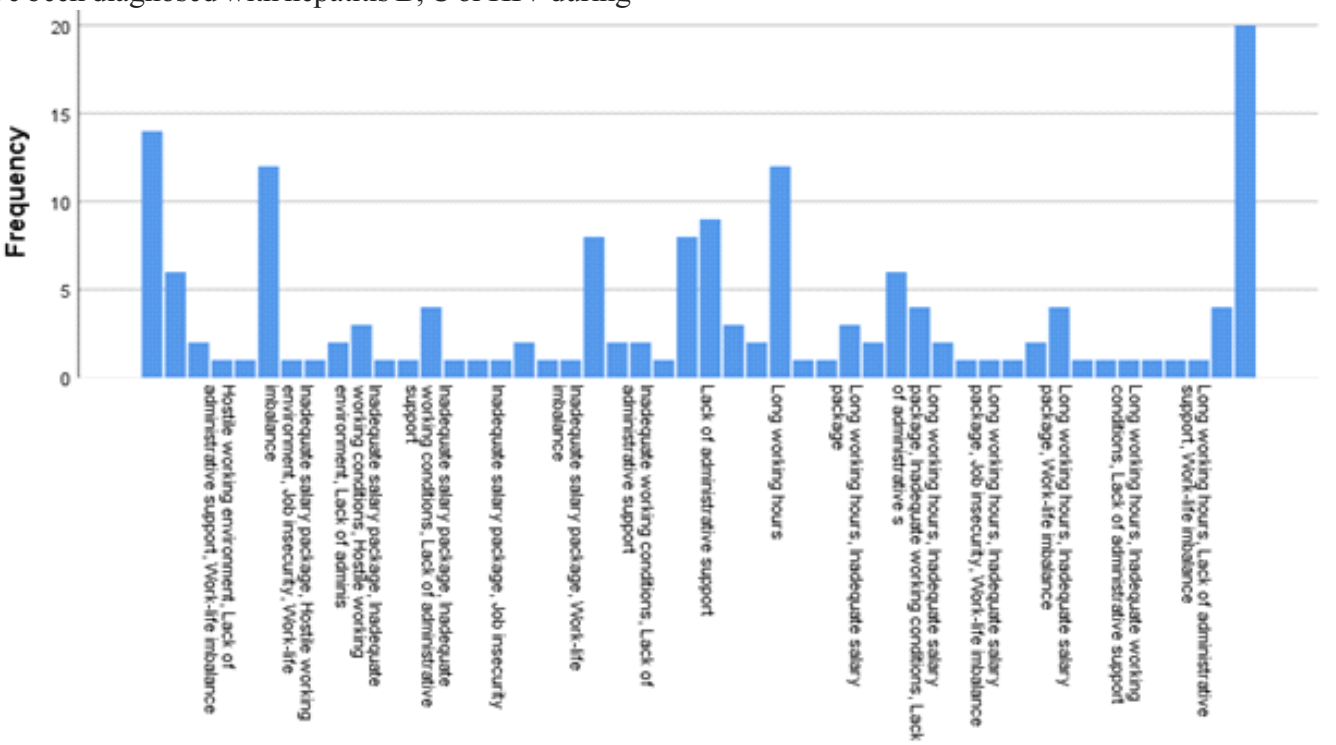

Fig. 2: *Factor (s) contributing to depression and anxiety in Patholgists*

seen in a study conducted in India where they found 37.8% of participants belonging to the age group of 36–45.[3] Female pathologists and residents constituted 74.5% of participants. Similarly, females were in major proportion in other similar study groups making 62.2% and 54%.[3,6] Consultants including both male and female pathologists constituted 62.7% of participants in comparison to 74.2% in another study.[6] Musculoskeletal disorders were found to be the most common problems seen in 93.2% of the study population. Similar disorders were documented in more than three-quarters of Swiss pathologists, 85% and 67% of pathologists in different studies.[6,8,3] Since pathologists frequently combine microscope and computer work, this can pose an additional musculoskeletal hazard. Musculoskeletal Pain remains the most common physical problem faced by pathologists worldwide. 57.8% of the pathologists mostly men (68%) were in the habit of taking small stretch breaks during working hours. However, most of them were not accustomed to any kind of exercise or regular walking to stay fit. Only 33.5 % were doing exercises regularly which is in agreement with an Indian study group (37.8%), however, 73.6% of the Swiss Pathologists were into regular sports/ exercise to help their wellbeing.[3,6]

49.1 % admitted that they follow the recommended posture (sometimes or always), while 50.9% didn't bother to follow instructed postures while working on the microscope and computers. There was strong evidence that high levels of static contraction, prolonged static loads, and awkward postures involving the neck and shoulder muscles were associated with an increased risk for musculoskeletal disorders.[8] Therefore, it is strongly encouraged to adopt preventive measures before the symptoms appear and to seek prompt medical advice if the symptoms appear. Although 67.1% of subjects were aware of the term ergonomics, the ergonomically designed workplace was available to only 23% as compared to 40.5% of pathologists in developed countries.[6] This fact supports the international studies saying that, in low- and middle-income countries (LMICs), occupational health is often neglected due to limited resources.[4] Stress/anxiety and feeling of burnout were the second most common health problem experienced by 90.1% of pathologists, with some having the feeling occasionally (67.1%) and others frequently (23%). Unfortunately, this is in sheer contrast to the results seen in the Swiss pathologist population, where less than 10% ever experience this feeling.[6] 65.8% of the subjects in this study complained of eye fatigue, which is much higher than in other study populations.[3,6] Formalin exposure was reported by 23% and 52% of them were Histopathologists. 76.4% of exposed ones suffered from some degree of discomfort but specific allergies to formalin and latex were not common. Although 62.7% of pathologists have been exposed to chemical and infectious materials, less than 5% of the pathologists have been diagnosed with hepatitis B, C, Tuberculosis or HIV during their profession. This contrasts with the results produced by Roy who has reported the high rate of transmission of bloodborne infections in health care workers of LMIC and increased risk of tuberculosis.[4] However, the possibility of latent tuberculosis in our subjects cannot be ruled out. Needle prick injury has been experienced by 50.3% while cutting injuries were reported by 37.9% of the study population which is even lower than seen in a Swiss study.[6] PPE was available to 62.1% (sometimes or always), however, cut-resistant gloves were never available to the large majority (69. 6%). This again supports the fact highlighted in some studies that safety measures and risk reduction strategies in Low-income countries are suboptimal, mainly due to resource limitations.

Conclusion

Pathologists face numerous problems, both mental and physical, which affect their overall well-being. We have emphasized the workplace-based problems faced by pathologists in our society can be reached by ---------- the importance of postural support, monitoring work hours, taking small stretch breaks and creating awareness about ergonomics which can play an important part in their professional well-being.

Conflict of Interest *None*

Funding source *None*

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Authors Contribution

AS, AB: Conceptualization of Project
AS, KHC: Data Collection
AS: Literature Search
AB, KHC: Statistical Analysis
AS: Drafting, Revision
MRA: Writing of Manuscript

Pattern of Haematological and Biochemical Parameters of Dengue Virus Infection in Children

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Abstract

Objective: This study was conducted to study pattern of clinical, hematological and biochemical parameters in children with dengue fever.

Method: A prospective comparative analysis of 120 suspected febrile children was done at social security teaching hospital in Lahore from September to November 2021. The study participants satisfying the inclusion criteria were registered for further assessment. Clinical findings were logged, hematological and biochemical parameters tests were performed.

Results: In this study, there were 56.66 % male participants and 43.33 % female participants. The most common clinical manifestation was fever (100%) followed by vomiting 85.4%, abdominal pain 68.75% and body pain / myalgia in 52.08% cases. Most frequent hematological parameter was thrombocytopenia (93.75%) followed by leucopenia 70.83% and the elevated levels of liver transaminases were seen in 68.75% subjects.

Conclusion: This study focuses on the patterns of laboratory parameters of pediatric dengue viral infections .This might prove helpful for the pediatricians to suspect, diagnose and manage the dengue virus infection.

Key Words: Dengue virus infection, Dengue fever, Dengue hemorrhagic fever, Hematological tests, Biochemical parameters.

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Introduction

Dengue is an Arbo viral disease which is transmitted by mosquito.[1] The Aedes aegypti is the culprit for its transmission. Dengue infection has rapidly spread across the globe in the recent decades.[2] The seasonal transmission is mainly seen in monsoon and post monsoon time of year.[3,4]

According to the estimation of WHO, this world's two third population is at the risk of the dengue virus infection, particularly the tropical and subtropical countries[1]. While dengue is endemic in many countries, majority cases are reported from Southeast Asia and the western Pacific regions.[3] In South East Asian region, India is one of the seven countries that has reported high incidence of dengue outbreaks threatening the health care system badly[4]. In 1940's, India reported firs confirmed case of dengue fever & after that more states started reporting this.[5,6] In Bangladesh its true magnitude was essentially unknown until it manifested heavily in 2000.[4,7]

In Pakistan, first outbreak of DHF was confirmed in Karachi that happened in 1994 with total 145 cases and only one case of fatality was reported.[8] Punjab has now encountered this infection for more than a decade and is passing on to hyperendemicity.[1,2]

Dengue infection has demonstrated great variations in presentation from mild illness to complicated dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[7,9] As compared to adults, the severity of this

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disease (DHF) is seen more in children belonging to the age group of under 15 years.[10,11] There are four discrete serotypes of dengue virus which are DENV 01, DENV 02, DENV 03 and DENV 04. Lifelong immunity is acquired only if the infection happens to be with one serotype of dengue virus (DENV), because the protection provided against the subsequent infection is partial and transient.[12] For the effective management of dengue outbreaks, the knowledge of exact clinical presentation, epidemiology and laboratory profile is of utmost importance. Since long time, several studies are being carried out to observe the trends in the epidemiological pattern of dengue transmission through geographical mapping of severe dengue fever cases, which has enabled to predict future outbreaks and to focus the system of public health.[13,14]

In clinical practice, Dengue virus infection is primarily diagnosed with the help of clinical presentations and laboratory data. There are some non-specific tests; e.g. hematological parameters, liver function tests, and serum protein concentration and few specific tests; such as viral antigen test and serology for antibody detection used to aid in diagnosis.[9,13,14]

Attempts must also be made to identify additional factors for early diagnosis of the disease severity and swift supportive treatment of infected patients. Specific treatment for dengue is not available, but early disease identification and appropriate fluid replacement therapy, use of antipyretics and analgesics along with quality nursing care certifies the decline in the mortality risk due to severe cases.[15]

It is crucial to comprehend the risks of developing dengue outbreaks as well as the biochemical picture of this disease in order to have proper utilization of the resources.[9,15] In the post-monsoon season, we usually get a resurgence of this infection. Hence, a hospital-based study in children was conducted, in order to determine the trends in laboratory parameters of DF & DHF. This study highlights the biochemical characteristics of dengue fever and might be helpful for future management of disease more effectively.

Material and Methods

The study involved 120 suspected cases of Dengue fever and were followed prospectively at Social Security Hospital, Multan road Lahore in the department of Pediatric Medicine. It was a simple comparative study. This was done during the dengue outbreak occurring between the months of September to November 2021. Patients were selected through convenient purposive sampling technique. These 120 patients of age group 1-15 years which were labelled as suspected, probable and confirmed dengue as per Dengue GCP guidelines. Confirmed dengue patients were then further classified as dengue fever, dengue hemorrhagic fever (grade I –IV) according to Dengue GCP guidelines.

A predesigned patient proforma with all details of epidemiology, clinical and laboratory parameters was used as a tool for data collection during the hospital stay, Clinical examinations was performed by a doctor on each study participants and all details were noted in the structured questionnaire.

Hematological profiles and biochemical investigations were done at the time of admission and were followed by daily (or bi-daily) investigations as per need. All of these parameters on day five were mainly assessed and used for comparison in this study.

All the routine investigations such as hematological determiners like total leukocyte count (TLC), differential leukocyte count, platelet count; hemoglobin (Hb) and hematocrit (Hct) were checked by the automated blood analyzer. Transaminases levels for liver function tests and total serum protein were done by the automated biochemistry analyzer. The cutoff values of each test results were considered based on reference ranges used by the laboratory.

Signs of plasma leakage were monitored by CXR and abdominal USG. Specific investigations were also done in some patients as required to avoid confusion with similar epidemic febrile illnesses, like cerebrospinal fluid analysis, neuroimaging, viral markers, peripheral smear and serology for plasmodium falciparum, blood culture and sensitivity. All the categorical variables such as clinical features and biochemical parameters were expressed as numbers and percentages. The predominant laboratory features in each group were documented and analysed for their statistical significance

Statistical analysis was performed by Chi Square test done by using the Statistical Package for Social Sciences (SPSS 15.0) .Comparison of two groups was assessed by applying t-test ,with $p < 0.05$ considered as statistically significant. The study protocol was approved by the Ethics and Research Committee of social security teaching hospital and a written informed consent was obtained from the parents or guardians.

Result

Out of 120 enrolled suspected dengue cases 68 (56.66%)

were male while 52 (43.33%)were female. Majority of the confirmed dengue patients were male 29 (60.41%) and 19 (39.58%)of the patients were female. The most dominant age group among the suspected and confirmed dengue patients was >10-15 yrs. Out of these 120 suspected Dengue cases, 90 (75 %) were labeled as probable dengue but 48 (40%) were later confirmed to have dengue infection. Of the confirmed dengue fever patients, 32(66.66%) patients had classic dengue fever while 16(33.33%) fulfilled the criteria of dengue hemorrhagic fever (DHF). Of these 16 patients with dengue hemorrhagic fever, 25% (12)patients were of DHF grade I/ II, 8.33% (4) patients were of DHF grade III and none with DHF grade I (Figure 1).

Thrombocytopenia (platelet count < 150,000/mm^3) was the most common hematological finding observed in 45(93.75%) cases, followed by leucopenia (TLC < 4,000/mm^3) seen in 44 (91.66%) cases. Platelet count of >100,000 /mm^3 to <150,000/ mm3 was seen in 15 (31.25%) cases while count below 100,000 / mm^3 in 30 cases. All the patient falling in group of DHF had platelets count of <100,000/mm^3. Anemia (Hb < 11.0 g/dl) was seen in 25 (52.08%) children. Hematocrit > 50 % was observed in 22 (45.83 %) of the cases. Neutrophil count of < 1500 in 5 (10.41%) and lymphocyte count of > 3000 in 3(6.25 %) cases was observed (Table 1).

The study of the biochemical investigations depicted that alanine aminotransferase (ALT) level > 45 IU/L (85±7 IU/L)was present in 28 (58.33 %) of cases and aspartate aminotransferase (AST) level > 35 IU/L(97 ± 9 IU/L)was observed in 31(64.58%) of cases. Hypoproteinemia (4.8±0.7 g/dl) was observed in 11 (22.91 %) cases. Deranged PT/APTT were found in 13 cases (27.08%) (Table 2). Serositis in the form of ascites and pleural effusion in 20 (41.66%) cases. Pericholecystic edema was found in 10 (20.83%) cases(Table 2).

On comparison of laboratory parameters, thrombocytopenia of less than 100,000/mm^3 was observed in 43.75% cases with DF but in all patients with DHF. HCT >50% was found in all patients with DHF but in 18.75% of patients with DF . 68.75 % cases with DHF showed prolonged PT/APTT in contrast to only 6.25 % of cases with DF that was statistically significant. Both groups showed rise in transaminases with no statistical difference. Hypoalbuminemia was observed in 9 out of 16 (56.25%) cases with DHF and only 2/32 (6.25%) patients with DF (Table 3 & Figure 2).

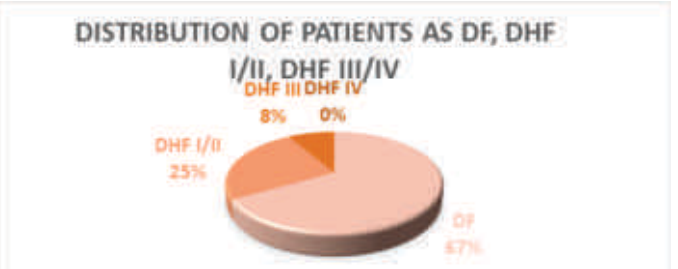

Figure No 1: *Distribution of patients as DF, DHF I/II, DHF III/IV (DSS).*

Table 1: *Hematological Profile Of Dengue Cases:*

Parameter	No. of Patients (n=48)	Percentage (%)
HEMOGLOBIN		
< 11 g/ dl (9.5 ±0.7g/dl)	25	52.08%
>11 g/dl (11.2 ±0.6g/dl)	23	47.91%
Hematocrit (%)		
>50% (54±2 %)	22	45.83%
TLC		
<4000 cell/cumm (2800 ± 500 cell/mm^3)	34	70.83%
>4000 cell/cumm (4800 ± 600 cell/mm^3)	14	29.16%
NEUTROPHILS		
>1500 cell/mm^3	43	89.58%
<1500 cell/mm^3	5	10.41%
LYMPHOCYTES		
>3000 cell/mm^3	3	6.25%
<3000 cell/mm^3	45	93.75%
PLATELETS		
>100,000-<150,000 cell/mm^3 (120,000 ±10,000 cell/mm^3)	15	31.25%
<100,000 cell/mm^3 (55,000 ± 20,000 cell/mm^3)	30	62.5%

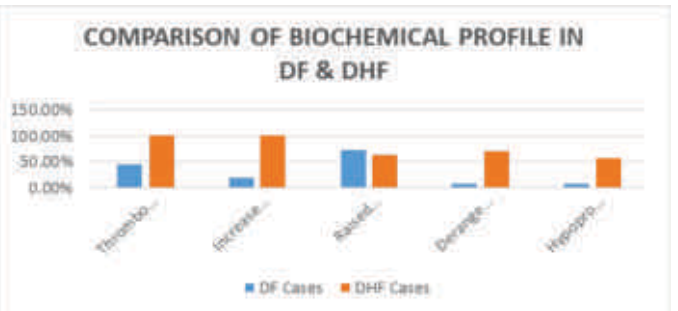

Figure No 2: *Comparison of Biochemical Profile in DF & DHF:*

Table 2: *Biochemical & Radiological Profile Of Dengue Cases:*

Parameter (± SD)	No. of Cases (n=48)	Percentage (%)
ALT >45 IU/L (85±7 IU/L)	28	58.33%
AST > 35 IU/L (97 ±9 IU/L)	31	64.58%
SERUM PROTEIN <5.5 g/dl (4.8±0.7 g/dl)	11	22.91%
PT/APTT ABNORMAL	13	27.08%
PLEURAL EFFUSION / ABDOMINOPELVIC ASCITES	20	41.66%
PERICHOLECYSTIC EDEMA	10	20.83%

Table 3: *Comparison Of Biochemical Profile In DF & DHF:*

Parameter	Confirmed Cases (n= 48)	DF	DHF	P Value
Thrombocytopenia <100,000cell/mm^3	30 (62.5%)	14 (43.75%)	16 (100%)	<0.05*
HCT >50%	22 (45.83%)	6 (18.75%)	16 (100%)	<0.05*
Raised Transaminases	33 (68.75%)	23 (71.87%)	10 (62.50%)	>0.05
Deranged PT/APTT	13 (27.08%)	2 (6.25%)	11 (68.75%)	<0.05*
Hypoproteinemia	11 (22.91%)	2 (6.25%)	9 (56.25%)	<0.05*

*P value of < 0.05 is considered to be significant.

Discussion

In past few years, the prevalence of dengue has increased globally. Therefore timely diagnosis and appropriate medical management are of prime importance.

This study has emphasized on patterns in hematological and biochemical profile of children with dengue infection. The evidence hence generated is crucial for better understanding of management of children presenting with dengue infection. Dengue fever shows laboratory alterations beginning on the third day and getting most evident on the 5th day and restoring to normal usually by the eleventh day.[13,14,15]

The most frequent finding was thrombocytopenia (platelet count < 150,000/mm^3), observed in 45(93.75%) cases. Thrombocytopenia might be related to decreased platelets production due to viral bone marrow suppression, or due to binding of dengue antigens to platelets and increased antibody mediated immunological platelets destruction. Tejas found thrombocytopenia to be 92.68 % while studying the trends in biochemical profile of dengue patients.[20] A study by Jayant also found thrombocytopenia to be the consistent finding as it was observed in 84% cases of classical dengue and 100% cases of dengue hemorrhagic fever.[17] Similar was found in Srilankan study by Jayadas.[18] Payal Jain reported a significant proportion of patients (80%) with platelet count below 100,000/cumm and 41.2% with platelet count below 50,000/cumm.[19]

Leucopenia is another hematological parameter which occurs in dengue infected patients due to dengue bone marrow suppression. This study found leucopenia (TLC < 4,000/mm^3) in 44 (91.66%) cases. This is in contrast to study by Ferede et al in which leucopenia was observed in 26.5% of the cases20. Tejas showed it to be 58.26%[16].

Jayadas from Sri Lanka observed leukopenia in 85% of the NS1 positive patients.[18]

Anemia (Hb < 11.0 g/dl) was seen in 25 (52.08%) children in our study. Ferede et al found Hemoglobin levels less than the cutoff values in 44.1% of the cases[20]. This could be explained due to mucosal bleed.

