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TABLE OF CONTENTS

Original Articles

Outcome of Bacterial Meningitis in Children Age 1 Month – 12 Years in a Public Sector Hospital Treated with 1st line Antibiotics 403
Aqeela Ayub, Tasleem Bano, Amna Khalid, Muhammad Khalid Masood, Hamna Ayub, Hashim Raza Syed

To Compare the Effect of Competitive and Non-Competitive Environment On Academic Performance in Medical Students 408
Saira Nawaz, Neesha Naveed, Bilal Nazar, Muhammad Hasham Akram Chaudhry, Amna Nadeem Kazi

Effect of COVID-19 Pandemic on Presentation and Outcomes of Gallstone Disease 412
Sidra Mehmood Dar, Musharaf Khalid Bhutta, Humaira Zia, Muhammad Nauman Bashir, Jahangir Sarwar Khan, Usman Qureshi, Gohar Rasheed

Evaluation of Helicobacter Pylori Infection Prevalence in Patients with Portal Hypertensive Gastropathy in Pakistani population-A Single Centered Study 417
Hira Sadaqat, Abida Pervaiz, Sadia Bashir, Zareen Gul Rohi, Ummara Ghias, Abeer Mutalib

Factors and Morbidities Associated with the Delayed Diagnosis of Congenital Heart Disease in Children Under 5 422
Zara Zahid, Hafiz Sajid Khan, Zunaira Mazhar, Misha Anam

Comparison of the Local Anesthetic Effect of Two Doses of Dexmedetomidine , 5µg and 10µg added to Intrathecal Hyperbaric Bupivacaine 427
Khalid Abaidullah, Khalid Javid Siddiqi, Muhammad Amjad Khan, Makhtoob Ahmad, Muhammad Awais, Rehab Khalid

Family History – An Indicator For Developing Type 2 Diabetes At Earlier Age 432
Sarah Shoaib Qureshi, Wasim Amer, Javeria Zunair, Bilal Mahmood Beg

Seroma Formation Between Flap and Non-flap Fixation Following Mastectomy in Term of Age and Type of Surgery in Breast Cancer Patients in A Tertiary Care Hospital 437
Ammarah Zia, Sidra Mehmood Dar, Sehrish Siddique, Jahangir Sarwar Khan, Rubina Shahzad

Prevalence of Diagonal Earlobe Crease (DELC) in General population of Lahore and its Association with Various Ailments, as a Marker of Forensic Significance 442
Muhammad Kashif Butt, Sundus Mona, Saad Adhami, Fawad Ahmad, Areesha Fatima, Muhammad Maqsood, Muhammad Zahid Bashir

Demographic and Clinical Correlates of Deliberate Self-harm in Patients with Substance Use Disorder 448
Nadia Haroon, Richard R. Howell, Aysha Butt, Ali Anjum, Sadia Nikhet, Sana Haroon

Diagnostic Accuracy of CT Scan in Necrotizing Pancreatitis Taking Surgical findings as Gold Standard 452
Rabia Shaukat, Ali Mansoor, Sadaf Arooj, Zoha Imran, Mahjabeen Masood, Aisha Asghar

Determination of Clinical Patterns of Onychomycosis in Patients presenting with Nail disorders to a Tertiary Care Hospital 457
Ayesha Sarwar, Asma Kanwal, Hira Tariq, Muhammad Shahid, Faria Asad, Salman Haseeb

Reasons for Delay in Presentation of Vesicovaginal Fistula Patients at Tertiary Health Facility 461
Athar Mahmood, Hamza Farooq, Asad Ali Shah, Muhammad Farooq, Shafi Ghouri, M. Shahzad Anwar

A Review of Ocular Surgeries Performed in 2020 and 2021 at Tertiary Care Hospital Sialkot 465
Shahid Anwar Bhatti, Tanveer Ahmed Choudry, Muhammad Asif, Rehana Mushtaq, Huda Asif

TABLE OF CONTENTS

Comparison of Ventricular Late Potentials in Patients with Ischemic and Non-Ischemic Cardiomyopathies 469
Hira Ashraf, Ammara Abid, Madiha Imran, Sara Naeem, M Alamgir