Hematocrit > 50 % was observed in 22 (45.83%) of the cases, which is related to the hemoconcentration due to increased intravascular plasma permeability, the basic pathophysiological mechanism in dengue infection. Increased hematocrit was observed in 6.9% cases by Ferede et al.[20]

Dengue virus is hepatotrophic and also cause damage to other organs; hence leading to excess release of AST (nonhepatic source like erythrocytes, brain & kidney tissue, skeletal & cardiac and muscle) during infection and ALT associated with hepatocytes injury that leads to more deranged AST than ALT. Elevated transaminases were seen in 33 children comprising 68.75% in our study group. AST was raised in 64.58% and ALT in 58.33% of our cases. Ferede et al also observed higher of AST in 45.1% and ALT in 17.6% of the cases with AST being in a greater proportion than ALT.[20] This observed pattern might be explained on the basis of excess AST release from damaged muscle cells (non-hepatic source) during infection leading to more derangement in AST than ALT. Payal Jain also documented mild to moderate elevation in the levels of AST and ALT in 85.1% and 80.7% of the patients, respectively.[19] In a study of Sri Lanka, Jayadas showed the raised aspartate transaminase (AST) levels in 63 (80.7%) patients and

elevated alanine transaminase (ALT) level was found in 32 (52.5%) patients.[18] Tejas documented raised liver enzymes in 79.94%16.

In our study, hypoproteinemia (total protein < 5.5 mg/dl) was observed in 11(22.91 %) cases. In studies by Ferede et al documented hypoproteinemia in 30.77% cases.[20] This could be probable that the complex interaction between virus, host immune response and endothelial cells, may affect the barrier integrity and vascular endothelial cells functioning leading to plasma leakage and hypoproteinemia. Our study revealed deranged PT/APTT in 13 cases (27.08%). Altered coagulation profile was observed in 37% patients in study by Jayant[17]. This abnormality in the coagulation profile is explainable on the basis of hepatotrophic effect of dengue virus.

Our study revealed serositis in 20(41.66%) cases. Contrary to this, Payal Jain's study showed the radiological evidence of serositis in 16.67% cases.[19] Our study showed pericholecystic edema in 10 (20.83%) cases. Tejas studied found it in 48.23% cases.[20]

Conclusion

The community infection of dengue virus is characterized by the ice berg phenomenon. The knowledge of pattern of hematological and biochemical profile will help the clinician in early diagnosis and effective management of the patients with dengue fever. More studies regarding this in pediatric age group will prove fruitful.

Conflict of Interest *None*

Funding source *None*

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Authors Contribution

SS: Conceptualization of Project
KMA: Data Collection
SS, MA: Literature Search
MAF: Statistical Analysis
KMA: Drafting, Revision
SSC, ME: Writing of Manuscript

Relation of Monocyte Count to Thrombus Burden in ST-Segment Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention

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Abstract

Objective: To determine the association of monocyte count to thrombus burden in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (P-PCI).

Method: This analytical, cross-sectional study was done in the Angiography Department of Rawalpindi Institute of Cardiology, Rawalpindi from October 30, 2020 to April 30, 2021. After taking ethical approval, 180 STEMI patients undergoing P-PCI who presented within 24 hours of symptoms were included using nonprobability convenient sampling. Informed written consent of the patients was obtained. Primary PCI with stenting was done and the thrombolysis in myocardial infarction (TIMI) scale was applied to determine intracoronary thrombus burden. The blood samples of patients were taken to estimate monocyte count. The data was analyzed through the Statistical Package for the Social Sciences (SPSS) version 25.

Results: The frequency of thrombus burden was high in 71(39.4%) patients and low in 109(60.6%) patients. The monocyte count showed a significant difference in patients with high thrombus versus low thrombus burden. In low thrombus burden patients, the mean monocyte count was 0.49±0.50 and in high thrombus burden patients, the mean monocyte count was 0.64±0.48. The results of stratification of thrombus burden with age group showed significant p-value and with others showed non-significant p-value.

Conclusion: The monocyte count is a reliable, inexpensive and simple-to-measure predictor of high thrombus burden in coronary arteries in STEMI patients undergoing primary PCI.

Keywords: Thrombus burden; Monocyte count; ST-segment elevation myocardial infarction; Primary Percutaneous coronary intervention

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Introduction

Myocardial infarction (MI) is the most severe form of cardiovascular disease. ST-segment elevation myocardial infarction (STEMI) contributes to a significant proportion of cardiovascular mortality and morbidity.[1] The prevalence of cardiovascular diseases particularly STEMI is rising continuously mainly in low-and middle-income countries (LMICs). The issue has worsened owing to the large population size in these countries. The World Health Organization has reported that 80% of cardiovascular mortality occurs in LMICs. There is an estimated increase of 3 million cases of STEMI annually in these countries. In addition, STEMI affects young people in LMICs in much larger numbers than in other countries. It is also a cause of significant

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financial burden for these countries leading to an annual loss of around $3.76 trillion.[2]

The pathogenesis of STEMI involves the formation of a thrombus in coronary arteries resulting from the rupture of atherosclerotic plaque and subsequent decrease in coronary blood supply.3 Despite the development of numerous pharmacological and invasive therapies, including thrombectomy and glycoprotein IIB/IIIa antagonists, the management of intracoronary thrombi remains challenging.[4] Primary percutaneous coronary intervention (P-PCI), which restores normal blood flow and has better clinical results, is the preferred treatment option.[5] But the occurrence of the phenomenon of slow flow/ no-reflow jeopardizes the advantages of P-PCI.[6] The available data revealed that this phenomenon occurs in 4% to 30% of patients after P-PCI.[7,8] High thrombus burden is the most significant predisposing factor of slow flow/no-reflow and adversely affects the success rate of P-PCI. During the procedure, a thrombus can embolize to the distal territory increasing the infarct size, thus decreasing cardiac function from microvascular obstruction.[9] High thrombus burden is linked to lack of flow, stent thrombosis or coronary artery spasm and worse clinical outcomes such as reinfarction, cardiac rupture, arrythmia, heart failure, embolization and even death.[10,11]

The treatment of STEMI may benefit from determining the predisposing factors of high thrombus burden. Two factors predicting the thrombus burden in STEMI patients are red cell distribution width (RDW) and bilirubin level.[4,12] Monocytes may play a role in coronary artery disease (CAD) pathogenesis, and a high monocyte count has been linked to an increased risk of MI.[13] It has been revealed that monocytes are involved in thrombus formation and plague rupture by secreting enzymes that breakdown the extracellular matrix, releasing various pro-coagulant factors and promoting inflammation.[13,14] High monocyte counts are an important indicator of inflammation and therefore high thrombus burden. Literature has reported that monocyte counts independently predict slow reflow/no-reflow following primary PPCI in STEMI patients.[14]

The current study was conducted to detect the frequency of high thrombus burden in STEMI patients undergoing P-PCI in our setup and also assessed the association of various cardiovascular risk factors with thrombus burden in these patients. The study also determined the difference in monocyte counts between patients with high thrombus and low thrombus burden. This will help us in the risk assessment of the patients with high thrombus burden undergoing P-PCI. Early identification of these patients will help us to improve our practice for better prevention and management of this condition.

Materials and Methods

This analytical, cross-sectional study was done in the Angiography Department of Rawalpindi Institute of Cardiology, Rawalpindi from October 30, 2020 to April 30, 2021. By using 100% confidence level, 7% margin of error and 34.8% STEMI patients with high thrombus burden, the sample size of 178 patients was calculated which was rounded off to 180 patients.[15]

After taking approval from hospital's ethical committee, all STEMI patients undergoing P-PCI with ages ranging from 18-80 years who presented within 24 hours of symptoms were included using a nonprobability convenient sampling technique. Informed written consent of the patients was obtained for this study. The exclusion criteria were patients with chronic stable or unstable angina, reinfarction or past history of CAD, P-PCI or coronary artery bypass grafting (CABG). All the patients were given aspirin, clopidogrel and unfractionated heparin. Primary PCI with stenting was done using the standard radial approach. The patients received tirofiban (glycoprotein IIb/IIIa receptor inhibitor) based on operator judgement. After ante-grade flow was achieved, the thrombolysis in myocardial infarction (TIMI) scale was applied in all patients to determine intracoronary thrombus burden. The TIMI thrombus grade 0-2 showed low thrombus burden and TIMI grade 3-4 indicated high thrombus burden. Before giving aspirin and clopidogrel, the blood samples of patients were taken in standard ethylenediaminetetraacetic acid (EDTA) containing vacutainers. The reference range for monocyte count was taken as 285-500×109/L. All the data including patient demographic profile & risk factors were collected through a pre-designed proforma.

Statistical Analysis

The data was analyzed through the Statistical Package for the Social Sciences (SPSS) version 25. Quantitative variables such as age and monocyte count were presented as mean and standard deviation (SD). Qualitative variables such as gender, hypertension, obesity, diabetes mellitus, tobacco consumption and thrombus burden were presented as frequency and percentage. Mean monocyte count was compared between high and low thrombus burden by using an independent sample t-test.

Data was stratified for gender, age, diabetes mellitus, hypertension, obesity and tobacco consumption by applying a Pearson Chi-Square test. The significant p-value was ≤0.05.

Results

In this study, 111(61.7%) patients were males and 69 (38.3%) were females. Patients had a mean age of 61.11 ±7.11 years. The patients of <60 years were 76 (42.2%) and ≥60 years were 104(57.8%). The mean TIMI score was 3.28±1.00. Hypertension was present in 108 (60%) patients,103(57.2%) patients had obesity, 69(38.3%) patients had diabetes mellitus while 74(41.1%) patients had the history of tobacco consumption. The frequency of thrombus burden was high in 71(39.4%) patients and low in 109(60.6%) patients. These results are shown in Table 1.

The monocyte count showed a significant difference

Table 1: *Various Parameters of the Study Participants*

Parameter	Frequency (Percentage)
Gender	
Male	111(61.7%)
Female	69(38.3%)
Age Groups	
< 60 years	76(42.2%)
>60 years	104(57.8%)
Hypertension	
Hypertensive	108(60%)
Nonhypertensive	72(40%)
Obesity	
Obese	103(57.2%)
Nonobese	77(42.8%)
Diabetes mellitus	
Diabetic	69(38.3%)
Nondiabetic	111(61.7%)
Smoking	
Smoker	74(41.1%)
Nonsmoker	106(58.9%)
Thrombus burden	
High	71(39.4%)
Low	109(60.6%)

in high thrombus versus low thrombus burden. In low thrombus burden patients, the mean monocyte count was 0.49±0.50 and in high thrombus burden patients, the mean monocyte count was 0.64±0.48. (Table 2)

The results of stratification of thrombus burden with age

Table 2: *Monocyte Count in High Thrombus vs Low Thrombus Burden Patients*

	Thrombus Burden	n	Mean	SD	P-Value
Monocyte count	**Low**	109(60.6%)	0.49	0.50	***0.047****
	High	71(39.4%)	0.64	0.48	

*Statistically significant

group showed significant p-value and with others showed non-significant p-value. These results are tabulated in Table 3.

Table 3: *Stratification of Thrombus Burden with Various Study Parameters*

Parameter	Thrombus Burden		Total	Chi-square statistics	p-value
	Low	High			
Gender					
Male	70(63.1%)	41(36.9%)	111(61.7%)	0.7622	0.382
Female	39(56.5%)	30(43.5%)	69(38.3%)		
Total	109(60.6%)	71(39.4%)	180(100%)		
Age groups					
<60 years	28(36.8%)	48(63.2%)	76(42.2%)	30.967	**0.00001***
>60 years	81(77.9%)	23(22.1%)	104(57.8%)		
Total	109(60.6%)	71(39.4%)	180(100%)		
Hypertension					
Hypertensive	67(62%)	41(38%)	108(60%)	0.248	0.618
Nonhyper-tensive	42(58.3%)	30(41.7%)	72(40%)		
Total	109(60.6%)	71(39.4%)	180(100%)		
Obesity					
Obese	65(63.1%)	38(36.9%)	103(57.2%)	0.656	0.417
Nonobese	44(57.1%)	33(42.9%)	77(42.8%)		
Total	109(60.6%)	71(39.4%)	180(100%)		
Diabetes mellitus					
Diabetic	42(60.9%)	27(39.1%)	69(38.3%)	0.0046	0.945
Non-diabetic	67(60.4%)	44(39.6%)	111(61.7%)		
Total	109(60.6%)	71(39.4%)	180(100%)		
Smoking					
Smoker	48(64.9%)	26(35.1%)	74(41.1%)	0.977	0.322
Non-smoker	61(57.5%)	45(42.5%)	106(58.9%)		
Total	109(60.6%)	71(39.4%)	180(100%)		

*Statistically significant

Discussion

Coronary artery thrombosis and atherosclerotic plague

rupture are the key phenomena involved in the pathogenesis of STEMI. The monocyte count significantly affects the prognosis in STEMI patients undergoing P-PCI. The monocytes, when activated, become macrophages and become deposited in the vessel wall leading to the formation of atherosclerotic plague.[16,17] The process of atherogenesis and rupture of plague involves chronic inflammation and oxidative stress. Monocytes have a key role in the inflammatory process.[18,19] Literature has reported that monocyte count is an independent predictor of high thrombus burden.[20,21] High thrombus burden is associated with higher rates of procedural complications during P-PCI, adverse outcomes and cardiovascular deaths.[22]

In our study, patients had a mean age of 61.11±7.11 years and 61.7% were males. Similarly, in a study by Wang et al., patients had an average age of 62.2 ± 13.6 years and 81% were male.15 The mean age was 62.6 + 12.8 years with the majority of male patients (76%) in a study.[20] On the other hand, the mean age of the study participants was 51.14 ± 9.02 years in a study by Soltan et al with 67.4% males.[23] The average patients' age was 40±5 years in another study.[22] Our results showed that 39.4% of the STEMI patients undergoing P-PCI had a high thrombus burden. Similar results were reported by Wang et al. with 34.8% of the STEMI patients undergoing P-PCI having high thrombus burden.[15] Other studies reported a very high frequency of high thrombus burden among patients with STEMI. In a study conducted at KRL Hospital, Islamabad, the frequency of high thrombus burden was 67.4%.24 In other studies, 56.3% and 50.3% of the STEMI patients undergoing P-PCI had high thrombus burden.[20,23] In a study by Ge et al., 54.9% of the STEMI patients had a high thrombus burden.[22]

In our study, high thrombus burden had no association with the risk factors of diabetes mellitus, hypertension, obesity and tobacco consumption but it was significantly linked to the patient's age. Another study reported no correlation between high thrombus burden and other parameters (age, gender, hypertension, diabetes mellitus, smoking and hyperlipidemia.[15] Separham found no significant association of monocyte count with age, gender and diabetes mellitus.[21] According to Soltan et al., gender and diabetes mellitus were significantly linked to high thrombus burden.[23] High thrombus burden was significantly associated with hypertension, according to another study.[22] In contrast, in another study, 100% of patients with high thrombus burden were hypertensive & smokers, 98.3% were diabetic and 60% were obese. There was a significant association of these risk factors with high thrombus burden.[24]

Our results showed a significant difference in the mean monocyte count in high thrombus (0.64+0.48) versus low thrombus burden (0.49+0.50) patients. Similarly, the mean monocyte count was 70.27 ± 3.24 in high thrombus burden and 61.89 ± 5.71 in low thrombus burden patients with a p-value of 0.00.21.24 Wang et al. reported a statistically higher monocyte count in high thrombus burden patients (0.61 ± 0.29×109/L) than in low thrombus burden patients (0.53 ± 0.24×109/L).[15] In a study by Arsoy et al., monocyte count to high-density lipoprotein cholesterol ratio (MHR) was measured, with a greater ratio in the high thrombus group (25.4) than the low thrombus group (16) with a significant p-value.[20] Similar results were seen in another study in which MHR was .052 ± 0.019 and 0.014 ± 0.008 in high thrombus and low thrombus burden groups, respectively., (p-value < 0.001).23 The mean monocyte count was 0.81 ± 0.33 and 0.59 ± 0.28 in high and low thrombus burden patients, respectively with statistically significant results in a study.[21]

Conclusion

The monocyte count is a reliable, inexpensive and simple-to-measure predictor of high thrombus burden in coronary arteries in STEMI patients undergoing primary PCI.

Limitations of the Study

- Our study recruited patients from a single tertiary care hospital. A large multicenter study should be conducted in the future.
- The patients with high thrombus burden were neither followed up for adverse clinical outcomes nor monocyte counts were measured after P-PCI.

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Authors Contribution

SR: Conceptualization of Project
MF: Data Collection
AS: Literature Search
KNS: Statistical Analysis
MM: Drafting, Revision
MM: Writing of Manuscript

Efficacy of Intraarticular Knee Injection of PRP (Platelet Rich Plasma) vs Steroid (Triamcinolone Acetate) for the Treatment of Primary Knee Osteoarthritis Grade I & II

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Abstract

Objective: To assess the effectiveness of PRP (Platelet Rich Plasma), and to compare with Triamcinolone 40mg (Steroid) on functional activity, stiffness and pain in Grade I & II Knee OA.

Method: A comparative cross sectional study was conducted at outdoor departments of Advanced Pain Relief Center, Lifeline Hospital Lahore (Pakistan) from January 2022 to December 2022. The present study included a total of 235 participants, out of whom 190 individuals were deemed eligible for inclusion based on predetermined criteria. The remaining 45 participants were excluded from the study due to non-adherence to eligibility criteria and lack of approval from institutional ethical committee. Out of a total of 190 subjects enrolled in the study, 64 (33%) were characterized as male while 126 (67%) were classified as female. The participants' mean age was 53.5 ± 6.4 years. Alternative patients were treated with intra-articular injection of either triamcinolone 40mg or PRP. Patients randomized in Steroid group (n=95) were gives intraarticular 40mg Triamcinolone acetate (1ml) along with 2ml of Local anaesthetic Lignocaine 1%, whereas patients randomized in PRP group (n=95) were injected 5ml PRP. "The Western Ontario and McMaster Universities Arthritis Index" (WOMAC) Scale was used for functional disability and pain before and after the therapy for the targeted knee joint at the baseline 1 week, 5 weeks, 8 weeks and 20 weeks follow-ups. Visual Analogue Scale (VAS) scores were also recorded for pain. Data analysis was done by using SPSS version 20.

Results: There wasn't any serious adverse effect observed during the study and follow-ups. 25 WOMAC functional activity scale showed statistically significant improvement with Intraarticular knee injection of PRP compared to steroids (40.64 ± 1.87 vs. 27.17 ± 6.01) (p = 0.000). WOMAC pain scale results also demonstrated that intraarticular knee injection of PRP was more effective in reducing knee pain than steroids (p = 0.000) at 20 weeks follow-up.

Conclusion: On the basis of the results of our study, we concluded that platelet rich plasma is more effective than intra-articular steroids in terms of improvement in functional activity and reduction of pain in patients with Grade I & II knee osteoarthritis. Both PRP and steroid intraarticular injections are safe.

Keywords: Platelet rich plasma; Osteoarthritis, Chronic; Pain; Visual Analogue Scale; WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

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Introduction

Knee osteoarthritis is a degenerative condition that involves the gradual deterioration of bone tissue and articular cartilages. The assessment of the progression of knee osteoarthritis degeneration is commonly accomplished through the implementation of the Kellgren-Lawrence Scale, which was originally devised by Sir Kellgren and Sir Lawrence in the latter part of 1957. In KL Scale radiographs of knee joint in AP standing view

are obtained and interpreted to not only diagnose Knee OA but also staging of degeneration. Knee OA is common disorder, which is also known as aging degenerative joint disorder, mostly observed in more than 60 years of age, and approximately 10% adult people > 65 years of age suffer from this it.[1]

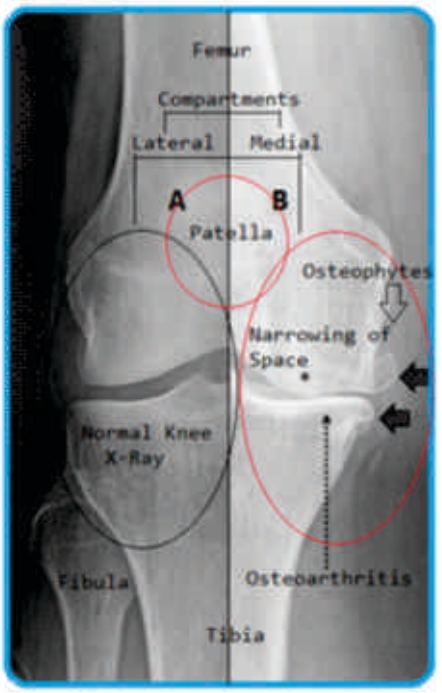

Fig. 1.1 *X-Ray Knee AP View (Standing) Normal vs Osteoarthritis*

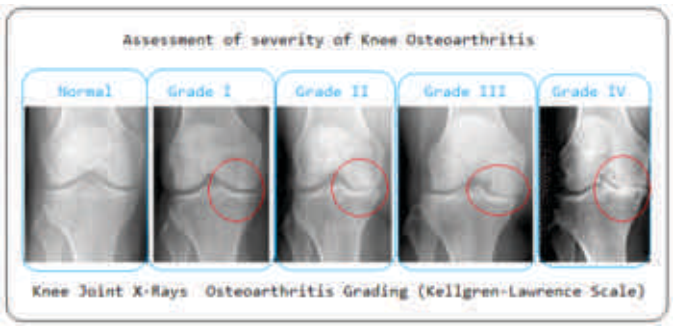

Fig. 1.2 *Osteoarthritis grading by Kellgren-Lawrance Scale*

The disease is more common in elderly women than in elderly males. World Health Organization estimates that more than 150 million of people globally are suffering from knee OA.[2] More than 30% of the population may have moderate to severe scores on WOMAC.[3] The statistics from Netherlands show that cost of this degenerative disease annually is more than 540 billion euros. In the earlier days, OA disease was considered solely due to deterioration of the synovium and the cartilage of the synovial joints.[4] but new research has shown that OA is not only limited to the synovium and cartilage of the joints, but is also responsible for the destruction of the surrounding ligaments and even the subchondral bones.

Steroids have been the mainstay of treatment of knee OA. Their effects have been thought to be due to their anti-inflammatory and analgesic effects. Traditionally, long acting steroids, e.g. triamcinolone or methyl prednisolone are injected in the synovial cavity of the joint. The use of PRP for this purpose has been suggested by many authors and is an emerging alternative regenerative therapy that outweigh steroids in efficacy and safety. Many prospective, randomized, controlled trials have substantiated the use of PRP as a therapeutic agent in Rheumatology, Pain Management, Sports Medicine, Orthopedics and Regenerative Medicine. It has been suggested that Platelet rich Plasma Therapy should be considered as therapeutic agent in the primary knee osteoarthritis of Grade I & II only, not just because of its promising therapeutic outcomes, but better safety profile as well[4], yet Total Knee Replacement (TKR) is still the mainstay treatment for knee OA of advanced stages. We conducted this randomized experimental trial to compare the effectiveness of PRP vs steroid (triamcinolone) on functional activity and the pain in patients with chronic primary OA of knee joints, as measured by using WOMAC Scale for functional disability and pain and (VAS) Visual Analogue Scale for pain assessment.

Material and Methods

Total number of patients selected for this prospective study was 235, of which 45 dropped and 190 meting inclusion criteria finally enrolled, randomized trial, reporting to the OPD of Advanced Pain Relief Center, Lifeline Hospital, Lahore, from January 2022 to December 2022. Demographic variables like Gender, Age, Ethnicity, BMI and radiologically diagnosed cases of knee OA were collected. The patients suffering from non-traumatic chronic pain in one or both knee for at least one year, radiologically diagnosed to have grade I & II knee OA (1-4 Kellgren–Lawrence scale) were enrolled under convenient sampling, whereas Grade III & IV were excluded from the study. Patient not responding to conservative and pharmacological management were enrolled in the study. Even number patients reporting for the treatment of primary knee OA were injected with PRP into intraarticular knee joint, isolated and extracted by the PRP method using FDA Registered

Dr's PRP USA Kits and Compatible Dr's USA Centrifuge. Mean thrombocyte count used was 2,209,000/µl, ±901,000/µl. On the other hand, odd number patients were injected with the steroid (triamcinolone 40 mg). Patients were evaluated for pain clinically using VAS, and by WOMAC for functional activity, before intra-articular injections of the PRP or steroids, and at 1 week, 5 weeks, 8 weeks and 20 weeks follow-ups and changes in scoring were recorded. The results were statistically analyzed and compared.

Differential Centrifugation is the process through which PRP is prepared. In the present method, the acceleration force is calibrated to segregate distinct cellular elements on the foundation of their corresponding specific gravities. There are various methods of platelet rich plasma preparation of which "PRP Method" and "Buffy-coat Method" are commonly used. However, we used PRP method. In this RBCs are separated by an initial centrifugation, then Platelets concentrate, suspended in final plasma volume are obtained followed by a second centrifugation. A double centrifugation PRP method is described as flowchart in Fig. 1.5. 20 ml of autologous whole blood (WB) is initially collected in anticoagulant containing sterile tubes through venipuncture. The first step is to spin Whole Blood (3,400 RPM × 4min) containing sterile tube at constant acceleration which separates Red Blood Cells (RBCs) from the remaining Whole Blood volume. Subsequent to the initial phase, the entirety of the Blood is divided into three distinct strata: Layer I, also known as the upper layer, predominantly comprises platelets and White Blood Cells (WBCs). The layer II, which is intermediate in thickness, is commonly referred to as the "Buffy Coat" and is abundant in white blood cells. Layer III, the lowest layer, predominantly comprises red blood cells (RBCs). After this step Layer I (Upper Layer) and Layer II (Buffy Coat) are transferred into an empty sterile tube for Second spin (3,500 RPM × 2 min) to produce pure Platelet Rich Plasma (P-PRP). The entire second layer (Buffy Coat) and few RBCs can be transferred for the production of Leucocyte Rich PRP (L-PRP). Next, a second centrifugation step is conducted to facilitate the creation of malleable aggregates of erythrocytes and platelets that are amenable to settling at the base of the tube. After this procedure, the upper segment within the tube is drawn out via a sterile syringe containing an 18G needle and subsequently discarded, as this portion primarily consists of Platelet Poor Plasma (PPP). The final step remaining lower 1/3rd (5 ml of plasma) is homogenized with Pallet to create the pure PRP (Platelet-Rich Plasma). Before intraarticular knee injection this pure PRP is activated through Photo-Bio-Modulation process. The statistical analysis was conducted utilizing SPSS Version 20.0. Categorical variables, such as gender, medical history, and adverse events, are typically reported in frequency and percentage form. The Chi-Square Test was utilized to discern the presence of a relationship between categorical variables within two distinct groups. In accordance with conventional statistical practices, a significance level of $p \leq 0.05$ was adopted as the threshold for determining statistical significance. The WOMAC pain scale assessment outcomes were recorded both prior to and subsequent to the administration of platelet-rich plasma (PRP) and steroid injection. Follow-up evaluations were carried out at 1, 5, 8, and 20 weeks post-treatment. The present study has revealed that the outcome measures of Platelet-Rich Plasma (PRP) treatment demonstrated nominal differences that did not surpass the levels of statistical significance ($p<0.05$). The statistical comparison revealed a p value of 0.00, indicating that PRP therapy is significantly more efficacious in mitigating knee pain than the administration of steroid treatment. Steroid intra-articular injections provided pain relief and functional improvement up to 8 weeks whereas PRP up to 20 weeks. It is also noted that PRP not only improved function but also joint space at 20 weeks.

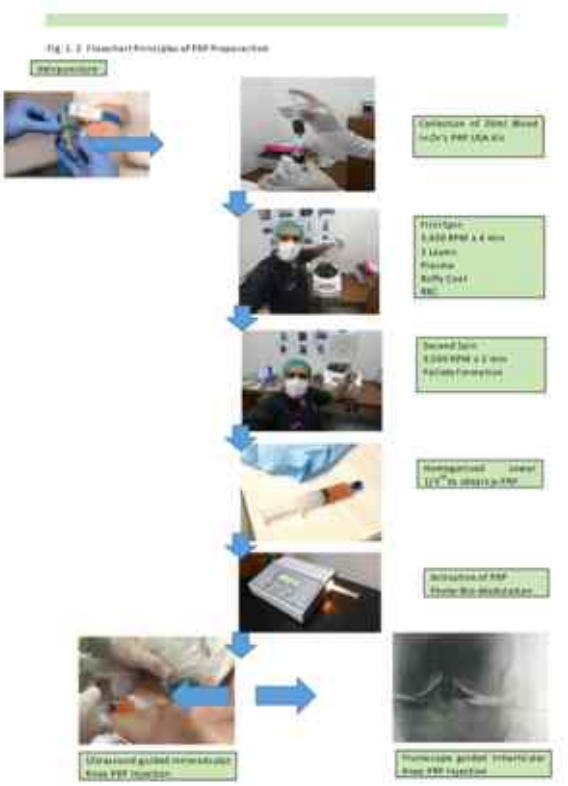

Table 1: *Comparison of different parameters before and after PRP and steroid injections*

Parameters	Differences noted in PRP Group		Differences noted in Steroid Group	
	Mean± S.D	p-value	Mean ± S.D	p-value
WOMAC Functional Activity Scale	40.64 ± 1.87	0.000	27.17 ± 6.01	0.071
VAS Score	6.38 ± 0.99	0.000	3.21 ± 0.87	0.086
WOMAC Pain Scale	8.29 ± 1.69	0.000	4.39 ± 1.63	0.061

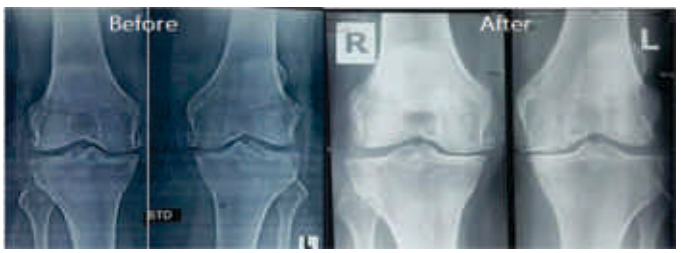

Fig.1.3 *Before & after Knee X-rays showing improvement at 20 weeks after PRP*

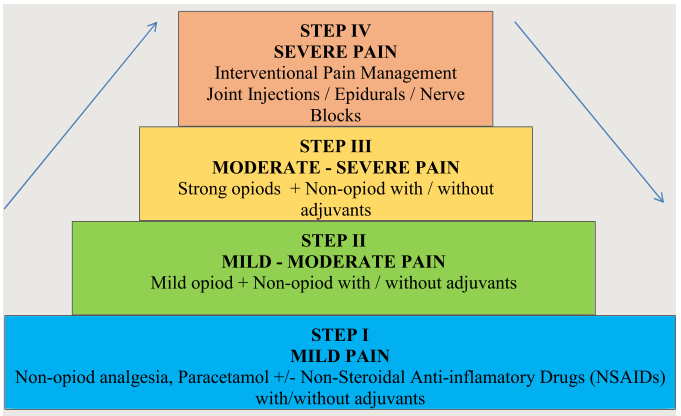

Fig. 1.4 *Modified WHO Analgesic Ladder (WHO 1986)*

Disscussion

Knee osteoarthritis (OA) is characterized by a pervasive degenerative process affecting the joint bone and cartilage, ultimately leading to the progressive decline of the joint and the adjacent structures. In primary osteoarthritis (OA), the joint that is most significantly impacted is the knee joint, as it is responsible for supporting the weight of the body. Female population is affected more than Males especially postmenopausal females. Risk factors includes but not limited to Age, Gender, Overuse of joint, obesity, calcium & Vitamin D deficiency, trauma and familial history. The primary objective of knee osteoarthritis treatment is to mitigate pain and stiffness, while simultaneously improving functional capabilities for day-to-day activities. There are many pharmacological (NSAIDS, Calcium & Vitamin D supplements, Glucosamine, Chondroitin) and nonpharmacological adjuvants (Acupuncture, Physiotherapy, Therapeutic Exercises) prescribed to manage primary knee OA however mainstay is to advised lifestyle modifications and strengthening of quadriceps and hamstring muscles to prevent further damage to joint. As per WHO analgesic ladder treatment should always start with conservative non-surgical approach (Step I and Step II) as described in the fig. 1.4. However, if conservative treatment fails then intervention should be considered. In the grade I & II primary knee OA, the utilization of plasma rich in growth factors, which contains a protein component, has been observed to yield favorable outcomes in augmenting functional capacities while mitigating painful sensations and musculoskeletal rigidity.[6] Platelet-rich plasma (PRP) has been employed for over two decades in various orthopedic ailments, with a primary focus on knee osteoarthritis (OA).[8] The present investigation noted that platelet-rich plasma (PRP) displays greater significance than steroids, not only in alleviating pain and stiffness, but also in functional restoration of the knee joint by initiating regeneration process of cartilage, hence improving knee joint space and enhancement was quantified utilizing the WOMAC scale across three domains, namely, Pain, Stiffness, and Functional activity. The results of the study indicate that a considerable percentage of patients, exceeding 80%, exhibited notable improvements in pain, stiffness and functional activities. Pain was also measured by the visual analogue scale and it was observed during the study that there was great improvement after intra-articular knee joint PRP injection. In literature review we came to find that there are researches which supported the same results as our study of which some are described below; In 2008, Sánchez et al. conducted a comparative study involving 50 patients who received platelet-rich plasma (PRP) therapy and an equal number of patients treated with hyaluronic acid injection. In the conclusive findings, it was observed that the outcomes of PRP injections were deemed more substantial in comparison to the application of hyaluronic acid within the context of pain management and promoting functional activities.[8]

Wang-Saegusa et al. conducted an additional study in 2011, which also showed improvement in WOMAC, VAS and SF-36in after intraarticular knee PRP injections in 260 patients suffering from grade I primary knee osteoarthritis.[9] Likewise, Kon et al., 2010 worked in 92 patients[10], Chang et al. (2014) resulted in improvement in primary knee osteoarthritis after administration of intraarticular knee PRP to the hyaluronic acid[11]. Sampson and colleagues conducted a study on the utilization of platelet-rich plasma (PRP) injections for the treatment of grade one knee osteoarthritis (OA) in a cohort of fourteen patients. Measurements were obtained prior to administering the platelet-rich plasma (PRP) injection, and subsequently, a three-month interval was observed. It was duly noted that the patient experienced significant relief from pain and stiffness following the treatment. The thickness of the cartilage at various levels was assessed by ultrasound, and it was observed that thirteen out of fourteen patients exhibited a significant increase in cartilage thickness. The findings of the study suggest that the administration of PRP injections can provide relief from both pain and stiffness, while also facilitating the regeneration and augmentation of cartilage thickness within the relevant joint.[12] The current investigation provides evidence for the effectiveness of Platelet-Rich Plasma (PRP) in individuals aged 40-60 years diagnosed with grade I & II primary knee Osteoarthritis (OA). It has been observed that this intervention not only facilitates pain and stiffness reduction but also effectively restores functional performance.

Conclusion

The observed findings indicate that platelet rich plasma (PRP) is highly efficacious and convenient for administration in individuals diagnosed with grade I and II knee osteoarthritis. The application of this intervention serves to alleviate pain, reduce stiffness, and improve functional activities among patients.

Conflict of Interest	*None*
Source of Funding	*None*

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Authors Contribution

SRD: Conceptualization of Project
NT: Data Collection
AS: Literature Search
SN: Statistical Analysis
WY: Drafting, Revision
WAC: Writing of Manuscript

Incidence of Acute Kidney Injury after Stroke and Its Association with 30-day Mortality of Stroke Patients

Amber Shahzadi,[1] Saima Ambreen,[2] Aimen Malik,[3] Mubariz Ahmed[4], Sidra Jahangir,[5] Basil Usman[6]

Abstract

Objective: To investigate the incidence of AKI in stroke patients and its association with 30-day mortality of stroke patients.

Method: This descriptive study was conducted in Medical Unit-I, Holy Family Hospital from June 2020 to January 2021. 130 patients with CT-confirmed stroke (both ischemic and hemorrhagic) with symptoms ranging from 1-24 hours were included in the study using consecutive (non-probability) sampling, after informed consent from the attendants. Patients with a history of recurrent stroke, renal dysfunction before stroke (urea > 52mg/dl and creatinine > 1.2mg/dl, eGFR < 90 ml/min, proteinuria, or patients on dialysis as per medical record), uncontrolled hypertension (BP ≥ 180/110 mmHg), alcohol use, intravenous drug abuse and diabetes (BSR > 200 mg/dl) were excluded from the study. Patients' baseline serum creatinine levels were recorded and were noted again after 72 hours. A > 0.3 mg/dl increase from the baseline was defined as acute kidney injury. Mortality was recorded in patients who died within 30 days of stroke.

Results: The mean age of the patients was 55.48 ± 10.85 years. 81 patients (62.3%) were male and 49 (37.7%) were female. 25 (19.2%) patients had acute kidney injury. 25 (19.2%) patients (amongst both with and without acute kidney injury) died within 30 days. There was a significant association between acute kidney injury and 30-day mortality of the stroke patients (p-value<0.001). This association was significant in all age groups, both genders, regardless of present or absent history of smoking and regardless of duration of symptoms prior to arrival (p value <0.001).

Conclusion: Acute kidney injury affects a proportion of patients of stroke. There is a significant association between AKI and 30-day mortality after stroke, suggesting there might be a link between them.

Keywords: stroke, mortality, acute kidney injury.

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Introduction

Globally, stroke is the second most common cause of death. It is also a major cause of neurological disability with great human and economic costs.[1] Epidemiological studies show that the incidence of stroke varies greatly between different populations and regions and has been on the decline in recent decades in high-income countries due to advances in prevention, early recognition and management of risk factors. Thus, currently low-and middle- income countries share the greatest burden of the disease.[2] In Pakistan, the estimated annual incidence of stroke is 250/100,000.[3]

Complications associated with stroke include post stroke depression (PSD), anxiety disorders, post-stroke fatigue, new onset dementia, falls and subsequent injuries and chronic pain among others.[4] One of the complications, which is sometimes under-recognized is Acute Kidney Injury (AKI).[5] Acute kidney injury (AKI), defined as

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a measurable increase in the serum creatinine (Cr) concentration (usually relative increase of 50% or absolute increase by 44–88 µmol/L [0.5–1.0 mg/dL]).[6] Many studies have shown that AKI is a common complication after stroke.[5,7-11] Diabetes, ischemic heart disease, history of heart failure and greater age have all been associated with a higher risk of developing AKI after stroke.[9] Studies have also found association of AKI after stroke with increased mortality.[8,12]

AKI after stroke may develop due to physiological changes e.g., hormone levels, blood pressure and physical disability, and may also be due to the treatments provided to stroke patients[13]. Activation of sympathetic nervous system, HPA axis and RAAS induced by stroke may alter hormone and neurotransmitter release, which in turn may mediate kidney dysfunction.[14] In resource-limited countries like Pakistan, patients with AKI after stroke have a very poor prognosis. Knowledge about this complication and early detection can be helpful in preventing poorer outcomes and can also help in formulating preventative and management protocols. Local data in this regard is scarce; therefore we decided to conduct this study. The objective of this study is to determine the incidence of acute kidney injury after stroke and to find the association of AKI after stroke with 30-day mortality of the patients.

Materials and Methods

This descriptive study was conducted in Medical Unit-I, Holy Family Hospital from June 2020 to January 2021, after ethical approval from Institutional Research Forum of Rawalpindi Medical University (Reference number 11/MU-1/HFH/RWP). 130 Male and female patients aged 35 to 85 with stroke were chosen using consecutive (non-probability) sampling. Stroke was diagnosed based on clinical features and the diagnosis was supported by positive CT scan findings i.e., presence of hypodense area on CT scan in case of ischemic stroke and hyperdense area in case of hemorrhagic stroke. Patients who had a history of recurrent stroke (on medical record), renal dysfunction before stroke (urea>52mg/dl & creatinine >1.2mg/dl, eGFR <90ml/min, proteinuria, or patients on dialysis as per medical record), uncontrolled hypertension (BP ≥ 180/110mmHg), alcohol use, intravenous drug abuse and diabetes (BSR>200mg/dl) were excluded from the study. Informed consent was obtained from the attendants. Demographic information including name, age, gender, duration of symptoms and history smoking were noted.

Blood samples were obtained through a disposable syringe under aseptic measures and were sent to the hospital laboratory for routine tests. Serum creatinine levels which were subsequently recorded. The patients were admitted and managed. After 72 hours, blood samples were again sent to the hospital laboratory for determining new creatinine levels. An increase of >0.3 mg/dl from the baseline was considered as acute kidney injury. If the patient died within his or her hospital stay, then in-hospital mortality was recorded. Otherwise, they were discharged and followed-up on an out-patient basis for 30 days. If the patient died within 30 days, then mortality was noted. The data was analyzed using SPSS version 20. Quantitative variables like age, duration of symptoms and creatinine levels were presented as mean and standard deviation. Qualitative variables like gender, history of smoking, acute kidney injury and mortality were presented as frequency and percentage. The Chi-square test was applied to compare the mortality between patients with acute kidney injury and those without. P-value ≤ 0.05 was considered as significant. Data was stratified for age, gender, duration of symptoms and history of smoking. Post-stratification, Chi-square test was applied to compare mortality in patients with or without acute kidney injury for each stratum. P-value ≤ 0.05 was considered as significant.

Results

The mean age of the patients was 55.48 ± 10.85 years, with the minimum being 35 years and maximum being 82 years. Out of 130, 81(62.3%) of the patients were male and 49 (37.7%) were female. 37 (28.5%) had a history of smoking and 93 (71.5%) had none. The mean duration of symptoms prior to hospital arrival was 13.51 ± 5.04 hours. The minimum duration of symptoms was 1 hour, and maximum was 24 hours. The mean creatinine level at baseline was 0.55 ± 0.26 mg/dL and after 72 hours it was 0.92 ± 0.71 mg/dL. A total of 25 (19.2%) patients out of 130 had acute kidney injury. A total of 25 (19.2%) patients with stroke died within 30 days. Among them 16 were male and 9 were female. There was a significant association between acute kidney injury in stroke patients and 30-day mortality (p-value <0.001) (Table-1). This significant association was reflected in all age groups i.e., 35-50 years, 51-65 years and more than 65 years (p-values: <0.001, <0.001 and <0.001) (Table-2). In addition, the significant association between acute kidney injury after stroke and mortality was present among both males and females (p-values:

<0.001 and <0.001). In 16 males with 30-day mortality, 15 (93.75%) had acute kidney injury. In 9 females with 30-day mortality, all had acute kidney injury. Mortality could have been caused by other factors such as degree of disability, aspiration pneumonia, urinary tract infections or seizures but we did not inquire about these variables. The association between acute kidney injury and mortality was significant regardless of presence or absence of history of smoking i.e., it was significant in both groups (table 3) (p-value<0.001). A total of 64 patients presented with symptom duration of 1-12 hours and 66 patients presented with symptom duration of 13-24 hours. 7 patients had 30-day mortality in the 1-12 hours group, out of which 6 (85.7%) had acute kidney injury. In the 13-24 hours group, 18 patients had 30-day mortality, and all had acute kidney injury. In both the groups there was significant association between acute kidney injury and mortality (p value <0.001).