Correlation of Perceived Stress on the Academic Achievement of Undergraduate Nursing Students of KPK 473
Amir Sultan, Sardar Ali, Haseen Jamal, Sohni, Fayaz Ahmed, Shabana

Ethanolic Extract of Azadirachta Indica Seeds and Leaves and its impact on Lipid Profile in Diabetes Mellitus 478
Tahira Saleem, Natasha Zahid, Abida Saleem, Naima Khalid, Aysha Zaheer, Naila Saleem

Impact of Chewing Cardamom and Fennel Seeds on Salivary Ph: A Hospital-Based Comparative Analysis 483
Thelma Farast Bashir, Rabia Arshad, Zunaira Khalid, Eman Aslam, Maryam Usman

Diagnostic Accuracy of Flamm and Geiger Scoring System as a Prediction Model for Outcome at the Time of Labour- A single-Centred Study 489
Saira Iqbal, Anum Asad Ullah, Anam Tassadaq, Maria Sharif, Faiza Ijaz, Aysha Afzal Qureshi

Prophylactic Anti-Ulcer Effect of Punica Granatum (Pomegranate) Peel and Seed Extract in Murine Peptic Ulcer Model 495
Mariyam Iftikhar Piracha, Saadia Shahzad Alam, Hassan Farooq, Tehreem Zulfiqar, Fariha Ahmad Khan, Mah-e-noor Zahra

Molecular Identification of Forensically Important Blowflies By DNA Barcoding to Effectively Determine Postmortem Interval 500
Sundus Mona, Muhammad Zahid Bashir, Abdul Ahad, Aimal Nasrullah, Muhammad Mubashir, Manal Mubarak, Mudassar Rashid

Perceived Academic Stress Among Undergraduate Medical Students and Their Coping Stategies 506
Syeda Shaista Waheed

Comparison between Efficacy of Flipped and Traditional Methods in Teaching- Learning Human Physiology 511
Zainab Riaz, Sana Javaid, Sana Qanber Abbasi, Rabia Ahsan, Quratulain, Maham Fatima, Ghazal Mansoor

How Accurate are the Clinical and Biochemical Markers in Predicting Histological Chorioamnionitis After PPROM? 516
Ameelia Sadaqat, Saira Rathore, Nayyer Sultana, Rashida Mushtaq, Sanam Mahmood

Outcomes After Close Reduction and Percutaneous Pinning of Gartland Type III & IV Supracondylar Distal Humerus Fracture in Children 521
Muhammad Akhtar, Shahzad Anver Qureshi, Muhammad Tasneem Javed, Omer Iqbal Cheema, Muhammad Taqi, Mumraiz Naqshband, Faisal Masood, Anwer Ali

Protective effect of Aqueous Garlic Extract on Monosodium Glutamate Induced Toxicity on Johnson's Scoring of Infertility in Adult Wistar Rats 525
Hafiza Sadia Ahmed, Fatima Inam, Asma Siddique, Faeza Rauf, Shagufta Nasreen, Sibgha Fatima

Outcome of Bacterial Meningitis in Children age 1 Month – 12 Years in a Public Sector Hospital Treated with 1st line Antibiotics

Aqeela Ayub,[1] Tasleem Bano,[2] Amna Khalid,[3] Muhammad Khalid Masood,[4] Hamna Ayub,[5] Hashim Raza Syed[6]

Abstract

Objective: To determine the effectiveness of using first line antibiotics for the treatment of acute bacterial meningitis in children admitted in a public sector hospital and assessing its outcome with the help of data by need for using second line antibiotics therapy and length of stay in hospital.