Table 1: *Frequency of mortality in patients with and without Acute Kidney Injury.*

Mortality	Kidney Injury		Total
	Yes	No	
Yes	24(96%)	1(1%)	**25**
No	1(4%)	104(99%)	**105**
Total	**25**	**105**	**130**
p-value		**<0.001**	

Table 2: *Frequency of mortality in patients with and without Acute Kidney Injury stratified for Age.*

		Kidney Injury		p-value
		Yes	No	
35-50	**Yes**	3(75%)	0(0%)	**<0.001**
	No	1(25%)	47(100%)	
51-65	**Yes**	11(100%)	1(2.2%)	**<0.001**
	No	0(0%)	44(97.8)	
>65	**Yes**	10(100%)	0(0%)	**<0.001**
	No	0(0%)	13(100%)	

Table 3: *Frequency of mortality in patients with and without Acute Kidney Injury stratified for History of Smoking.*

Smoking	Mortality	Kidney Injury		p-value
		Yes	No	
Yes	Yes	13(100%)	1(4.2%)	**<0.001**
	No	0(0%)	23(95.8%)	
No	Yes	11(91.7%)	0(0%)	**<0.001**
	No	1(8.3%)	81(100%)	

Discussion

Our results showed that 19.2 % of the patients had acute kidney injury after stroke and there was a significant association between acute kidney injury in stroke patients and mortality within 30 days. Compared to this, Tsagalis et al reported a 14.5% incidence of AKI that was associated with an increased 30-day mortality.[5] A meta-analysis study conducted in the USA taking into account 12 studies containing more than 5 million stroke patients, found that AKI prevalence in stroke patients was 11.6% (95% CI: 10.6-12.7%).1[5] Another meta-analysis described an overall incidence of AKI to be 12%.[16] The study also concluded that AKI after stroke was associated with higher 1-month mortality, a finding similar to ours. One of the main causes for the different reported rates might be the various different diagnostic criteria used in labelling AKI. Therefore, in our opinion, a single standard for determining AKI should be applied in evaluating the frequency of AKI following stroke.

According to Lima et al 2019, the presence of acute kidney injury is an important complication after ischemic stroke and a predictor of mortality within 30 days when severity of stroke is not considered.[7] Another study demonstrated that AKI frequently follows stroke and has association with greater hospital mortality.[8] Covic et al., found the 30-day mortality rate following AKI after stroke to be as high as 17.2%.[9] Our results that AKI is significantly associated with 30-day mortality in stroke patients support all this previous literature.

Several studies reported that older patients with AKI associated with stroke are a predictor of higher 30-day mortality.[5,17] Older people might be more likely to have a worse prognosis after a stroke. This may be due to previous disease and a higher severity of stroke compared to the young[18]. In contrast, our results showed significant association between acute kidney injury and mortality among all the age groups i.e., 35-50 years, 51-65 and above 65 years. Perhaps a larger sample size could have better elucidated this relationship.

It is important to note that our results don't address whether there is causal association between AKI and mortality even though we adjusted for a few possible risk factors, such as history of smoking and the time passed since symptoms started prior to arrival. Factors such as hemodynamic abnormalities, dehydration due to poor nutritional intake, and myocardial infarction could all cause AKI and lead to higher mortality. Evidence suggests that there is increased insulin resistance in patients with AKI, which potentially might cause hyperglycemia.[19] Hyperglycemia can worsen outcomes in both ischemic and hemorrhagic stroke.[20,21] AKI can also cause other physiologic derangements e.g., greater

inflammation and oxidative stress, which might hypothetically worsen outcomes in patients suffering from stroke.[22,23] Our study had certain limitations. Firstly, we did not consider stroke severity (e.g., that categorized by NIHSS score) while determining the incidence of AKI and its effect on 30-day mortality. Secondly, we did not conduct stratification by type of stroke i.e., ischemic or hemorrhagic. In addition, there was no stratification by types of ischemic stroke. Thirdly, we did not explore the impact of period of hospital stay and in-hospital abnormalities such infections etc., on outcomes. We propose further studies on this topic, preferably with a larger sample size, so robust data relevant to our part of the world becomes available which would further shed light on incidence of AKI in stroke patients and its association with 30-day mortality. This could then be used as a basis to formulate better preventative and management protocols especially relevant to resource-limited settings.

Conclusion

Acute kidney injury is a complication that affects a proportion of patients of stroke. There is a significant association between AKI and 30-day mortality after stroke. This association is significant in all age groups after 35 and in both males and females. It is also significant regardless of a positive history of smoking and regardless of duration of stroke symptoms prior to arrival.

Conflict of Interest: *None*

Funding Source: *None*

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Authors Contribution

AS: Conceptualization of Project
AS, SA, AM: Data Collection
AS, SA, SJ: Literature Search
AM, MA: Statistical Analysis
AS, SA, AM, SJ: Drafting, Revision
AM, MA, BU: Writing of Manuscript

Reasons of TB Treatment Non Compliance

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Abstract

Objective: To assess the prevalence and reasons of non compliance to treatment of tuberculosis among the patients of Sharif medical city Hospital Lahore.

Method: 150 patients of tuberculosis were taken as a sample based upon non-probability convenient sampling. The data was collected by the investigators themselves with the use of semi-structured questionnaire that was finalized after pre-testing.

Results: The data was analysed by putting into IBM statistics SPSS software. All the respondents(100%) have already heard about tuberculosis. The pooled prevalence of non compliance to TB is 44.4%.

Conclusions: Overall level of knowledge about tuberculosis and its practices among the patients of tuberculosis attending Sharif medical city hospital Lahore was found satisfactory (40%). The majority of respondents are not taking medicine because of side effects of drugs (41.3%), fear of drugs (40%), long duration of TB treatment (62.7%) and TB clinic is far from home (66.7%).

Key words: Tuberculosis, Drug resistance, Patient education, infectious disease, Respiratory infections.

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Introduction

Tuberculosis (TB) continues to be a significant global health challenge, affecting millions of people each year. Despite the availability of effective treatment options, the successful management of TB heavily relies on patients completing their prescribed treatment regimen. However, a persistent problem in TB control programs is the non-compliance of patients with their treatment plans, leading to unfavourable outcomes such as treatment failure, relapse, and the emergence of drug-resistant strains. To address this issue, it is crucial to delve into the underlying reasons for TB treatment non-compliance.

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Noncompliance to TB treatment was found to be mainly due to side effects of medicines, lack of time, and unawareness.[5] So educating the patient about various aspects of tuberculosis and some measures to decrease side effects are of utmost importance. Main risk factors for its spread include overcrowding, malnutrition, alcoholism, diabetes mellitus[1] certain medication and genetic suseptibility[2] increase the risk of TB. Multi drugs resistance TB(MDR)[3] is caused by[4] resistance of atleast two of isoniazid, rifampicin, ethambutol, pyrazinamide and XDR by resistance of 2nd line drugs like fluoroquinolones etc. Tuberculosis continues to be a worldwide pandemic, with half of all new cases reported from six asian countries. Pakistan with a population of over 230 million, ranks 5th in the estimated global TB burden list with an incidence rate of 275/100 000 and a prevalence rate of 342/100 000[6] population. It is estimated that 51% of cases are concentrated in the Province of Punjab, followed by 23% in Sindh, 15% in the North West Frontier (NWFP), and 3.59% in Baluchistan, with the remainder being distributed within the northern areas and in Azad Kashmir.

Objectives

- **Identify Sociodemographic Factors:** Investigate the influence of sociodemographic factors such as age, gender, education level, income and occupation on TB treatment non-compliance
- **Assess Healthcare Access and Utilization:** Examine the role of healthcare access and utilization in TB treatment non-compliance. Explore factors such as distance to healthcare facilities, proper counselling of patient about TB and its treatment
- **Examine Treatment Regimen Complexity:** Investigate the impact of treatment regimen complexity on non-compliance. Analyse factors such as the number of medications, frequency of dosing, duration of treatment, potential side effects and fear of drugs on non compliance to treatment.

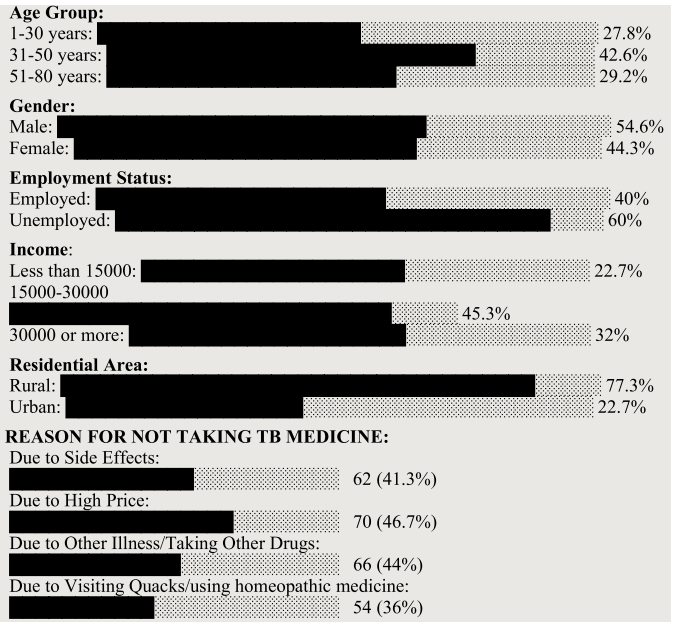
Material and Methods

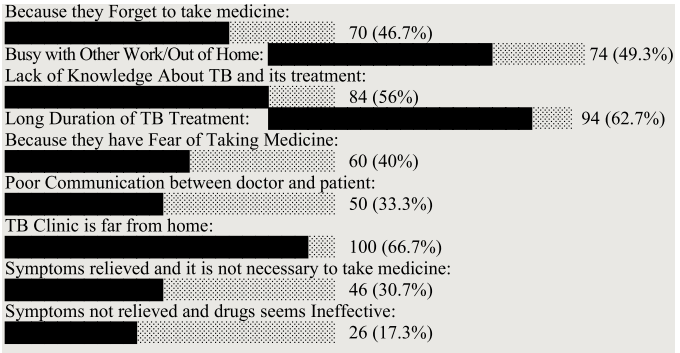
It was a cross sectional epidemiological descriptive study. The study was conducted at Sharif medical city hospital Lahore. It is a tertiary care hospital which is located in Jati Umra Raiwind road, Lahore, Punjab Pakistan. The duration of the study was one month after approval of synopsis. Sample size calculated as one hundred and fifty (150) keeping confidence level 95% calculated by using openepi.com taking reference value (9% prevalence of TB treatment non compliance[21]) The convenient, non-probability sampling technique was used to select the required number of sample size. A semi structured questionnaire was designed by researchers to obtain relevant data about knowledge and practices of non-compliance of Tuberculosis. The questionnaire was finalized after pre-testing. The patients were interviewed by the researchers themselves and corresponding responses were entered in the questionnaire. All the patients attending OPD of Sharif medical city hospital were included in the study. The patients atten-ding other hospitals and unwilling respondents were excluded from the study. The data was entered, clean, and analysed using statistical package for social sciences. Frequency tables were generated for all possible vari-ables. Means were calculated for continuous data. Formal consent and permission was taken from Sharif medical city hospital to conduct the study. Verbal consent was taken from the responders. Privacy and confidentiality of data was ensured to the responders.

Results

Result showed that patients with age group 1-30 years were 42(27.8%) and with age group 31-50 years were 64(42.6%) and with age group 51-80 years were 44 (29.2%), 82(54.6%) were male and 68(44.3%) were female, 60(40%) of TB patients were employed and 90(60%) of TB patients were unemployed, 32(22.7%) of TB patients have income less than 15000 and 68 (45.3%) of TB patients have income more than 15000 and 48(32%) of TB patients have income more than 30000, 116(77.3%) of TB patients were living in rural areas and 34(22.7%) were living in urban areas.

Result showed that 62(41.3%) of TB patients are not taking medicine due to side effect of drugs, 70(46.7%) of TB patients are not taking medicine due to high price of drugs, 66(44%) of TB patients are not taking medicine due to other illness or taking other drugs, 54(36%) of TB patients are not taking medicine due to visiting quacks, 70(46.7%) of TB patients are not taking medicine because they forget to take medicine, 74(49.3%) of TB patients are not taking medicine because they are busy in other work or out of home, 84(56%) of TB patients are not taking medicine due to lack of knowledge about TB or its treatment, 94(62.7%) of TB patients not taking medicine due to long duration of TB treatment, 60(40%) of TB patients are not taking medicine due to fear of taking medicine, 50(33.3%) of TB patients are not taking medicine due to poor communication between doctor and patient, 100(66.7%) of TB patients are not medicine because TB clinic is far from home, 46(30.7%) of TB patients are not taking medicine because they think symptoms are relieved and it is not necessary to take medicine,





26(17.3%) of TB patients are not taking medicine because they think symptoms are not alleviated and drugs seem ineffective.

Demographic Information:

Discussion

The results of the study provide insights into various factors influencing medication adherence among tuberculosis (TB) patients. The demographic analysis revealed that the majority of the patients in the study were between the ages of 31 and 50 years (42.6%), followed by those in the age group of 1-30 years (27.8%) and 51-80 years (29.2%). This distribution suggests that TB affects individuals across different age groups, emphasizing the need for adherence interventions targeted at various age segments.

Regarding gender, the study found that there were more male TB patients (54.6%) than female patients (44.3%). This disparity could be attributed to several factors, including differences in healthcare-seeking behaviour, occupational exposure, and biological factors. Further research is needed to explore the underlying causes of this gender imbalance in TB incidence and adherence. Employment status was found to have an impact on medication adherence, with 60% of TB patients being unemployed. This finding implies that socio-economic factors, such as financial constraints and access to healthcare, can influence adherence behaviour. Additionally, income levels revealed that a significant proportion of TB patients (45.3%) had an income above 15,000, indicating that financial challenges may not be the sole determinant of non-adherence. Geographical location also played a role, as the majority of TB patients (77.3%) were living in rural areas. Rural areas often face unique challenges in terms of healthcare infrastructure, access to services, and health literacy. These factors can contribute to poor medication adherence rates among rural TB patients.

Reasons for non-adherence were explored, and several prominent factors were identified. Side effects of drugs were the most commonly cited reason (41.3%), followed by the high price of drugs (46.7%) and other illness or concomitant medication use (44%). These findings highlight the importance of addressing drug side effects, affordability, and the need for comprehensive patient education to mitigate these barriers. Other reasons for non-adherence included visiting quacks (36%), forgetting to take medicine (46.7%), being busy with other work or being away from home (49.3%), lack of knowledge about TB and its treatment (56%), long duration of treatment (62.7%), fear of taking medicine (40%), poor communication between doctors and patients (33.3%), distance to the TB clinic (66.7%), and perceptions of symptom relief or ineffectiveness of drugs (30.7%). These results emphasize the multifactorial nature of non-adherence and underscore the importance of addressing patient education, healthcare infrastructure, and support systems to improve adherence rates

Conclusion

The findings of this study shed light on the factors influencing medication adherence among TB patients. Addressing these factors is crucial to improve treatment outcomes, reduce the spread of TB, and minimize the development of drug resistance. Interventions should focus on addressing drug side effects, improving affordability and accessibility of medications, enhancing patient education and health literacy, ensuring effective doctor-patient communication, and providing support for patients in rural areas. Implementing comprehensive strategies that target these factors can contribute to better adherence rates and ultimately enhance the effectiveness of TB treatment programs.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

KIA: Conceptualization of Project
S: Data Collection
MAR: Literature Search
ZE: Statistical Analysis

Stone Clearance in Patients with Upper Ureteric Stones Using Extracorporeal Shock Wave Lithotripsy Compared with Extracorporeal Shock Wave Lithotripsy Combined with Tamsulosin Therapy

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Abstract

Objective: To assess its role in stone clearance along with ESWL in patients with upper ureteric stones.

Method: This clinical trial was conducted from February 2018 to December 2021 at the Department of Urology, Services Hospital Lahore.. A total of 164 patients (82 in each group) of both sexes between the ages of 18 and 70 years with upper ureteric stone (6mm-15mm) were included in this study. These patients were randomly divided into two groups. Patients in group A received ESWL alone, while patients in group B received ESWL in combination with tamsulosin therapy. Follow-up visits with CT KUB Plain were planned 4 weeks postoperatively to assess stone clearance

Results: The mean age of patients was 44.01±10.88 years. The study included 124 (75.6%) male and 40 (24.4%) female patients. The mean size of stones was 9.59±2.72 mm. Both the groups were comparable in terms of mean age (p=0.539), mean stone size (p=0.936), age groups (p=0.507), stone size groups (p=0.817), and gender distribution (p=0.631). The stone clearance rate was significantly higher in patients treated with ESWL in combination with tasmsulosin therapy (92.7% vs. 65.9%; p=0.003) compared to ESWL alone.

Conclusion: The clearance rate was significantly higher in patients treated with ESWL in combination with tasmsulosin therapy compared to ESWL alone.

Keywords: ESWL, Tamsulosin therapy, Ureteric stones, Stone clearance

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Introduction

In the early 1980's, the advent of extracorporeal shock-wave lithotripsy (ESWL) revolutionized the treatment of ureteric stones. It has been recommended as first-line therapy for upper ureteric stones up to 20mm in size with a stone clearance rate of 60-90%.[1] A number of factors determine the success of ESWL, including stone size, shape, composition, and subsequent narrowing of the ureteric lumen, which impedes the removal of stone fragments after an ESWL session.[2] Tamsulosin is an α-blocker which is widely used in urological practice to relax the smooth muscles in prostate and bladder neck. Over the past decade, the role of tamsulosin as part of medical expulsion therapy for the treatment of patients with kidney and ureteric stones has been extensively researched with notable success.[3] A possible mechanism underlying this effect may be ureteric smooth muscle relaxation, alleviation of muscle spasms, resulting in easy and accelerated passage of stones.[4] Recently, tamsulosin has been used in a number of randomized controlled trials along with ESWL for the management of

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lower ureteric stone, and all of these studies report a significantly increased frequency of stone removal with ESWL and tamsulosin combination therapy, likely due to increased and accelerated passage of stone fragments with tamsulosin.[5] However, the results need further confirmation as there are some studies that do not support the role of tamsulosin therapy in removing ureteral stones after ESWL.[6] Taking into account the controversies in the available literature and the absence of locally published studies, the intent of this study is to replicate this trial and confirm the results. Thus, if the results of this study show a significantly increased frequency of stone clearance with the addition of tamsulosin, this study may represent a useful treatment option for future patients presenting with upper ureteric stones.

Materials & Methods

This clinical trial was conducted from February 2018 to December 2021 at the Department of Urology, Services Hospital Lahore. The sample size of 144 patients was computed with a power of 90% and a confidence level of 95%, while the expected stone clearance rate was assumed to be 79.3% in the ESWL group and 96.6% in the ESWL in combination with tamsulosin group.[7] However, for more accurate results, a larger sample of 164 patients (82 patients in each group) was adopted. The study enrolled patients of both sexes, aged between 18 and 70 years, presenting with a single upper ureteric stone between 6 and 15 mm in the largest diameter. Patients with urinary tract infection (more than 10 pus cells/HPF on complete urine examination), distal ureteric stricture, prior unsuccessful ESWL, concomitant use of alpha-adrenergic antagonists or calcium channel blockers, patients with coagulopathy (INR greater than 1.5), obesity (BMI over 30 kg/m^2) and deranged renal function tests (serum creatinine over 2 mg/dl) were excluded from the study. Upon approval by the hospital ethics committee, patients who met the inclusion criteria were admitted through the emergency department and outpatient department. All patients provided informed consent. The patients were randomly divided into two groups. Group A received ESWL, while group B received ESWL along with tamsulosin therapy. Patients in both groups received an ESWL session with an electromagnetic lithotripter at 12 to 15 KV. The stone was located with a C-arm. Patients in Group-B were also advised to take tamsulosin tablet (0.4 mg) once daily for 4 weeks. All patients were assessed for stone clearance after 4 weeks with CT KUB. Patient demographic details along with stone size, duration and healing at follow-up were noted on the predesigned proforma. The data collected were entered and analyzed in SPSS version 20. Continuous variables such as age and stone size were presented as means with standard deviation. Categorical variables such as gender and stone clearance were presented as frequencies and percentages. Stone clearance between groups was compared using the chi-square test. Data were stratified by age, sex, and stone size to account for effect modifiers. The post-stratification chi-square test was applied.