Method: This Crosssectional study was conducted at department of Pediatrics, Pakistan Institute of Medical Sciences, Islamabad over a period of 6 months from January 2019 to July 2019. All children between the age of 1 month – 12 years, of both genders admitted in pediatric ward with acute bacterial meningitis, based on clinical features plus CSF findings, were enrolled in the study. These children were started with first line antibiotic therapy after admission in ward which included ceftriaxone alone or a combination of ampicillin and cefotaxime or cefotaxime plus amikacin depending on age specific recommendations for that age group. All children were closely observed in ward for improvement or deterioration of symptoms. If there was deterioration of symptoms, then second line antibiotics were started which in our case was vancomycin combined with ceftriaxone or meropenem combined with vancomycin. Duration of hospital stay was also noted. Data was analyzed by SPSS version 22.

Results: A total of 51 patients were enrolled in the study. Mean age of children in the study was 3.23 ± 3.3 years. There were 33(65.1%) males and 18(34.9%) females. Only 30(58.6%) children were completely vaccinated, rest were either partially vaccinated or not vaccinated at all.]In the first line antibiotics course, ceftriaxone was the most common antibiotic, which was prescribed to 32(61.3%) children, followed by a combination of cefotaxime with amikacin 13(23.7%) and ampicillin plus cefotaximeto 6(4.3%). Second line therapy was needed in only15(29%) children. The commonly prescribed was a combination of vancomycin and meropenem. The total duration of stay in hospital was for 10-14 days.

Conclusion: Our study concluded that first line antibiotic therapy is still an effective treatment for acute bacterial meningitis. So, in the wake of emerging antibiotic resistance, irrational use of antibiotics should be avoided.

Keywords: Acute bacterial meningitis, first line antibiotics, second line antibiotics, antibiotic resistance.

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Introduction

Acute bacterial meningitis is one of the major causes of febrile illnesses in childhood.[1] It is still a major cause of morbidity & mortality in infants and children of age less than five years. Each year, in Pakistan about 23000 children die because of acute bacterial meningitis.[2] Acute bacterial meningitis results from hematogenous dissemination of microorganisms from a distant site of infection. More than sixty percent cases of meningitis develop during first two years of

life, owing to weak immune system, partial vaccination, and high vascularity of the brain.[3] The clinical presentation of bacterial meningitis is often vague in infants and children because of the immaturity of central nervous system in less than five years age, so there should be a high index of suspicion.[4] Acute bacterial meningitis therefore should be considered as a neurological emergency and early treatment with intravenous antibiotics is highly recommended. If left untreated, mortality may approach 100% but with recent developments in antibiotic preparation and with advanced intensive care, the meningitis related mortality has been reduced to approximately 5-10%. Worldwide, the risk of neurological sequelae in survivors of acute bacterial meningitis approaches 20%.[5]

Most common etiological organisms are streptococcus pneumoniae, Hemophilus Influenzae type b, Neisseria meningitides, group B streptococcus, E. coli and Listeria monocytogenes. Since the introduction of Hib and pneumococcal conjugate vaccine, there is an overall reduction in incidence of acute bacterial meningitis. However, the mortality from acute bacterial meningitis remains substantial and the case fatality rate did not change.[6] Slack M et al reported in 2015 that Hib still accounts for >29,000 deaths worldwide in children of age <5 years, while up to 40% children can suffer from permanent disabilities. It is therefore essential for clinicians to recognize the clinical signs and symptoms of bacterial meningitis and perform cerebrospinal fluid examination to confirm the diagnosis of meningitis. Although for confirmation of diagnosis of acute bacterial meningitis, the microbiological culture of the cerebrospinal fluid (CSF) is considered to be the gold standard.[8] However, this method is time-consuming and furthermore, there is low bacterial growth owing to prior antibiotic use. Moreover, the sensitivity of culture is also seriously hampered by use of antibiotics prior to cultures (both blood and CSF). Emergence of microbial resistance has further added to the complexity of managing this problem. Therefore, where available, use of PCR (polymerase chain reaction) can give rapid results and is also sensitive. This can improve the speed and accuracy of detection of pathogens like Hib and pneumococcus.[9]

Treatment of bacterial meningitis depends largely on using intravenous antibiotics targeted to the suspected organism according to prevalent organism for each age group and generally involves a treatment with third generation cephalosporin. Special consideration is given to the ability of drug to cross the blood brain barrier. Despite antibiotic therapy numerous patients experience severe neurologic complications and sequelae.[10] To decrease morbidity and mortality; clinicians therefore are jumping to 2nd and 3rd line antibiotics in the absence of culture sensitivity reports. This in return is further adding to the problem of increasing antimicrobial resistance. Present study therefore was conducted to determine the effectiveness of 1st line antibiotics in treating acute bacterial meningitis in children admitted in a public sector hospital.