Results

In this study, the mean age was 44.01 ± 10.88 years. The mean age in group A was 44.76 ± 10.82 years, while in group B it was 43.27 ± 11.03 years in group B. Of 164 patients, 124 (75.6%) were male and 40 (24.4%) were female. The mean size of stones was 9.59±2.72 mm. Both the groups were comparable in terms of mean age (p=0.539), mean stone size (p=0.936), and age groups (p=0.507), stone size groups (p=0.817), and gender distribution (p=0.631) as elaborated in (Table-1). In this study the stone clearance was found in 54(65.9%) patients after ESWL group, while the stone clearance was found in 76(92.7%) patients in ESWL combined with tamsulosin group. The difference was statistically significant (p=0.003) as illustrated in (Table-2). The stone clearance rate in younger patients (18 to 44 years) was significantly higher in the ESWL combined with

Table 1: *Baseline characteristics of patients.*

		Group A	Group B	p-value
Age (years)		44.76±10.82	43.27±11.03	0.539
Age groups	18-44 years	40 (48.8%)	46 (56.1%)	0.507
	45-65 years	42 (51.2%)	34 (43.9%)	
Gender	Male	60 (73.2%)	64 (78.1%)	0.631
	Female	22 (26.8%)	18 (21.9%)	
Stone size (mm)		9.61±2.82	9.56±2.65	0.936
Stone size Group	6-10 mm	54 (65.9%)	52 (63.4%)	0.817
	11-15 mm	28 (34.1%)	30 (36.6%)	

Table 2: *Comparison of outcome*

	Stone Clearance		p-value
	Yes	No	
Group A	54 (65.9%)	28 (34.1%)	0.003
Group B	76 (92.7%)	6 (7.3%)	

Table 3: *Stratification of stone clearance with respect to age, gender and size of stone*

		Stone clearance in group A	Stone clearance in group B	p-value
Age (years)	18-44	26 (65.0%)	42 (91.3%)	0.034
	45-65	28 (66.7%)	34 (94.4%)	0.032
Gender	Male	41 (68.3%)	59 (92.2%)	0.034
	Female	14 (63.6%)	17 (94.4%)	0.033
Size of stones (mm)	6-10	38 (70.4%)	48 (92.3%)	0.041
	11-15	16 (57.1%)	28 (93.3%)	0.023

tamsulosin group than in the ESWL group. Similarly, it was found that the stone clearance rate was higher in male patients and in patients with smaller stones (6-10 mm) in the ESWL combined with tamsulosin than in the ESWL group.

Discussion

The main objective of treating kidney stones is to attain stone clearance with minimum possible morbidity for the patient. The advent of ESWL and continued advances in the field of urology have made it possible to treat most patients with kidney stones in a minimally invasive manner. Today, ESWL is the mainstay of treatment for kidney stones less than 2cm in size. For kidney stones, removal can be affected by many factors, comprising stone size, stone location, stone composition, kidney and ureter anatomy, and distal blockage due to edema, spasm, or stricture. The relaxation of the ureter in the stone area is considered a decisive factor in promoting the passage of the stone. Recently attention has been paid to medical expulsion treatment targeting some of the reversible factors involved in the passage of stones through the ureter. There is evidence of alpha-1 adrenergic receptors in the ureter. Therefore, the rationale for using alpha-1 adrenergic antagonist in clearing upper ureteric stones after ESWL is its ability to reduce tone of ureteric muscles and peristaltic ureteric contractions, dilating the lumen and thereby promoting stone passage through the ureter.8-10 Hence, this randomized controlled trial was conducted to assess the role of alpha-1 blockers (tamsulosin) in clearing upper ureteric stone after ESWL.

In this study, stone clearance rate was significantly higher in patients receiving ESWL therapy in combination with tamsulosin therapy than in patients receiving ESWL therapy alone (92.7% vs. 65.9%; p=0.003). The evaluation took place 4 weeks after the therapy with CT KUB. In a randomized controlled trial conducted by Bhagat and colleagues in patients with mixed ureteric and renal stones, the stone clearance was significantly higher in the patients receiving ESWL together with tamsulosin therapy than in ESWL therapy alone (96.6% vs 79.3%; p=0.04).[7] These results are consistent with our study. Similarly, Gravina et al. concluded in their study that patients treated with ESWL and tamsulosin had achieved greater clinical success after 3 months than patients treated with ESWL alone (78.5% vs 60.0%; p=0.03)[11]. A meta-analysis of 49 studies including 6436 patients also concluded that use of tamsulosin therapy not only augmented the stone clearance (80.5% vs 70.5%; p< .00001) but also shorten the time of stone expulsion.[12] Our study further suggested that smaller stones have a greater clearance rate with tamsulosin therapy. However, in the above studies, larger stones (more than 10mm) had a better stone clearance rate in the patients treated with tamsulosin compared to the controls after ESWL session. Contrary to our results, other authors have described a limited role of alpha-1 blockers (tamsulosin) after ESWL for ureteric stone clearance. A randomized prospective study conducted by Karim and his coworkers indicated that stone clearance rate was not significantly affected by the addition of tamsulosin therapy (92.5% in tamsulosin group vs. 86.9% in placebo; p=0.2), however, the tamsulosin therapy was associated with less post-ESWL pain.[13] De Nunzio et al. showed in their study that there was no statistically significant difference in stone clearance between the patients treated with tamsulosin and controls (58% vs. 47%; p=0.399) after a single cycle of ESWL.14 Similarly, Ahmed et al. also found no significant difference in the stone clearance between tamsulosin-treated patients and controls (78% vs. 69%; p=0.108) in a randomized controlled trial lasting up to 12-week study.[15] Such findings were also observed by Zaytoun et al.[16] and Falahatkar et al.[17] in their studies. This work suffers from a number of limita-

tions. First, the results are based on a single-center trial. Second, the vexing problem that patients suffer after ESWL is the excruciating pain due to stones being pushed in and out through the ureter. However, we did not measure post-treatment pain scores between groups, as this may lead to further usefulness of tamsulosin therapy in reducing post-treatment pain symptoms. However, there are some notable strengths of this study such as its prospective controlled randomized design and the inclusion of CT KUB as an evaluation tool, which allowed accurate measurement of stone clearance (outcome) in the patients.

Conclusions

Stone removal in patients receiving ESWL therapy in combination with tamsulosin therapy was significantly greater in patients with a single upper ureteric stone compared to patients treated with ESWL therapy alone. Therefore, we recommend the concomitant use of tamsulosin therapy with ESWL for the treatment of upper ureteric stones.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

MR, MSA: Conceptualization of Project
OUR, FURH: Data Collection
NAG, MR: Literature Search
NAJ: Statistical Analysis
SHC, MSA: Drafting, Revision
SHC: Writing of Manuscript

Immunohistochemical Expression of Clustered Differentiation 10 (CD10) Across Various Grade & Stage of Urinary Bladder Carcinoma

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Abstract

Objective: To assess the Clustered Differentiation 10 (CD10) expression in Urothelial carcinoma and to ascertain how its expression relates to grade and stage.

Method: Descriptive cross sectional research was carried out over a period of six months in Pathology Department on eighty five cases of bladder carcinoma from transurethral resection of bladder (TURBT) specimens diagnosed on Hematoxylin-eosin (H & E) stained sections irrespective of patient's age and gender were included in the study. These were stained for CD10 by Immunohistochemical technique.

Results: Sixty seven (78.8%) urothelial carcinomas showed positive CD10 staining while 18 cases (21.17%) demonstrated negative expression. In 67 positive cases, 42 high grade tumors had 2+ expression while 13 grade had 1+ staining . All low-grade tumors (12) displayed 1+ score. Sixteen tumors in pT1, 21 tumors in pT2 and 3 tumors in pT3 stage displayed 2+ score. Nineteen tumors in pT1 while 4 tumors in pT2 had 1+ score.

Conclusion: Our findings indicate that CD10 expression is greater in high grade and invasive urothelial carcinomas and is associated with progression of bladder carcinomas.

Keywords: Urothelial carcinoma, Clustered Differentiation 10(CD10), Immunohistochemistry.

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Introduction

Urothelial carcinoma ranks as tenth most prevalent tumor worldwide.[1] In Pakistan, Punjab Cancer Registry reported the percentage of bladder cancer to be 3.2% for the year 2018.[2] Smoking and genetic alterations constitute key factor responsible for development of carcinogenesis.[3] Many genes related to several signaling pathways, undergo mutations over a long period of time.[3] Clustered Differentiation 10(CD10) is a single chain zinc dependent metalloprotease.[4] It is additionally referred to by the names neutral endopeptidase (NEP 24.11), neprilysin and enkephalinase as well as common acute lymphocytic leukemia antigen (CALLA).[5] Pre-B cells, Pre-T cells, germinal centre B cells, granulocytes, uterine connective tissue, myoepithelial cells, fibroblasts, epithelial cells of hepatocytes, renal parenchyma, mammary tissue, adrenal cortex, lung and cells of central nervous system all routinely express CD10.4 Its expression has been demonstrated in many hematopoietic and non-hematopoietic tumors e.g. acute lymphoblastic leukemia, terminal phase of chronic myelogenous leukemia, urinary bladder carcinoma and colon adenocarcinoma.[5] A variety of biologically active peptides are inactivated by CD 10.6 It plays an important role in controlling cell proliferation and death[5]. Additionally, it may induce carcinogenesis by neoplastic transformation in cells lining the urinary bladder[7]. By changing the cellular microenvironment, it is believed to have an impact on invasion into the underlying tissue as well enhancing the capacity of these malignant cells to spread to distant sites.[7] The purpose of this study is to evaluate

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the expression of CD10 in relation to grade and stage of tumor. Expression of CD10 has not been recently evaluated in Pakistan, even though urothelial carcinoma is commonly encountered in our practice. Hence this study will help to compare our local population data with the international ones.

Material and Method

This research was carried out in Pathology Department of Tertiary care Hospital (IRB Reference No. 39122) for six months. Eighty five cases diagnosed cases of urinary bladder malignancy irrespective of gender, degree of differentiation and pathological stage received via Transurethral resection of bladder (TURBT) were selected by Non-Probability, consecutive sampling technique were included in the study. Poorly fixed specimens and specimens with scant tumor tissue and those diagnosed either as adenocarcinoma, sarcoma, lymphoma or metastatic carcinoma carcinoma on microscopic evaluation were excluded from the study. Tumors were categorized depending upon their degree of differentiation as per WHO guidelines. For histopathological staging purposes, AJCC staging 8th edition was employed on these TURBT specimen.

IHC results were interpreted on light microscopy using high power field objective. Cell membrane and or cytoplasmic staining was considered positive pattern[7]. Healthy renal tissue served as the positive control for the CD10 specificity. Cells of both glomeruli and tubules exhibited brown membranous and cytoplasmic staining, which was indicative of positive[7]. Depending on the proportion of positive cells stained for CD10, scoring was carried out as follows:

- Negative 0 (< 5% membranous or cytoplasmic staining of cells)
- Positive 1+ (>5 - 50% membranous or cytoplasmic staining of cells)
- Positive 2+ (>50% membranous or cytoplasmic staining of cells)

In order to evaluate the data, SPSS version 20.0 was utilized. Findings were expressed as percentages. The post-stratification chi-square test was performed, with a p value of 0.05 accepted as significant.

Results

The recruited cases were between the ages of 40 and 90, with a mean age of 63.96 10.13 years (Figure I).Out of 85 cases, 77 (90.59%) were men and 8 (9.41%) were women resulting in male to female ratio of 9.6:1. Regarding histological grade, 57(67.1%) were high grade while 28(32.9%) had low grade morphology. Regarding pathological staging, 9 (10.6%) were in pTa stage, 5 (5.9%) belonged to pTis, 43 (50.6%) in pT1, 25 (29.4%) in pT2 while 3 (3.5%) in pT3 . Among 85 cases, 67 cases (78.8%) demonstrated positive staining while 18 cases (21.17%) exhibited negative staining for CD10 (Table 1).

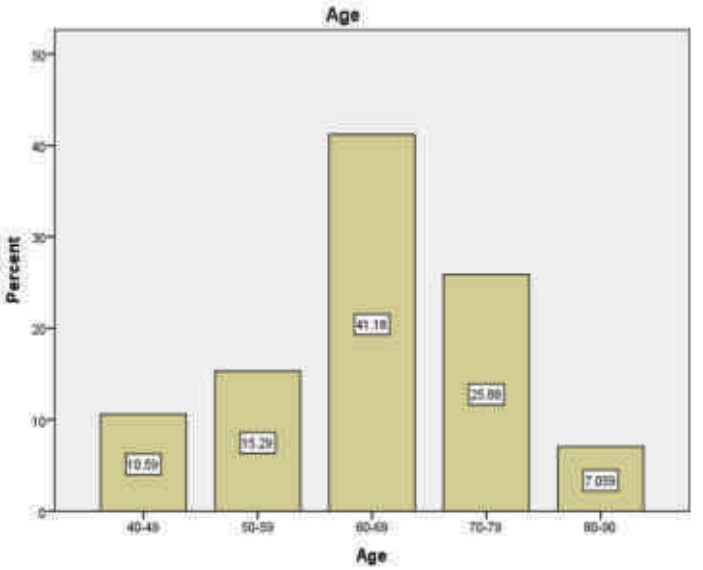


Figure I: *Distribution of cases according to Age groups (n=85)*

Figure II: Non- invasive urothelial carcinoma (pTa) (1+ CD10 immunostain at 40x)

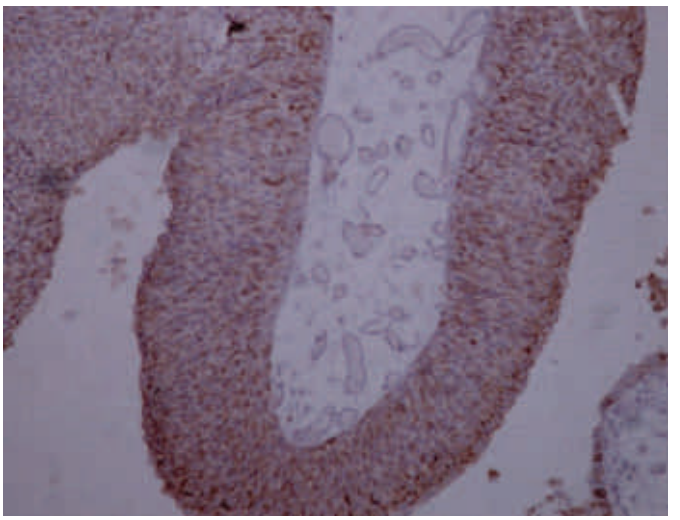


Figure 2: *Invasive (pT1) High grade urothelial carcinoma (2+CD10 immunostain at 40x)*

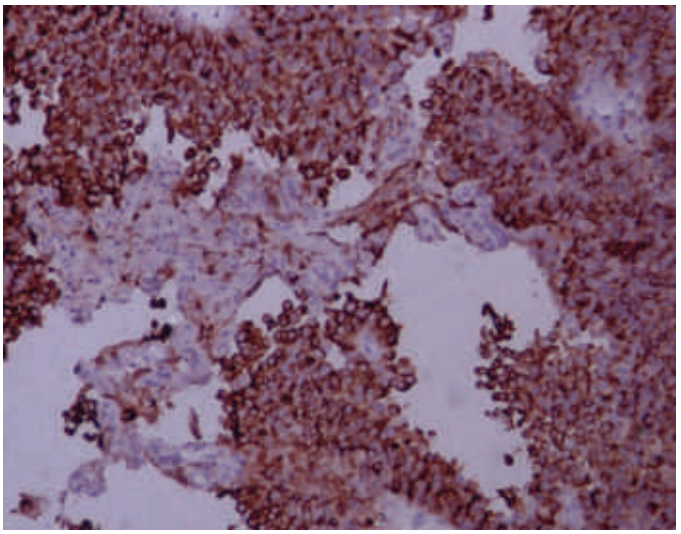
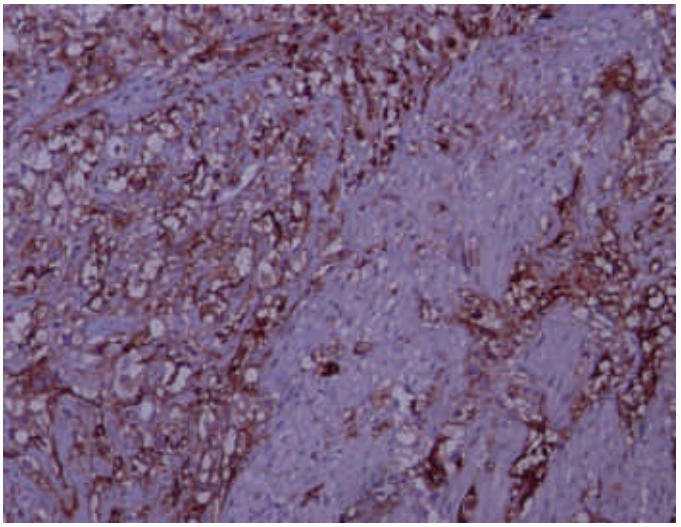


Figure 3: *Invasive (pT2) High grade urothelial carcinoma (2+CD10 immunostain at 40x)*



Discussion

Urothelial carcinoma of bladder is the 10th most frequent and 8th most fatal cancer primarily affecting males[8]. It is an insidious malignancy that killed close to 20,0000 globally in 2018 alone. As per the data compiled by Globocan and published in 2019, Bray et al calculated the numbers of reported new bladder cancers to be at 549,393 in the world, constituting 3% of the total cancer disease burden for the year 2018.[9] Although most of the bladder tumors are confined to the mucosa at the time of diagnosis but a significant percentage of tumors are advanced and muscle infiltrative.[10] According to Cancer Facts & Figures 2020 published by American Cancer Society, mortality due to bladder cancer remains higher among men.[11] Higher mortality can be attributed to diagnostic challenges resulting in delay in diagnosis and higher stage of disease at the time of presentation.[12]

Table 1: *Stratification of CD10 immunoexpression with respect to Grade and Stage of tumor*

Histological Grade	CD 10 Expression		Total = n	p-value
	1+	2+		
Low Grade	12 (17.9%)	0 (0%)	28 (17.9%)	
				< 0.001
High Grade	13 (19.4%)	42 (62.6%)	57 (82.1%)	
Pathological Stage	**CD 10 Expression**		**Total = n**	**p-value**
	1+	**2+**		
PTa	2 (2.9%)	2 (2.9%)	4 (5.9%)	
pT1	19 (28.3%)	16 (23.8%)	35 (52.2%)	
pT2	4 (31.3%)	21(31.3%)	25 (37.3%)	***< 0.001***
pT3	0 (0%)	3 (4.4%)	3 (4.4%)	

In our study, CD10 positivity was seen in 78.82% with positive correlation with histological grade and pathological stage. 2+ positivity was seen in 42 while 1+ reaction was visualized in 13 high grade tumors. 1+ positivity was present in each of the 12 low grade carcinomas. With a p-value < 0.001, the association between CD10 and tumor grade is highly significant (Table 1). These findings concurred with those of the study conducted in Egypt.[12] With a p value 0.001, the association between CD10 expression and tumour stage for urothelial carcinomas is likewise statistically noteworthy (Table 1). CD10 expression was seen in 4 out of 9 pTa tumor , 35 out of 43 in pT1, 25 pT2 and 3 pT3 tumors. While none of the five tumors in pTis revealed any positive expression. Additionally, Atique et al.[13], Shukla et al,[14] Muhammad et al.[15], and Asmaa Hussein et[12] noted this apparent relationship to stage. A substantial correlation between CD10 staining and tumour grade was seen after stratifying the data. Out of 57 high grade tumors, 42 displayed +2 and 13 exhibited +1 staining. Contrarily, none of the 28 low grade tumors displayed +2 staining, 12 revealed +1 staining, and 16 did not exhibit any expression. Having p-value <0.001, the link between CD10 expression and carcinoma grade is of statistical importance (Table I). These results coincided with the one research.[11] When data was stratified for stage, similar direct association of CD10 expression was observed. While 24 out of 28 pT2 carcinomas demonstrated +2 staining, mere 16 out of 43 pT1 carcinomas did so. With a p-value < 0.001, the connection

involving CD10 expression with tumour stage is noteworthy as well (Table I).This close association with both grade and stage was also observed by Atique et al,[12] Shukla et al,[13] Muhamed et al9 and Asmaa Hussein et al.[11] In 2000, Chu and Arber16 reported CD10 positivity in 54% of urothelial carcinomas. Murali conducted the first study on the relationship between CD10 expression and tumour grade or stage in 2005.He concluded that high grade urothelial neoplasms express strong CD10 positivity.[17] He came to numerous conclusions about the role of CD10 in carcinogenesis, one of which was that the buildup of mutant, nonfunctional CD10 may be the root cause of elevated CD10 expression.

Shukla et al.[13] also came to the conclusion that there is a strong relationship between CD10 with degree of differentiation, stage, and longevity in patients hence establishing its role in prognosis.

Conclusion

CD10 expression advances with increasing grade and stage. This raises the possibility that CD10 has a role in the onset and progression of urothelial carcinoma, which can be studied more thoroughly in order to develop a molecular customized therapy. More comprehensive studies with a longer follow-up period would be beneficial to examine CD10's efficacy in patient management and determine its precise significance as a prognostic marker in bladder malignancy.