Material and Methods

This cross- sectional analytic study was conducted in department of Paediatrics, Pakistan Institute of Medical Sciences Islamabad over a period of 6 months from January 2019 to July 2019. 51 patients of both genders, between ages of 1 month till 12 years admitted in pediatric medicine ward during the study period with signs and symptoms and positive CSF findings suggestive of meningitis were enrolled in the study. Non-probability, consecutive sampling technique was used. Children with diagnosis of recurrent bacterial meningitis, children already receiving oral or intravenous antibiotics treatment for this illness, and children with spinal malformation and hydro-cephalous were not included in the study. Children presenting with fever, fits, altered state of consciousness, having a bulging fontanelle, increased body tone, neck stiffness, positive Kernig's or Brudzinski sign plus positive CSF findings were assigned the diagnosis of acute bacterial meningitis. A total of 51 patients fulfilling the inclusion criteria, were enrolled in the study. Ethical approval was taken from IRB. Informed consent was taken from parents before enrollment of the child in the study and before performing lumbar puncture. Demographic details were recorded in the proformas for the study purpose. Children were then started with first line antibiotic therapy according to the recommendations for that age group which included ceftriaxone alone or a combination of ampicillin with cefotaxime or cefotaxime with amikacin. All children were closely observed in pediatric ward for progression or resolution of signs and symptoms. If symptomsdo not improve within 48-72 hours of starting intravenous antibiotic therapy, then second line antibiotics were started. Second line antibiotics in our study included addition of vancomycin with ceftriaxone or a combination of vancomycin with meropenem. Improvement of general condition of child, duration

of hospital stay and any complication during stay in hospital for treatment purpose were also noted in the proforma along with report of cerebrospinal fluid including biochemistry, cytology and culture.

Data was analyzed by using SPSS v. 22. Gender, duration of hospital stay, antibiotics, steroid use and vaccination status were presented as frequency and percentage. Age, CSF findings were presented as mean ± Standard deviation.

Results

The mean age of children included in the study was 3.23±3.31 years. There were about 25(47.8%) children of age <1 year, 12(24.2%) children were of age 1-5 years while 14(28.0%) were of age > 5 years (up to 12 years). There were 33(65.1%) males and 18(34.9%) females (Table-1). Complete vaccination was done in only 20(39.2%) children while 31(60.7%) children had either incomplete vaccination or not vaccinated at all. First line antibiotics were started according to age specific recommendations (Table 2). Among them, Ceftriaxone was the most common antibiotic, which was prescribed to 32(62%) children, while a combination of cefotaxime with amikacin was prescribed to 13(25.4%) and a combination of ampicillin and cefotaximeto 6(11.7%) children (Table 2).

Second line therapy was given to only 15 children. The most commonly prescribed was a combination of vancomycin and meropenem 8(15.6%), followed by a combination of ceftriaxone and vancomycin to 3(5.8%) children. Tanzobactum and cefepime were prescribed to 4(7.8%) children. In addition to antibiotics steroids were given to 38 (52.7%) children as a part of treatment of meningitis. (Table-2) Out of 51 children, 18(35.2%) stayed at the hospital for >14 days while 33(64.7%) children stayed for <14 days in the hospital. (Fig-1)

Table 1: *Characteristics of children with bacterial meningitis*

Demographic detail	Total(N=51)	Percentage
Age		
1 month-12 months	25	(47.8%)
1-5 years old	12	(24.2%)
> 5 years	14	(28.0%)
Gender		
Male	33	(65.1%)
Female	18	(34.9%)
Vaccination status		
Completely vaccinated	20	(39.2%)
Incomplete/no vaccination	31	(60.7%)

Table 2: *Distribution of First Line and Second Line Antibiotics.*

First line antibiotics	Total(N=51)	percentage
Ceftriaxone	32	(62.7%)
Cefotaxime + Amikacin	13	(25.4%)
Ampicillin + cefotaxime	06	(11.7%)
Second line antibiotics		
Vancomycin + Meropenem	8	(15.6%)
Vancomycin + Ceftriaxone	3	(5.8%)
Tanzo/ cefepime	4	(7.8%)
Steroids		
Given	38	(74.5%)
Not given	13	(25.4%)

Table 3: *Age wise distribution of first line antibiotics.*

Age	Choice of 1st line antibiotic
1-2 months	Cefotaxime + Amikacin
2-3 months	Ampicillin + cefotaxime
> 3 months age	Ceftriaxone

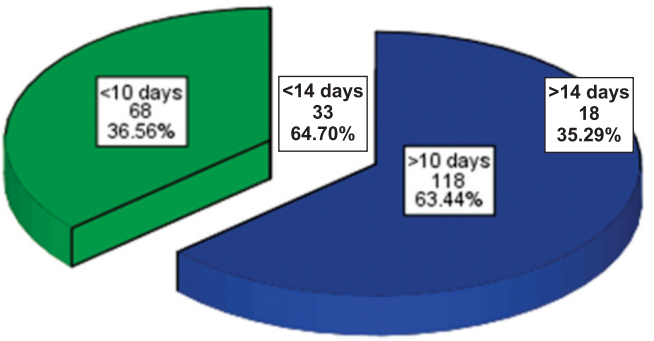

Fig 1: *Distribution of Hospital Stay*

Discussion

The invention of antibiotics has significantly improved the outcome of patients with severe infections. Antibiotics discovery has also improved the prognosis of several infectious diseases and outcome of surgical procedures. The capability of antibiotics to cure and prevent infections has considerably improved the quality of life and has decreased mortality rate significantly along with improving the morbidity. However, the injudicious and extensive use of antibiotics, especially when available over-the-counter and where not indicated

has caused the emergence of multi-drug resistant bacterial strains. These emergent bacterial strains fail to respond to the conventional antibiotic therapies.[12] This is an emergency health concern which poses a threat noticeably in low and middle income countries because of easy availability of antibiotics and poor regulations by the government.[13] Many general practitioners (GPs) and unlicensed health care providers prescribe broad spectrum antibiotics even for mild, self-limiting infections and viral illnesses.[14] World health organization (WHO) has thus placed antibiotic stewardship program at the heart of its Global Action Plan to curb antibiotic resistance.[15] Recently, a significant increase has been noticed in these pathogenic strains, which thus limits the choice of antibiotics against severe infections. Antibiotics are essential for the success of certain commonly performed surgical procedures which includes gynecological and orthopedic along with general surgeries and transplant procedures. The resistance to antibiotics is growing in all type of pathogens, particularly noticeable are methicillin resistant staphylococcus aureus and salmonella typhi.

In our study, there were 33(65%) males and 18 females (34%), which were comparable to another study where males were more affected with bacterial meningitis. This can be attributed to good immune status of females.[16] Predominant age group of children affected in our study was of less than 1 year 25(47.8%) which are comparable with another study which showed that patients of extreme ages are more affected with bacterial meningitis owing mainly to their weak immune system. Also children in this group are mostly unvaccinated or partially vaccinated owing to multiple factors.[17]

Our study showed that microorganisms are susceptible to 1st line antibiotics as 2nd line antibiotics were used in only 15(29%) patients. Our results of good response to first line antibiotics are comparable with another study which showed that pneumococcal isolates were not found resistant to ceftriaxone and vancomycin.[18] Although in our study very few bacteria were isolated so sensitivity of antibiotic spectrum could not be assessed with certainty but clinical response to first line antibiotics was very good.