Conflict of Interest *None*

Funding source *None*

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Authors Contribution

UR, SS: Conceptualization of Project
SS, SS: Data Collection
FI, SS: Literature Search
AB, AS: Statistical Analysis
UR, AB, AS: Drafting, Revision
AS, AB: Writing of Manuscript

Original Article

Frequency of Vitamin D Deficiency and associated Factors Among Pregnant Women Visiting Tertiary Care Hospital, Gujranwala, Pakistan

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Abstract

Objectives: To assess the frequency of deficiency of vitamin D and associated factor among gravid women following up at antenatal clinic of social security hospital, Gujranwala

Method: It was a cross-sectional study carried out at antenatal clinic social security hospital, Gujranwala. Total 100 pregnant females who were on follow-up visits and gave consent were enrolled in this study through a non-probability purposive sampling technique. A semi-structured and pre-tested questionnaire with anthropometric measurements and blood sample for vitamin D levels assessment was used to collect data and analysis was performed through SPSS version 23

Results: Among one hundred participants, two participants had deficient levels, 41 had insufficient and 57 had sufficient levels of vitamin D. Study participants had mean age of 28.8 ± 4.23 years. Mean duration of marriage and gestational period were 6.49 ± 4.0 years and 30.49 ± 10.49 weeks respectively. The mean vitamin D level was 29.9 ± 8.1ng/ml. Complaints such as backache, leg cramps, fatigue, gravidity, parity and low systolic Blood pressure were significantly associated with insufficient/low vitamin D levels.

Conclusion: Deficiency of vitamin D is high in study participants hence need based supplementation to gravid women is suggested.

Keywords: Vitamin D levels, pregnant women, Body mass index.

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Introduction

Vitamin D is a significant vitamin for development, growth and maintenance of healthy bones from cradle to death. Requirements in humans are fulfilled by vitamin D ingestion or sun exposure.[1]

Vitamin D decreases cell proliferation, enhances cell differentiation and has substantial anti-inflammatory effects. Vitamin D has a protective effect against cancers, cardiovascular diseases, pelvic floor disorders and age-related macular degeneration (AMD). It is identified to support the body in absorption of calcium and contributes in bone health.[1,2]

Deficiency of vitamin D is noted globally in all age groups. Vitamin D deficiency (VDD) or insufficiency has been assessed globally in 1 billion people. Deficiency of vitamin D is labeled when 25-hydroxyvitamin D concentration is less than 30ng/ml.[3,4] Scarcity of vitamin D is prevalent in South Asia due to dark complexion and its geographical location. Sunscreen of sun protection factor (SPF) 360 leads to 95% less vitamin D protection. Dark complexion individuals need 3-5 times more exposure than fair skin tone due to natural sun protection. Obesity is inversely proportional to VDD especially with body mass index (BMI) more than 30

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kg/m^2.[5,6,7]

Vitamin D deficiency is evident through National Nutritional Survey (2018) which reflected Vitamin D deficiency in 79.9% women in reproductive age. Studies conducted in Karachi and Rawalpindi showed 99.5% and 61.5% vitamin D deficiency among women respectively.[3]

Vitamin D is indispensable for fetal progress and development as it enhances the calcium absorption in the digestive tract.[8] Undesirable obstetric outcomes including maternal osteomalacia, abortion, preeclampsia, gestational diabetes, primary cesarean section and neonatal outcomes for instance fetal intrauterine growth restriction (IUGR), low birth weight (LBW), premature birth, neonatal hypocalcaemia, and juvenile obesity are also associated with lower levels of maternal vitamin D.[8]

According to literature review, there is scarcity of local data available regarding vitamin D deficiency in pregnant women in Gujranwala. The estimation of frequency will help define burden of disease. Hence, this study has been formulated to determine the frequency of vitamin D deficiency and associated factors among gravid women at ante-natal OPD of social security hospital, Gujranwala.

Material and Methods

It was a cross-sectional study carried out at antenatal clinic social security hospital, Gujranwala. Total 100 pregnant females who were on follow-up visits and gave consent were enrolled in this study. The selection of females was done by using non-probability purposive sampling technique. Duration of study was one month. After the approval by ethical committee and informed consent, with the help of a semi-structured pilot tested questionnaire, data were collected along with anthropometric measurements & blood sample for serum vitamin D calculation. Questionnaire included sociodemographic characteristics (age, education, occupation, residence place, family income), Obstetric history (duration of marriage, parity status, duration of current pregnancy, number of children, abortions) common complaints associated with vitamin D deficiency (Backache, leg cramps, fatigue) and attributes related to vitamin D deficiency(physical activity, sun exposure, duration of sun exposure, outside work, covering clothing, type of fabric, sunscreen application, vitamin D and calcium supplementation, dietary calcium intake). Anthropometric measurements (weight and height) were obtained. A digital weight machine was used to measure weight and stadiometer was used to measure height. These measurements were used to calculate. Body Mass Index (BMI) through the following formula: BMI = kg/m^2

Blood pressure was measured through a digital instrument, three readings were taken and a mean was recorded. Then a competent phlebotomist drew blood in clotted vial through aseptic technique. Vials were labeled with serial no and name of the participant and stored in a cold box. Later all vials were centrifuged and frozen. On the next day, whole batch was thawed and ELISA was performed as per directions by manufacturer's instructions. ELISA kit used was from Global Diagnostics B 25 – OH Vitamin D (total) ELISA Kit and its reference range was used to interpret results for classification of 25 OH Vitamin D status: deficiency: 0-10 ng/ml, insufficiency: 10-29 ng/ml, sufficiency: 30-100 ng/ml, potential toxicity:>100 ng/ml.[9]

Data were then entered and analyzed through SPSS (Statistical Package for Social Sciences) 24.0. The qualitative and quantitative variables were presented in mean & standard deviation and frequency & percentages respectively. Chi square test was applied to find out statistically significance. Means were compared using student's t-test. p -value ≤0.05 was taken as statistically significant.

Results

The present study comprised of 100 pregnant females with average age of 28.8 ± 4.23 years. About 13% were uneducated and 92% were housewives. About 57% women were residing in urban area and 71% were living in joint family system. Mean duration of marriage was 6.49±4.0 years and mean monthly family income was 19400±8689 rupees. In terms of their obstetrical history, the mean duration of gestational period was 30.49 ± 10.49 weeks. About 60% of women were ≤ 3 gravidity, 21% were primigravida, 24% had a history of abortion and 47% had spontaneous vaginal delivery(SVD) in previous pregnancy. About 23% of study participants were hypertensive, with mean BMI and mean vitamin D levels to be 27.7 ± 5.03 and 29.9 ± 8.1 respectively. The distribution of the study members on the basis of their levels of vitamin D is displayed in Table-1. The physical aspects of the study participants such as their physical activity, presence of sun exposure, place of work as well as the type of clothing worn in outdoors are shown in Figu-1. The various symptoms observed in the study

participants were backache (60%), leg cramps (78%) and fatigue (59%).

Various factors were analyzed for an association with vitamin D levels, and it was observed that complaints recorded such as backaches, leg cramps and fatigue were found to have a significant association. Analysis was executed to measure the association of various categorical and continuous variables with levels of Vitamin D. Through which gravidity, parity and blood pressure (systolic) were found to have a significant association. Variables associated with vitamin D are shown in Table 2 and 3 .

Table 1: *Frequency Distribution of Vitamin D Levels among Participants.*

Vitamin D Levels	Frequency	Percentage
Deficient (<10 ng/ml)	2	2
Insufficient (10-29 ng/ml)	41	41
Sufficient (30-100 ng/ml)	57	57
Total	100	100

Table 2: *Comparison of VDD with different factors in pregnant women.*

Variables	Deficient /Insufficient		Sufficient		P values
	n	%	n	%	
Backache					0.003
No	10	25	30	75	
Yes	33	55	27	45	
Leg cramps					0.001
No	27	34.6	51	65.4	
Yes	16	72.7	6	27.3	
Fatigue					0.001
No	14	27.5	37	72.5	
Yes	29	59.2	20	40.8	

P-value <0.05 significant.
Test Applied: Chi-square

Table 3: *Comparison of VDD with different factors in pregnant women*

Variables	Deficient/Insufficient Mean ± SD	Sufficient Mean ± SD	P Value
Gravidity	4.3 ± 2.1	2.8 ± 1.7	<0.00
Parity	2.7 ± 1.7	2.7 ± 1.8	0.003
Systolic Blood Pressure	111.9±12.2	122.3 ± 17.5	0.001

P-value <0.05 significant.
Test Applied: t-test

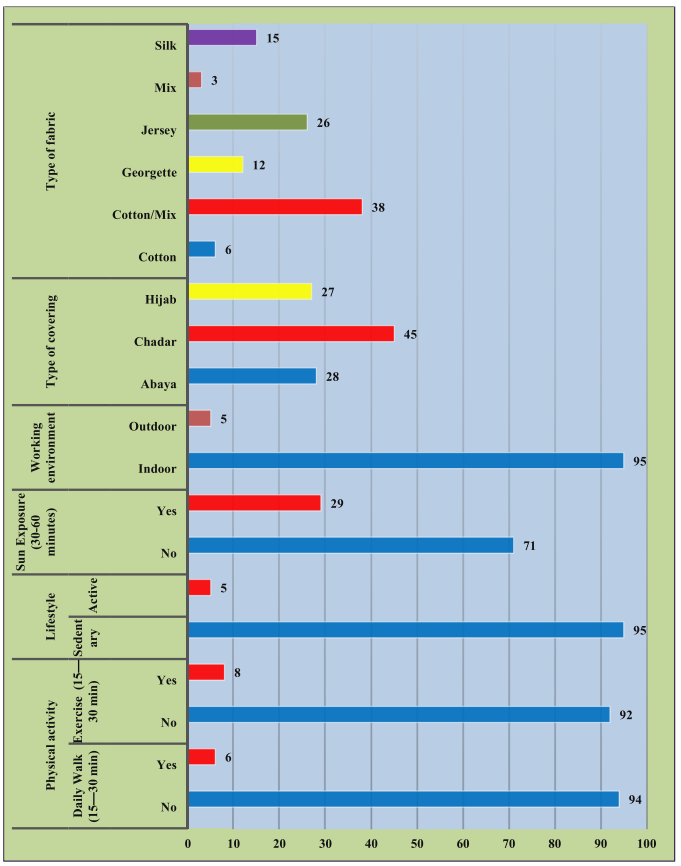

Fig-1: *Various attributes of the study participants.*

Discussion

This study found high frequency of deficiency of vitamin D among pregnant females in Gujranwala, Pakistan. The current study showed the average age of the study participants was 28.8±4.23 years, which was comparable to a Chinese study carried out by Song Hong-Bi in which the reported mean of the pregnant mothers was 29.3 ± 4.5 years.[10] Another factor observed in the current investigation was the systolic blood pressure (p-value: 0.001) with readings of 111.9±12.2 mmHg and 122.3±17.5mmHg respectively. However, a different study piloted by Aji et al. in expecting Indonesian mothers did not find a significant relation between vitamin D levels and systolic blood pressure (p-value: 0.994) with readings of 110.39±11.32 mmHg.[11]

The current analysis showed that 43% of expectant women were vitamin D deficient/insufficient. Deficiency of vitamin D has been stated in more than a few investigations in recent studies.[11,12,13] The frequency of VDD among pregnant women was found to be 61.3% in a

recent research performed in West Sumatra, Indonesia.[11] In a study conducted in Pakistan, 99.5% and 89% women were vitamin D deficient in Karachi and Jehlum.[12] In a recent systemic review and metanalysis, it was concluded that Pakistan has highest prevalence of vitamin D deficiency (76%) following then India (67%), Bangladesh (64%) and then Nepal(14%).[13]

Deficient vitamin D concentration is related to osteomalacia while insufficiency can lead to hyperparathyroidism, augmented bone turnover and osteoporosis.[14,15] Investigations have shown that in the Middle East and North Africa (MENA) region, about 54-90% pregnant women are vitamin D deficient.[16] In Beijing, China, a study showed vitamin D deficit in 99.4% women with mean 25-(OH)D levels of 27.28 ± 6.64 nmol/L6. Wang et al.[17] described that nearly 90% of pregnant women had vitamin D dearth. In Nanjing city, Jiangsu Province, the average Vitamin D levels in pregnant women were 26.4 ± 10.7 nmol/L and 22.7 ± 4.8 nmol/L in summer and winter respectively as stated by Xie et al.[18] Owing to religious and cultural reasons, women who cover their whole body, had decreased sun exposure and decreased vitamin D production.[19] In the same way, earlier investigations performed in countries such as Iran, Malaysia 20 and a local study from Pakistan described high frequency of vitamin D deficit[20,21] In the Netherlands, vitamin D levels were 15.2 nmol/l & 20.1nmol/l among Turkish & Moroccan women respectively, which were comparatively lesser than those found for Western females.[22] Alago et al. found that there was a significant difference in vitamin D levels depending upon body covering.[23] In our study, most of the participants had covered dressing style and vitamin D3 levels were evidently lower than numerous former investigations. In our study, parity was a substantial risk factor for vitamin D deficiency, as vitamin D dearth was less in nulliparous compared to multiparous.[24,25] The strength of this study is the addition of lab testing. Data was calculated through a questionnaire regarding sociodemographic characteristics, clinical complaints regarding vitamin D deficiency, different attributes leading to vitamin deficiency and Laboratory test determining serum vitamin D levels which provides a scientific evidence for the study. Limitations included purposive sampling and a small sample size, as results cannot be generalized for whole community.

Conclusion

Pakistan has abundant sunlight all the year. Lack of vitamin D was remarkably predominant among the pregnant women. Mode of delivery, backache, leg cramps, fatigue, gravidity, parity and high blood pressure were associated with the Vitamin D deficiency among pregnant females.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

DF: Conceptualization of Project
DF: Data Collection
SK: Literature Search
AR: Statistical Analysis
RH: Drafting, Revision
SA: Writing of Manuscript

Original Article

Relationship Between Craniocervical Posture and Vertical Face Pattern in Class II Division 1 Malocclusion

Saba Sikandar,[1] Naseer Ahmad Chaudhry,[2] Muhammad Imran Rahbar,[3] Asim Riaz,[4] Muhammad Mohsin Kamal,[5] Farhan Ali[6]

Abstract

Objective: To evaluate the cervical inclination and craniocervical posture (CCP) in a sample of Class II Division 1 malocclusion with different vertical patterns among adult population in Lahore.

Method: A total of 70 adult skeletal Class II division 1 cases (ANB0 > 4) with Dental Class II malocclusion (molar relation half cusp or full cusp Class II) and Overjet > 5mm, were enrolled in this study. Clinical examination and lateral cephalograms taken in natural head position were traced to classify the malocclusion, determine vertical pattern and evaluation of craniocervical posture.

Results: Results of the study showed that extended craniocervical posture (forward cervical inclination with backward head rotation) was found in 47.1 % of the study group and was significantly correlated to the vertical pattern of the face (r = 0.496, p =0.000). This indicated that the CCP is not only related to sagittal craniofacial relations but also vertical pattern of the face and as the vertical pattern of face increased the cervical spine inclined forward and the head rotated backwards on spine. Flexed head posture was found to be the least prevalent. Subjects with high vertical pattern of facial development had extended CCP whereas subjects with normal vertical pattern mainly had normal CCP.

Conclusion: Results of this study suggest a significant relationship between Type of malocclusion and craniocervical posture. There was a moderately strong relationship between vertical pattern of the patient and cervical inclination and craniocervical posture which was highly significant.

Keywords: Class II division 1, Craniocervical posture, Malocclusion.

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Introduction

Posture refers to the alignment of body parts. Craniocervical posture is alignment of the neck in space and alignment of head in relation to neck.[1]

Craniocervical junction is defined as the region comprising the occiput, atlas and axis, as well as ligaments and other associated structures. They are specialized to allow a wide range of head movement in flexion, extension, lateral bending, and lateral rotation.[2]

Cranium, face and cervical spine are adjacent structures acting in synergy to provide complex stomatognathic functions. These are functionally related and mutually influenced.

A forwardly inclined cervical column with extended head is collectively called a forward head posture. D`Attilio et al found that the lower part of cervical spine is strongly related to the size and position of the mandible in sagittal plane specially.[3] A recent systematic review concluded that increased cervical inclination is associated with the posterior mandibular position.[4] On the contrary research on adult Pakistani population reported that only cervical curvature is weakly correlated with the skeletal malocclusion and cervical inclination is

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not associated with it.[5]

Schwartz suggested a relationship between head position and dentofacial morphology.6 When the head tilts back on cervical spine it is considered extended and when it tilts downwards anteriorly it is called flexed head posture. Michael Marcotte related the flexed head posture with Class III malocclusion and concave profile and those with convex profile tended to bend head backward.[7,8]

In a recent study extended head posture was showed to be related to Class II malocclusion, crowding of teeth, Overjet, Overbite, Dental proclination, increased lower facial height and high vertical pattern.[9] The mechanism of this remains unclear. The influence of gravity on craniofacial form is rejected in a recent study.[10] Solow et al gave soft tissue stretching hypothesis which states that as the head posture varies from flexed to extended, the soft tissue envelope stretches and the passive pressure on the underlying skeletal structures increases and redirects their growth.[11] (Fig.1)

This also is supported by Proffit's equilibrium theory, that even the lightest of soft tissue pressure from muscles, fascia and skin maintained over long term and more than 6 hours a day can influence craniofacial skeleton.[12,13]

The cause-and-effect relationship is not yet established but it is now well known that craniocervical posture is a substantial yet neglected factor in development of facial skeleton.

Fig. 1: *Soft tissue stretch with change in Craniocervical posture.*[11]

One study emphasized that evaluation of craniocervical posture 2-4 years before the peak pubertal growth can give predictive information about subsequent facial development.[10]

Thus, a comprehensive knowledge of biological and functional dynamics regulating the growth of craniofacial complex is essential for proper diagnosis and treatment planning. It can be speculated that evaluation and intervention to correct faulty head posture may as well server as an interceptive measure against future skeletal jaw disproportion. Moreover, Treatment aiming at both the anatomic and functional disturbances is more likely to be successful and stable in long term. In the light of above discussion, this study aimed to evaluate a craniocervical posture in a subtype of skeletal Class II malocclusion i.e., Class II Division 1 which is more prevalent. No existing study distinguished between Class II Division 1 and Class II Division 2 which are entirely different entities with respect to skeletal, dental and muscular features.[14]

Materials and Methods

The study was approved by Institutional Review Board of FMH College of Medicine & Dentistry. Informed consent was taken once the sample is selected. The primary outcome variable was the craniocervical posture assessed through cephalometric analysis. Lateral cephalograms of all participants were taken in natural head position and were drawn manually. Outcome variable in terms of various types of craniocervical posture i.e., flexed, normal and extended were noted as per operational definition.

A total of 70 adult skeletal Class II division 1 cases (ANB0 > 4) with Dental Class II malocclusion (molar relation half cusp or full cusp Class II) and Overjet > 5mm, were enrolled in this study. There was absence of history of previous Orthodontic treatment and any bone, muscle or joint diseases. Absence of upper respiratory disease or allergic rhinitis and deviated nasal septum were also ensured.

Reference lines and angles used for cephalometric analysis in Fig.2.

NSL Nasion-sella plane: Line through Nasion and Sella points

SNA angle: Angular relationship of maxilla to cranial base.

SNB angle: Angular relationship of mandible to cranial base.

ANB angle: Angular relationship of maxilla to mandible

MP: anatomical plane of mandible

PP: anatomical plane of maxilla

HOR: true horizontal plane, perpendicular to true

vertical plane

OPT (Odontoid process tangent): Posterior tangent to the odontoid process. Drawn through the most posterior and inferior point on the corpus of the second cervical vertebra. Represents upper part of column

CVT (Cervical tangent): Drawn as posterior tangent to the most posterior and inferior point on the corpus of the fourth cervical vertebra. Represents mid part of cervical column

Angles that describe the vertical skeletal pattern:

SN/MP: angle formed b/w NSL and MP.

MMA: angle formed b/w PP and MP

Angle that describes the cranial posture with upper part of cervical spine:

NSL/OPT; Angle formed between NSL and OPT

Angle that describes the cranial posture with middle part of cervical spine:

NSL/CVT; Angle formed between NSL and CVT

Angles that describe neck position

OPT/HOR: Angle between OPT and true horizontal plane

CVT/HOR: Angle between CVT and true horizontal plane

Lateral cephalograms of patients fulfilling inclusion criteria were taken in natural head posture and traced by a single researcher. Maxillary and mandibular skeletal bases were measured by SNA and SNB respectively and ANB angle and Overjet was taken to classify skeletal malocclusion.

Two angles were used to find out vertical skeletal pattern, SN/MP (32+4) and MMA (25+4). The angle SN/MP was taken between Nasion-Sella line and Mandibular plane. MMA was between the anatomical planes of both maxilla and mandible. Vertical pattern was labelled as normal when both of these angles fell within norms. It was considered high when either of the angles was above the normal range and low when either of the angles was below the norms.

Two angles NSL/OPT and NSL/CVT were recorded to define craniocervical posture. Normal range of angle NSL/OPT is 89-105 degrees. Normal range of angle NSL/CVT is 96-112 degrees.