However, our results of good response to first line antibiotics are in contrast to the list published by world Health Organization in 2017 in which it has placed H. Influenzae and streptococcus pneumoniae in medium priority list 3 of pathogens in need of new antibiotics.[19] This can be attributed to the overuse of extended spectrum of cephalosporins. Study by H Bilal et al also shows resistance of E. coli to ampicillin and 100% susceptibility to colistin and 92% to meropenem.[20] This is a point of concern as these antibiotics (colistin and meropenem) are considered third line or sometimes fourth line antibiotics.

Development of antibiotic resistance by Enterobacter species causes a high mortality, prolonged hospital stay, and increased cost of treatment involved during the hospital stay. Resistance of Enterobacter species should thus be primarily minimized.[21,22]

After several years of discovery and use of antibiotics against infection control, bacterial infections are again becoming a great risk, owing largely to unnecessary use. We are threatening their availability for our future generations so that they can enjoy infection free atmosphere.[23] The crisis of antibiotic resistance occurred due to the overuse as well as misuse of antibiotics, coupled to the lack of development of new antibiotics by pharmaceutical industry owing mainly to the decreased economic incentives and thought-provoking regulatory requirements.[24] A combination of dropping profits, monitoring system by government and inappropriate and inadvisable use of antibiotics by clinicians is hereby-leading to this alarming situation.[25]

Conclusion

Thus in our study, first line antibiotic therapy was effective in 80.6% cases and the need for second line therapy was needed in only 29.4%. Thus to prevent the emergence of antibiotic resistant strains, it is recommended to start empirical treatment with first line antibiotics which can later be changed according to the response to treatment and culture sensitivity reports. Every hospital should develop SOPs (standard operating protocols) for starting the first line and second line antibiotic regimens which should be practiced in their hospital for treating severe infections in admitted patients.

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Authors Contribution

AA: Conceptualization of Project
TB: Data Collection
AK: Literature Search
TB: Statistical Analysis
HA: Drafting, Revision
HRS: Writing of Manuscript

To Compare the Effect of Competitive and Non-Competitive Environment On Academic Performance in Medical Students

Saira Nawaz,[1] Neesha Naveed,[2] Bilal Nazar,[3] Muhammad Hasham Akram Chaudhry,[4] Amna Nadeem Kazi[5]

Abstract

Objectives: To compare the effect of competitive and non-competitive environment on academic progress of students, to assess the effect of competitive environment on motivation levels, anxiety levels and learning strategies of students.

Methods: This is a cross-sectional study. In this, we assigned target to all the students in one exam (Module 2 Pathology) to create competitive environment. For a non-competitive environment, no target was assigned and students gave their exam (Module 1 Pathology) without any target. The results were taken by informed consent of students. The whole procedure was explained efficiently to the students. To keep the results accurate students were unaware about the non-competitive environment.

Results: We found that students performed academically better in competitive environment rather than in non-competitive environment. Positive correlation was found between competitive environment and exam results. We also found positive correlation between motivation and learning strategy and compared them between boys and girls. We also found correlation between sleep hours, study hours and academic progress in competitive environment.

Conclusion: Competitive environment in institutes is good for better and improved academic performance. However, it effects the motivation level, anxiety level and learning strategy of students.

Keywords: competitive environment, non-competitive environment, academic progress, motivation levels, anxiety levels, learning strategy.

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Introduction

Including competition in any environment causes the change of behavior and people tend to become more focused. Competitive learning is when students prepare for exam keeping a target in mind. Competitive environment may enhance student's motivation or may increase their attention towards their goal, to win from others, to improve their learning strategies. It may have a negative aspect that probably it causes participants to focus more on competition than the quality of learning and students may get anxiety attacks or become stressed.