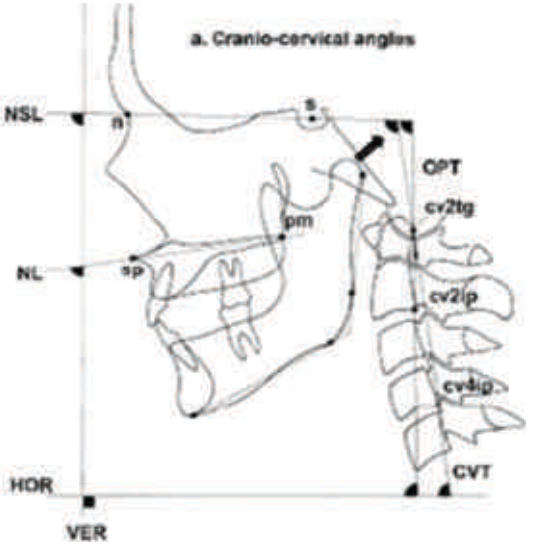

Fig. 2: *cephalometric landmarks and planes*

Normal Craniocervical posture is when the value of angle NSL/OPT is within the range of 89-105 degrees. And angle NSL/CVT is within the range of 96-112 degrees.

Extended Craniocervical posture is when the angle NSL/OPT is >105 degrees and angle NSL/CVT is >112 degrees.

Flexed Craniocervical posture is when the value of angle NSL/OPT is <89 degrees and angle NSL/CVT is <96 degrees.

Cervical inclination was measured by two angles i.e., OPT/HOR (93+5) and CVT/HOR (86+4). It is labelled as forward neck inclination if the angle OPT/HOR is <880 and the angle CVT/HOR is <820. Forward neck posture with extended craniocervical inclination is called forward head posture.

Results

A total of 70 Class II Division 1 cases were enrolled in this study. Data obtained was mainly organized into tables. The mean age of the patients was 21.5±1.9 years with a range of 19 & 26 years respectively. Out of the sample 43 (61%) were females and 27 (39%) were males. Frequency distribution of molar relation showed that there were 38.6% patients were of class 2 and 61.4% patients were end on class II. The results of descriptive statistical analysis of this cross-sectional study are shown in Table 2. Craniocervical posture was determined by two angles, namely NSL/CVT and NSL/OPT. The mean NSL/OPT of the patients was 104.2±8.^{6} degrees with a range of 83-121 degrees. Mean NSL/CVT of the patients was 108.3±7.4 with a range of 89-127 degrees.

(Table 1) With regards to angle made between the mid-section of cervical spine and cranial base i.e., NSL/CVT Craniocervical posture was found to be Extended in 20(28.6%) of the sample, Flexed in 3(4.3%) and Normal in a majority of 47(67.1%). As per angle formed between the upper section of the cervical spine and cranial base i.e., NSL/OPT Craniocervical posture was Extended in 33(47.1%), Flexed in 2(2.9%) and Normal in 35 (50%) of the subjects. (Table 2) The cervical inclination and position were forward in 24.3 % of the sample as per angle OPT/HOR and in 44.3% of population as per angle CVT/HOR. (Table 2)

The vertical skeletal pattern had significant correlation with both the variables i.e., cervical inclination and craniocervical posture (p= 0.000). The correlation was positive with craniocervical angles which means that both the parameters increased in proportion to each other. If the vertical skeletal pattern was high the craniocervical posture was also extended.

The correlation was negative and significant for cervical inclination (P=0.000). This denotes that as the vertical skeletal pattern became high the cervical angles reduced which brought the cervical spine in more forward/ horizontal position in relation to the true horizontal plane. (Table 3)

Table 1: *Descriptive statistics of NSL/CVT and NSL/OPT*

	N	Minimum	Maximum	Mean	Std. Deviation
NSL/CVT	70	89	127	108.26	7.450
NSL/OPT	70	83	121	104.16	8.551

Table 2: *Descriptive statistics of Craniocervical posture though angle NSL/CVT*

	Frequency	Percent	Valid Percent	Cumulative Percent
Flexed	3	4.3	4.3	4.3
Normal	47	67.1	67.1	71.4
Extended	20	28.6	28.6	100.0
Total	70	100.0	100.0	
Descriptive statistics of Craniocervical posture through angle NSL/OPT				
Flexed	1	1.4	1.4	1.4
Normal	36	51.4	51.4	52.9
Extended	33	47.1	47.1	100.0
Total	70	100.0	100.0	
Descriptive statistics of cervical inclination as per angle OPT/HOR				
Forward	17	24.3	24.3	24.3
Normal	24	34.3	34.3	58.6
Backward	29	41.4	41.4	100.0
Total	70	100.0	100.0	
Descriptive statistics of cervical inclination as per angle CVT/HOR				
Forward	31	44.3	44.3	44.3
Normal	24	34.3	34.3	78.6
Backward	15	21.4	21.4	100.0
Total	70	100.0	100.0	

Table 3: *Correlation coefficient between craniocervical posture angles, cervical inclination angles and vertical pattern of face:*

		SN/MP (face length)	MMA (face length)
NSL/CVT	Pearson Correlation	.475**	.405**
	Sig. (2-tailed)	.000	.001
	N	70	70
NSL/OPT	Pearson Correlation	.496**	.401**
	Sig. (2-tailed)	.000	.001
	N	70	70
OPT/HOR	Pearson Correlation	-.445**	-.423**
	Sig. (2-tailed)	.000	.000
	N	70	70
CVT/HOR	Pearson Correlation	-.420**	-.412**
	Sig. (2-tailed)	.000	.000
	N	70	70

Discussion

Craniocervical posture is the position of the head in a standing or sitting subject. The head is balanced by the post-cervical, suprahyoid, and infrahyoid muscle groups. In the present study, all the lateral cephalograms were obtained in the natural head position. In the present study, the relationship between head posture, cervical inclination and the anteroposterior skeletal relationship was investigated. The frequency of various types of Craniocervical posture in Class II Division 1 malocclusion and cervical inclination was recorded and their correlation with several variables was calculated.

According to this study the highest percentage of craniocervical posture in Class II division 1 was Normal i.e., 51.4 -67.1%. The next most prevalent type of head posture was Extended (posterior head rotation) i.e., 28.6-47.1%; whereas Flexed type of head posture (anterior head rotation) was seen in only 1.4-4.3% of the Class II division 1 sample according to the two angles NSL/OPT and NSL/CVT. Both angles showed moderate

positive correlation with the vertical pattern of the face but did not show any significant correlation with sagittal skeletal variables. This suggested an increase in craniocervical angle along with the increase in vertical height of the face. This tendency was reported in a recent study as a significant increase in lower anterior facial height, maxilla-mandibular plane angle, mandibular angle with the cranial base, and posterior vertical maxillary height with craniocervical extension in Class II malocclusion group[8].

Another study by Aditya et al. related extended craniocervical posture to Class II malocclusion, crowding, increased lower facial height and bimaxillary dentoalveolar proclination[9].

There has been contradicting findings regarding this topic in the literature. Findings of this study do not agree authors who stated there is no difference between craniocervical posture among different malocclusions.[15] In this study the cervical inclination was forward in 24-44% of the sample. Both cervical inclination angles showed negative moderate correlation with vertical pattern of the face which indicated that as the vertical height of the face increases the cervical spine inclines forward. This in turn needs the head to be tilted backwards upon cervical spine to maintain a straight line of sight. These results agree with a recent study reporting that posteroinferior angle of the cervical spine decreased in Class II subjects showing forward neck extension.[16]

Adeel Tahir also reported that there is increased cervical curvature in cervical spine of children of Class II malocclusion which shortens the length of neck resulting in increased cervical spine inclination and increased cranial rotation on spine.[17] These results agree with previous studies in that craniovertical and craniocervical angles significantly correlated with mandibular growth direction and facial development. The correlation coefficients ranged from low to moderate.[18]

Results of this study were found in contradiction with studies of Bernal et al. who did not find any significant difference in cervical inclination or curvature among different classes of skeletal malocclusion.[19] Likewise, D'Attillio et al. found changes in middle part of cervical spine but not in the upper part of it with different skeletal malocclusions.[3] Same results were described by Tauheed S et al. who reported no association between cervical inclination and skeletal malocclusion but found a weak and significant correlation of cervical curvature with the skeletal Class of the patients.[5] Based on a number of studies suggesting a link between a systematic review concluded that significant associations are found between head posture and craniofacial morphology but it should be interpreted with caution as correlation coefficients ranged from weak to moderate[19], which is in agreement with this study.

However, a recent study did recommend that any postural alterations should be corrected as early as possible before the growth spurt so that any disproportion in the development of craniofacial structures is not aggravated and all musculoskeletal systems can be used efficiently to achieve optimum growth.[17]

Conclusion

Results of this study suggest a significant relationship between Type of malocclusion and craniocervical posture. There was a moderately strong relationship between vertical pattern of the patient and cervical inclination and craniocervical posture which was highly significant. Therefore, it is concluded that craniocervical posture of skeletal malocclusion patients should be evaluated and corrected as part of their Orthodontic treatment plan. This may have significant effects on treatment outcomes and their stability.

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Authors Contribution

SS: Conceptualization of Project
AR, SS: Data Collection
IR: Literature Search
NAC: Statistical Analysis
FA: Drafting, Revision
MMA: Writing of Manuscript

Impact of Active Learning Approach on Students Evaluation of Teaching

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Abstract

Objective: The present study was designed to evaluate the extent to which students were benefited from active learning approach of teaching. It was intended to check the usefulness of whiteboard as a teaching medium instead of more commonly used audio-visual aids like PowerPoint.

Method: It is a cross-sectional descriptive questionnaire-based study. Interactive teaching strategy was used instead of diagnostic lecture. Instructor used only whiteboard as a teaching medium encouraging interactivity. At the end of the session, 150 students filled the form which comprised of 12 statements regarding evaluation of the instructor. Students were supposed to respond to them according to 5-point Likert-scale. Only students ≥ 18 Years and those willing to fill the form were included in the study. Exclusion criteria included students not willing to fill the form and those returning incompletely filled forms. The reliability of form was checked using Cronbach's Alpha which came out to be 0.8 proving it to be reliable.

Results: The average overall score for the proforma was 54.5±3.901 out of 60. This showed that there was more positive perception about the instructor than negative after employing active learning approach.

Conclusion: From the results of this study, it can be concluded that active learning approach using whiteboard along with enhanced student interactivity is an effective way of teaching.

Keywords: Active learning, SET, power point, whiteboard.

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Introduction

Evaluation is an important aspect for improving teaching practices not only in medical education but also in other disciplines. Besides improving teaching, it is also done for other purposes like developing a resume for job application, for promotion or for personnel decisions.[1] Student evaluation of teaching (SET) has a long history, has grown in prevalence and importance over a period of decades, and is now commonplace in many universities internationally.[2] Regarding improvement in teaching practices, the best method to adopt is student evaluation of teaching (SET) as students are directly affected by the teacher and are in an appropriate position to tell about the clarity, relevance, affectivity and other aspects of teaching of a particular instructor.[3] In addition, literature has also proven the validity of SET for evaluation of teaching particularly for nonclinical courses.[4] However, there are some concerns regarding use of only students' feedback for evaluation of an instructor as there are multiple factors that can influence individual students' response like the subject being taught by instructor or some other attributes of instructor that cannot be highlighted in a classroom setting.[5] So generally, it is advisable to gather feedback for the purpose

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of evaluation from multiple sources like peers, chairperson etc. known as triangulation to increase its validity even further.[6] Interactive teaching methods belong to the constructivist philosophy of learning, which gives special importance to student-centered active learning where the lecturer takes on a facilitator's role. This method made students more involved in their own understanding of the material and aware of their level of learning. It also provides scaffolding for education using questioning.[7] Numerous studies in medical education have proved the importance of active learning approach in making teaching effective and meaningful.[8]

To meet the challenges of modern era and present generation Z we need to do some innovation in our teaching practices. It is also essential because every student has a different learning style and accordingly requires multiple opportunities.[9] Teaching methodologies in medical education also need to be revolutionized.[10] Innovation in medical education has always been difficult due to its vast curriculum but it's the need of hour. So present study was designed to evaluate the extent to which students were benefited from active learning approach. It was intended to check the usefulness of whiteboard as a teaching medium when used alone which increases interactivity instead of more commonly used audio-visual aids like PowerPoint.

Materials and Methods

This was a cross-sectional descriptive questionnaire-based study of 150 undergraduate medical students during afternoon tutorial sessions of 3rd year MBBS. Interactive lecture was used as a teaching strategy and only white board was used as a teaching medium and there was no PowerPoint presentation; however only a small video related to the topic was shown. Students were encouraged to participate and share their knowledge with their peers and instructor on the basis of which new knowledge was delivered. At the end of the teaching session students were supposed to fill a form within approx. 5 minutes which consisted of statements evaluating the instructor's teaching skills. Prealidated Proforma was derived from DREEMs questionnaire which comprised of 12 statements regarding teaching evaluation.[11] Students were supposed to respond to those statements according to 5 point Likert-scale. Details of 5-point scoring are: 5 for strongly agree, 4 for agree, 3 for unsure, 2 for disagree and 1 for strongly disagree.[12,13] 12 statements with 5 points for each gives a total score of 60 perceived as an ideal instructor. These results in the form of score were interpreted as:

0-15= very poor performance

16-30= multiple problems exist in teaching methodology that needs to be addressed

31-45= more positive things about the instructor and minimal problems

46-60= ideal instructor

Students were supposed to fill the statements based form in the last 15 minutes of my teaching session. Students were told that these are anonymous and will not affect their grades to ensure greater student participation. Study duration for data collection was from 1st August 2017 to 15th Dec 2017. Study site was Department of Pharma-cology and Therapeutics, King Edward Medical Uni-versity Lahore. The reliability of form was checked using Cronbach's Alpha which came out to be 0.8 which exceeds Nunnally's 14 threshold of 0.70, suggesting that the instrument is highly reliable. Simple Random Sampling technique was used for data collection to minimize the bias. Participation was voluntary and only students willing to fill the form were included in the study. It's difficult to get feedback because students are usually not interested in filling such proformas. So, to motivate them objective of the study and impor-tance of their response were explained to them before-hand. Only student's ≥ 18 years and those willing to fill the form were included in the study. Exclusion criteria included students not willing to fill the form and those returning incompletely filled forms. Total 160 for were distributed, 155 were collected back out of which 150 were included in the study based on inclusion and exclusion criteria. Identity and data of the participants of this study was kept strictly confidential. Data obtained from Proforma was analyzed using SPSS version 21 Descriptive statistics were used and data was reported as mean ± S.D and percentage. To compare means of the DREEMs score obtained from male and female students, independent-t test was applied.

Results

A total of 150 students participated in the study which included 62 male (M) students and 88 female (F) students. Overall average score of the Statement based form derived from DREEMs inventory regarding evaluation of teaching came out to be 54.5±3.901 out of a total score of 60. This showed that students had a more positive perception about the instructors teaching style

than negative. After analyzing the available data using descriptive statistics, we found that 86.7% students agreed that overall instructor and the instruction methodology was good whereas 6% of the students strongly agreed to this. Only 7.3% students were unsure about their opinion and didn't give any positive or negative response. (Table 1 and Fig-1)

Table 1: *Table showing percentage and frequency of student's response for Student Evaluation of Teaching (SET) form.*

		Frequency	Percent
Valid	Agree	130	86.7
	SA	9	6.0
	Unsure	11	7.3
	Total	150	100.0

SA: Strongly Agree

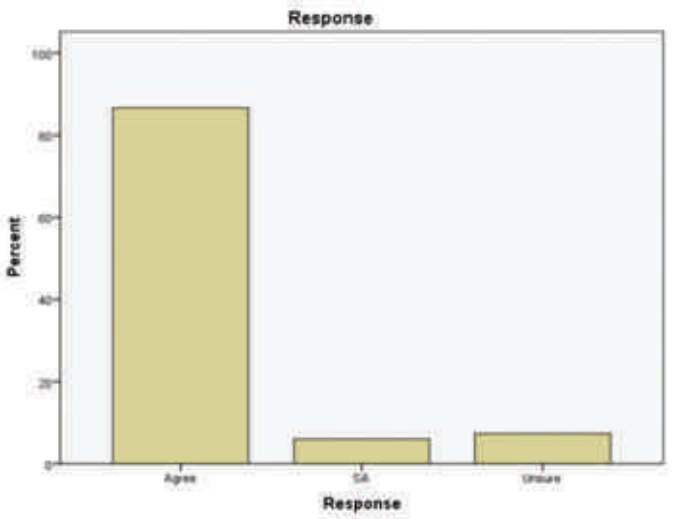

Fig-1: *Graph showing percentage of student's response for Student Evaluation of Teaching (SET) form.*

While analyzing results of individual questions, it was seen that 56.7% students strongly agreed that learning outcomes of the session were clearly communicated at

Table 2: *Students response for each individual statement.*

Sr #	Statements	Strongly Agree (5)	Agree (4)	Unsure (3)	Disagree (2)	Strongly Disagree (1)
1	Learning outcomes of the session were clearly communicated at the start	85 (56.7%)	62 (41.3%)	3 (2%)	Nil	Nil
2	Instructor is well prepared and has command on the topic	106 (70.7%)	44 (29.3%)	Nil	Nil	Nil
3	Instructor relates the topic content with real life examples	26 (17.3%)	65 (43.3%)	51 (34%)	8 (5.3%)	Nil
4	Instructor encouraged interactivity (student participation)	118 (78.7%)	26 (17.3%)	6 (4%)	Nil	Nil
5	Instructor responded to students' questions effectively when asked	94 (62.7%)	46 (30.7%)	8 (5.3%)	2 (1.3%)	Nil
6	Instructor communicates clearly using verbal, nonverbal and written language.	99 (66%)	50 (33.3%)	1 (7%)	Nil	Nil
7	Instructor challenged and ensured equal participation of all students	99 (66%)	50 (30.7%)	5 (3.3%)	Nil	Nil
8	Instructor used any form of technology to increase student interest.	74 (49.3%)	46 (30.7%)	24 (16%)	4 (4%)	Nil
9	Instructor used the allotted teaching time effectively	99 (66%)	44 (29.3%)	7 (4.7%)	Nil	Nil
10	Instructor creates a positive learning environment.	100 (66.7%)	48(32%)	2 (1.3%)	Nil	Nil
11	I have gained knowledge regarding this particular topic from Instructor	108 (72%)	40 (26.7%)	2 (1.3%)	Nil	Nil
12	Instructor presented the content in a way that we can understand easily	112 (74.7%)	34 (22.7%)	4 (2.7%)	Nil	Nil

the start of the session. Regarding preparedness of the instructor about the topic more than 70% of the students strongly agreed that instructor was well prepared. 43.3% students agreed that teacher related real life examples with the topic. When asked about the interactivity more than 80% students agreed that instructor encouraged students' participation. 62.7% and 66% students strongly agreed that instructor responded to student's questions when asked and had good communication skills respectively. Instructor also challenged students to think and reflect as proven by student's response (66% SA). Instructor also used technology (short video) to enhance understanding of the topic as 49.3% students strongly agreed with this. 66% students strongly agreed that teaching time was used effectively and efficiently by the instructor. More than 70% students strongly agreed that instructor created a Positive learning environment in the class which facilitated their learning and enhanced understanding of the topic. (Table 2 and Fig-2)

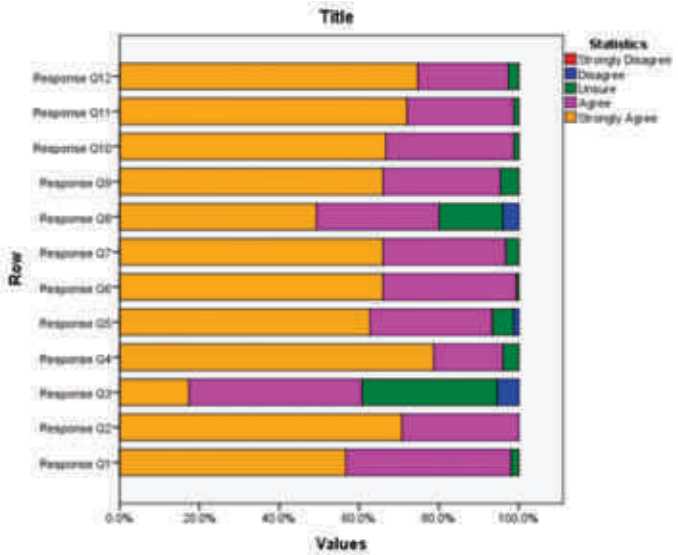

Fig-2: *Students response for each individual statement.*

Discussion

Students' evaluation of teaching (SET) has long been used as a mode of evaluating teaching effectiveness of an instructor. Cohen 1981 strongly supported the validity of SET as a mean of determining teaching effectiveness. He declared it to be a bona fide index of instructional effectiveness.[15] Another study showed that higher rating on SET was also associated with higher external exam scores proving that good instruction has an influence on students learning.[16] However a meta-analysis of these previous studies declared that teaching effectiveness and exam score are not influenced by higher SET scores.[17] A recent study has shown that SET should not be used in medical schools for coarse evaluation or for making critical decisions about faculty promotion, salary increase.[18] Keeping in mind all these perspectives, the present study was designed in the form of a questionnaire with the objective to elicit the perception of the students about the particular instructors teaching style employing active learning approach by interactive lecture using white board only through which students are encouraged more to participate in their learning process rather than didactic lectures. This evaluation of the instructor by students can be used as a mean of useful feedback that is obtained through a designed questionnaire. Numerous psychometric research has shown the accuracy and soundness of student's opinion and its direct correlation with teacher's teaching effectiveness.[19] In this regard many objections that were previously attributed to student evaluators are likely to be of minimal importance.[20] It has also been seen in literature that there is an association between evaluation scores and gender of students.[21] Female students were found to be giving higher scores than male students.[22] Contrary to it our study showed that gender of students didn't influence SET score.

In our study encouraging more student participation enabled the instructor to get a high SET score. It has also been observed in literature that many teachers tried to improve their rating by involving students more in their learning process.[23] So, it is evident that interactive learning imposes a positive impact on SET score that reflects a particular instructor's performance. It has been seen in literature that teaching by Interactive lectures is most popular mode of instruction among the students as well. A study reported that 42.1% students preferred interactive lectures as compared to other methods of teaching which was highest.[24] PowerPoint presentation is mostly used nowadays as a means of delivering lectures to enhance students understanding by adding useful illustrations but unfortunately its use has decreased interactivity in classroom. Whiteboard or blackboard teaching is a good way to attract student's attention by taking frequent feedbacks and ensuring active participation by them. It is considered one of the most favorite modes of instruction by students as is evident from literature.[25] Interactive learning has a positive influence on student evaluation of teaching, but this does not ensure student learning as a recent meta-analysis has shown that SET and student's learning are not related.[26] So having a positive perception about the instructor using SET shows that students had a plea-

sant learning experience and environment in the class, but it does not guarantee good student grades. In andragogy, adult learners are self-motivated to study and get good grades.[27] Teacher is only a facilitator and responsible for providing favorable learning environment in the class. The present modern generation needs some innovative teaching learning practices that can foster more student teacher interaction, enhance students' communication skills ultimately creating positive learning environment to generate highly skilled future medical practitioners.

Conclusion

Our study has made it clear that when students are involved more in their learning process through interaction by using white board as a teaching medium and not PowerPoint presentation, they acknowledge it positively as evident from a very high SET score in our study. Teachers' performance was appreciated by the students that might have also helped them in understanding the subject and in their own learning process as well but that still needs to be explored through future research in this respect.

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Authors Contribution

TZ: Conceptualization of Project
SM: Data Collection
M: Literature Search
BFA: Statistical Analysis
MIP: Drafting, Revision
UI: Writing of Manuscript

Post-Coital Rectovaginal Fistula: A Rare Case

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Abstract

Background: The most common cases of rectovaginal fistula are reported after obstetrical injury however rarely post-coital injuries may also result in a rectovaginal fistula. Coital injuries reported in the literature mostly are due to sexual abuse or violence. Consenting sexual intercourse is a very rare cause as in this case.

Case: The case of a 27-year-old woman who had a post-coital injury after first intercourse leading to the formation of a rectovaginal fistula is reported. She has two failed repairs previously. On examination she has a 1.5cm low fistula. The patient was admitted, after gut preparation her repair was done by the vaginal route by converting the fistula to a fourth degree tear and by doing layered closure.

Conclusions: Rectovaginal fistula after consenting sexual intercourse is rare and may occur due to lack of sex education.

Keywords: Postcoital, rectovaginal fistula

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Introduction

A rectovaginal fistula (RVF) is defined as an epithelium-lined communication between the rectum and the vagina which causes stool to pass from the vagina.[1] It has a significantly negative impact on the social, sexual and psychological life of the female patient. The common causes of rectovaginal fistulas are obstetric trauma, inflammatory bowel disease, peri-anal sepsis, congenital abnormalities or iatrogenic causes. The primary treatment of RVF is surgical. Repair of RVF is difficult and different surgical options are available like muscle interposition, advancement flaps, fistula excision and layered repairs. The success rate of surgical repair ranges from 0 to 80%.[2-6] Many patients need repeated surgeries.[5] A rare cause of rectovaginal fistula is post-coital injury. Usually in post-coital injuries there is damage to the vaginal mucosa and skin. Extension of these injuries to involve the rectum causing a rectovaginal fistula is rare.[7] A case of rectovaginal fistula that occurred during first sexual intercourse after marriage which had failed repairs twice in a woman who did not have any genital malformation is reported.

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Case Report

A 27-year-old housewife presented in outpatient department with complaint of fecal incontinence. She was married for 7 years and had 3 children delivered by cesarean section. She had a post-coital tear after first intercourse 7 years ago. She had bleeding and fecal incontinence since then. She had a repair done 20 days after the tear which was unsuccessful. She had another repair done 1.5 year later by a surgeon but that repair also failed. Since 7 years she was living with the fistula which had affected her physical, psychological and social health badly. She was now at the verge of divorce. She was advised a repair with a diversion colostomy by a surgeon. When she presented to us she was examined. She has a fistula about 1.5cm in size about 1cm from the anal verge. (figure1) It was a low fistula. In our opinion a diversion colostomy was not required. A multidisciplinary team meeting was held with the colorectal surgery team and it was decided that a transvaginal repair would be done without a diversion colostomy. The patient was explained that in case of failure of this repair she may need a repair with diversion colostomy in future. Gut preparation was done preoperatively The repair was done by the vaginal route by performing a episio-

proctotmy and layered closure like a fresh fourth degree perineal repair. (figure 2) The rectal mucosa was sutured with interrupted vicryl 3/0 sutures. Strengthening of repair was done an additional layer of longitudinal rectal muscles over the first layer. The levator Ani muscles were interposed between rectum and vagina to create an additional layer between rectum and vagina and to strengthen the perineal body. The sphincter was stitched with an overlapping technique. Tube drain was placed and vaginal mucosa was stitched. Skin was approximated and digital rectal examination was done. Patient was kept nil by mouth for 5 days. Fluids were allowed on the sixth day. During the hospital stay she passed stool twice normally. She was discharged with laxatives to prevent constipation.

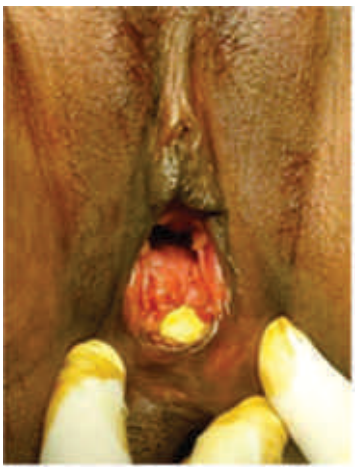

Figure 1

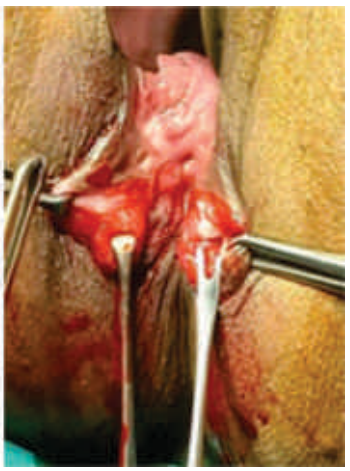

Figure 2

Discussion

Rectovaginal fistula is a distressing condition which is mainly caused by obstetric injuries especially in developing countries where everyone does not have access to a comprehensive healthcare.[8] Rectovaginal fistulas that occur after coitus are usually reported in cases of sexual violence and abuse.[9] 91 cases of genital trauma with fecal incontinence were reported in Ethiopia by Muleta et al that were due to forced marriage, kidnapping, and rape of young girls.[10] However there are few cases reported of rectovaginal fistulas after consensual intercourse.[11,12] Consensual vaginal sex usually does not give rise to any significant injury except for minor vaginal tears sustained during vaginal sex for the first time. Symeonidis et al reported that large rectovaginal tears following consensual intercourse is a very rare occurrence.[13] It is most commonly caused by virginity, young age, genital disproportion and fear of sex[14]. In the reported case, lack of sex education and virginity were the main contributing factors. In conservative communities' sex remains a taboo subject and sex education is lacking which also contributes to such problems.

There are different surgical techniques to repair a rectovaginal fistula. These can be performed by transvaginal or transanal route. In this case the transvaginal route was used. The rectovaginal fistula is treated as a fourth degree tear through open and deliberate section of the anal sphincter. Others techniques include interposition of healthy tissues, such as the gracilis muscle or the bulbocavernosus muscle can be used in complicated cases. Rectovaginal fistulas caused by trauma or infections and less than 2.5cm in size are considered uncomplicated fistulas. The outcome is better and treatment can be performed via the perineal route.[15]

Conclusion

Rectovaginal fistula occurring after consensual coital activity are very rare. Lack of sex education and marriages at young age are an important cause of such cases. There should be proper guidance and sex education must be given to both females and males to prevent such injuries. Rectovaginal fistulas have a devastating effect on the quality of life of the female. It not only causes physical trauma but also has a deep psychological impact. The female is also not accepted socially. In case of such injuries the initial repair must be done by an experienced clinician to prevent recurrence and failure of repair which further adds to misery of the patient and family.

Conflict of Interest *None*

Source of Funding *None*

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Authors Contribution

NH: Conceptualization of Project
NH: Data Collection
SM: Literature Search
SM: Statistical Analysis
NH: Drafting, Revision
SM: Writing of Manuscript

Rare Case of Bladder Endometriosis Imitating Bladder Growth in a Pregnant Female : A diagnostic Challenge

Noman Ali Ghazanfar,[1] Sohail Hassan,[2] Uzma Aslam[3]

Abstract

Background: Endometriosis is deposition of endometrial tissue outside the uterine cavity. Isolated Bladder endometriosis in absence of uterine endometriosis is a less frequent event .The presence of pregnancy in these situations is even rarer. The clinical presentation may be lack of any symptoms, dysmennorhea, dyspareunia, excessive or irregular menstrual bleeding, lower urinary tract symptoms, hematuria or recurrent urinary tract infections. We present a unique case of bladder endometriosis in a 10 weeks pregnant female mimicking bladder growth that underwent transurethral resection with histopathology confirming the diagnosis of endometriosis.

Keywords: Endometriosis, Vesical Endometriosis, Bladder Growth, Pregnancy

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Introduction

Endometriosis is a disease of women in their reproductive age with peak incidence between 30 and 45 years of age. The involvement of urinary tract is less than 1 % and rare.[1,2,3] Among these cases bladder is the most common site. Endometriosis is also a common cause of infertility in women. Complications with pregnancy includes tubal pregnancy, early miscarriage, placenta previa and post-partum heamorrhage.[4]

Vesical Endometriosis in presence of pregnancy is very rare. It is a diagnostic challenge for clinicians as on Ultrasound it may imitate bladder growth and option of CT scan for work up is not suitable in pregnancy. Trans vaginal Ultrasound is superior to abdominal ultrasound in diagnostic accuracy. MRI also provides a good alternative in these situations.[10,11] Use of Flexible cystoscopy under local anesthesia is also a viable option to narrow down the diagnosis but that also do not provides option of biopsy and histopathology. The accurate diagnosis can only be made through Cystoscopy with biopsy followed by Histopathology which is pathognomonic.[5] This can only be achieved under regional or general anesthesia carrying a risk of termination of pregnancy. We present a unique case of vesical endometriosis mimicking bladder growth in presence of pregnancy having undergone transurethral resection and biopsy with histopathology confirming the diagnosis.[5]

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Case Report:

A 23 years old female presented to us in Urology outpatient with 8-10 weeks of pregnancy having being referred by radiologist due to suspicion of incidental bladder growth on abdominal ultrasound (Figure 1) . She had no history of hematuria or other urinary symptoms. She previously had two uneventful pregnancies in last four years done through cesarean section. She denied having any menstrual irregularities, dyspareunia or any other gynaecological complains however she did admit having complains of dysmenorrhea few years back in her teenage which settled spontaneously. Physical examination did not reveal anything unexpected with presence of caesarean scar from previous pregnancies. We organized a transvaginal ultrasound which showed single alive intrauterine pregnancy of 8 weeks and 3 days with no signs of uterine endometriosis .

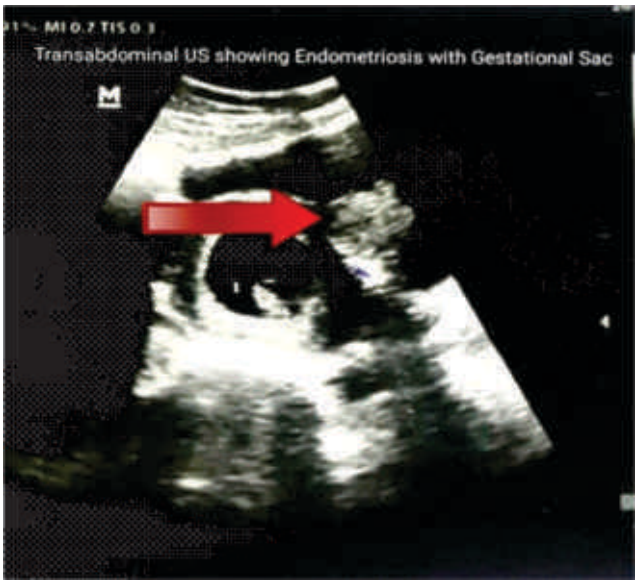

Fig-1: *Transabdominal Ultrasound of patient showing Endometriosis and gestational Sac with Embryo*

She also underwent an MRI which showed well defined abnormal signal intensity area within the anterior cul de sac at the site of uterine scar that seemed to be inseparable from the serosa and adherent to vesical base causing its elevation. Urinary bladder itself was said to be normal on MRI with no intraluminal mass lesion. (Fig-2)

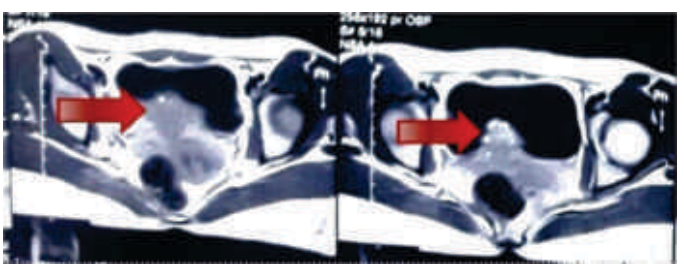

Fig-2: *MRI of patient showing Vesical Endometriosis*

She was consented for cystoscopy and proceed for transurethral resection of mass involving risk of termination of pregnancy. Spinal anesthesia was opted to minimize the risk of termination of pregnancy and Bipolar resection technique was adopted to minimize the circuit of current during transurethral resection. Single dose of intravenous ceftriaxone was given before the resection only .A well-defined solid looking mass was seen on left poster lateral wall of bladder (Figure 3). Complete resection was achieved using bipolar technique and biopsy was sent for histopathology. It is worth mentioning that per operative bleeding was minimal with no need of bladder irrigation after the surgery as is normally seen with bladder growths.

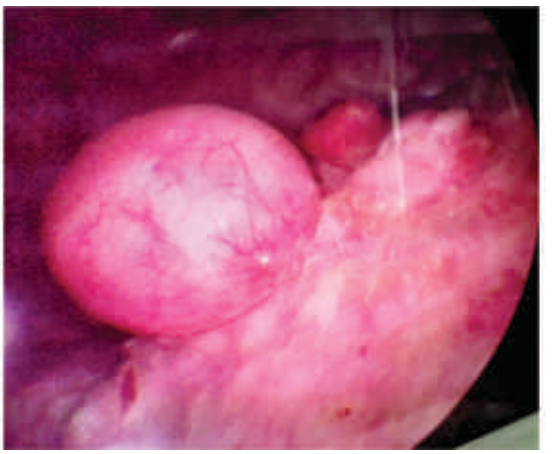

Fig-3: *Cystoscopy showing Vesical endometriosis imitating Bladder Growth*

The histopathology showed endometrial gland and stroma predominantly in muscularis propria with focal extension into the mucosa and pseudodecidual changes in endometrial stroma. No atypia or atypical mitosis was seen. No malignant cells of bladder origin were seen. (Fig.4-5)

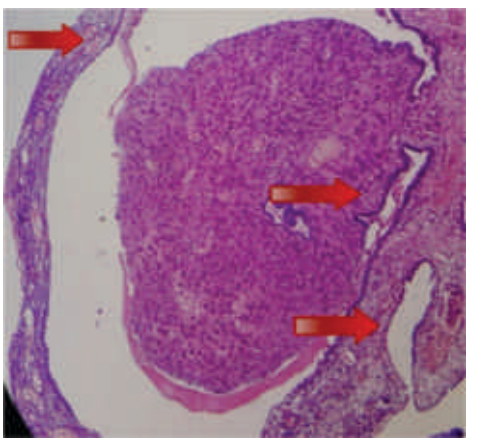

Fig-4: *Histopathology Showing Endometriosis*

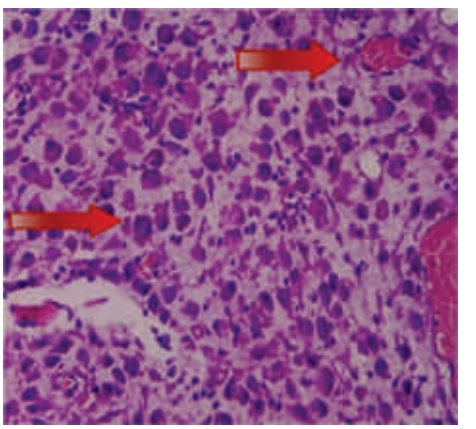

Fig-5: *Histopathology Showing Endometriosis*

The patient was re-evaluated by ultrasound for fetal well being in same admission which showed alive intrauterine pregnancy with normal fetal cardiac activity. The patient was seen by obstetrician with satisfactory evaluation. The patient was discharged home and was kept in follow up for pregnancy.

Discussion

With vesical endometriosis being uncommon[1,2,6] our case was particularly rare due to presence of pregnancy in endometriosis posing a diagnostic and therapeutic challenge including care of fetal well being.[4] There have been 3 previous documented cases of vesical endometriosis with uneventful pregnancy and this is the 4th case of such nature. Our case was also rare in a sense that it do not caused any symptoms but was only diagnosed during work up for pregnancy. Previous two pregnancies in the patient were also remarkably uneventful causing no antenatal or postnatal complications done through caesarian section which itself is a risk factor for development of endometriosis due to its scar.[7,8] The establishment of diagnosis in these situations can be difficult as endometriosis may mimic a bladder growth.[1,9]

Use of transvaginal ultrasound,[12] Flexible cystoscopy and MRI[10,11] can narrow the diagnosis with CT being un-useful during pregnancy. Single dose of antibiotics is adequate to cover urological surgery in pregnancy. Spinal anesthesia is the safest option with use of Bipolar cautery for resection minimizing the risk of current passage through the womb.

There are a few number of cases being documented on vesical endometriosis during pregnancy and there is a need to gather more data to establish guidelines for diagnosis and treatment for such cases for safe surgical practices.

Conclusion

Vesical endometriosis in presence of pregnancy is a rare finding and poses a diagnostic and therapeutic challenge. The clinical presentation may be varied. Use of Transvaginal ultrasound and MRI can narrow down the diagnosis with histopathology being confirmatory and pathognomonic.

Conflict of Interest: *None*

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Dr. Adil Qayyum	Associate Professor	Combined Military Hospital, Mangla
Dr Abdur Rehman	Associate Professor	Allama Iqbal Medical College, Lahore
Dr Nukhbakht	Associate Professor	King Edward Medical University, Lahore.
Dr Shamsul-Islam	Associate professor	Fatima Jinnah Medical University, Lahore.
Dr Sabeeh Ubaid	Associate Professor	Shalimar Medical and Dental College, Lahore
Dr Sadia Yaseen	AssociateProfessor	Rashid Latif Medical College Lahore,
Dr Sadia Shairf	Associate professor	Amna Innayat Medical College
Dr. Faryad	Associate Professor	Fatima Jinnah Medical University Lahore
Dr. Razi Zaidi	Associate Professor	Faisalabad Medical University/PMC
Dr. Ameena Nasir	Associate Professor	King Edward Medical University, Lahore.
Dr Kamran Islam	Associate Professor	Consultant cardiologist Social Security Hospital Islamaba
Dr Mujeeb Khan	Associate Professor	Holy family hospital
Dr.Lubna Miraj	Associate Professor	Benazir Bhutto Hospital Rawalpindi
Dr. Bilal Azeem Butt	Associate Professor	Fatima Jinnah Medical college
Dr Samina Fida	Associate Professor	Akhtar Saeed Medical College, Lahore
Dr. Shumaila Husnain	Associate Professor	Central Park medical college Lahore
Dr. Atif Qureshi	Associate Professor	Azra Naheed Medical College Lahore
Dr, Rabia Rathore	Associate Professor	King Edward Medical University, Lahore.
Dr Huma Amin	Associate Professor	NustCollege of health sciences. Islamabad
Dr Fauzia Saliq	Associate Professor	Lahore Medical and dental college
Dr. Rabia Usmani	Associate Professor	Independent Medical College Faisalabad
Dr. Shahid Mahmood	Associate Professor	Allama Iqbal Medical College Lahore
Dr. Atika Masood	Associate Professor	Akhtar Saeed Medical College, Lahore
Dr Usman Zaheer	Associate Professor	Lahore Medical and Dental College
Dr Saeed Mustafa	Associate Professor	Orthodontics School of Dentistry PIMS
Dr. Uzma Rihan	Associate Professor	Gujranwala Medical College, Gujranwala
Dr. Samina Wasim	Associate Professor	Sheikh Zayed Medical College, Rahim yar khan.
Dr. Faeza Rauf	Associate Professor	Fatima Jinnah Medical University, Lahore
Dr. Faiqa Arshad	AssociateProfessor	Gujranwala Medical College Gujranwala