Previously, in a study the effect of cross-lagged study on student's motivation, academic achievement and relation with teachers was observed (Majolein et al, 2020).[1] Student's task motivation and relation with teacher was observed via models of student-teacher interaction. It was found that student's motivation and its relation with teacher has better impact on academic grades. In another research, the relation between student's satisfaction and academic progress was analyzed (Mahad and nor Abdulle, 2016)[2]. Some other factors effecting the academics were also explored. It was found that

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student's satisfaction has positive impact on academics. Another research was conducted to find out the factors effecting the student's performance (Irfan and Shabana 2012).[3] The main aim was to correlate the communication approach, facilities, guidance and family stress. It was concluded that all these factors have impact on performance of students. In another research, the effect of team based learning on academic results were analyzed (Koles et al, 2010).[4] The effect of participation in TBL on academics was analyzed. Also it was determined that TBL whether increases or decreases the performance. In another research, the effect of teaching methodology on academics was observed. (Hinojo Lucena, 2020).[5] In that study, students mark sheets were analyzed. It was observed that student-teacher interaction method was most effective. In another research, it was investigated whether the competition is useful to promote performance or not. (Frank C Worrel et al, 2016).[6] The relation between competition and performance was analyzed. The effect of competition on psychology, performance and creativity was observed. In another research, the relation between academic performance and motivation was observed on medical students (Blašková M et al, 2019)7 It was observed that competition and tasks used as motivational source shows better results.

Materials and Method

This was a cross sectional comparative study. The research was conducted in CMH LMC & IOD. Duration of research was: December 2020 – March 2021. Participants were undergraduate medical students of CMH LMC & IOD. All the undergraduate medical students were selected currently studying in CMH LMC & IOD. Only those were included who gave written consent to use their results for this research purpose. Convenient sampling technique was used. The formula used for calculating sample size was N= [(Zα/2+Zβ)22 (Sd)2]/ (μ1- μ2)2. The sample size calculated was 137. Sleep hours were calculated by question form filled by participants along with consent form. Informed consent was taken. Data was collected by mark sheets of students who gave their consent. In this, we assigned target to all the students in one exam (Module 2 Pathology) to create competitive environment. For non-competitive environment, no target was assigned and students gave their exam (Module 1 Pathology) without any target and then we compared the results of both modules. The data was analyzed by using SPSS25. Test of normality was performed. Mann Whitney test was applied. Results were expressed as mean±SD. Correlations were also found.

Results

We found the mean of both results of the pathology module1 and module 2 examinations, which were 49.9 and 54.9 respectively. A positive correlation was found between the competitive environment and the results.

Table 1: *Statistics 1*

Biostats	Module 1	Module 2
Mean	49.99	54.93
Std. Deviation	16.605	14.624

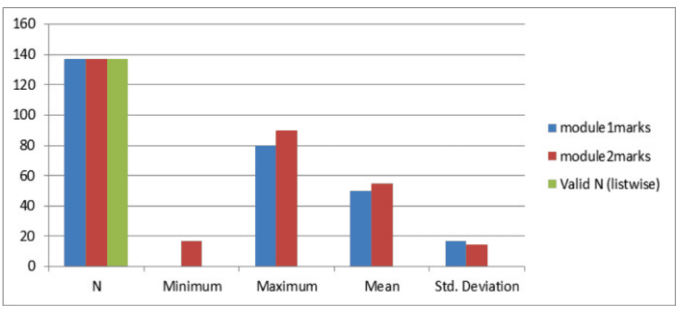

Table 2: *Correlations 1*

Correlation variable	gender		Yes/no	Yes/no	Yes/no
Motivation level	Male, female	correlation	1.00	0.423	0.070
		significance	.	0.00	0.421
Learning strategy	Male, female	correlation	0.423	1.000	0.018
		significance	.000	.	0.836
Anxiety attacks	Male, female	correlation	0.070	0.018	1.000
		significance	0.421	0.836	.

Table 3: *Correlations 2*

		Module 2 marks	Study hours	Module 2 marks	Sleep hours
Module 2 marks	Correlation	1	0.154	1	-0.082
	Significance		0.072		0.338
Study/sleep hours	correlation	0.154	1	-0.082	1
	Significance	0.072		0.338	

Also, positive correlation was found between motivation and learning strategy, as shown in correlation 1. It was found that a competitive environment enhances the motivation level, learning strategy and anxiety levels of students. Girls had higher motivation levels than boys. It was also seen that girls had improved learning strategies. However, they got more anxiety attacks shown by correlation 1. In correlation 2, we found a relation between the results of the competitive environment with sleep hours and study hours. Students with fewer sleep hours and more study hours had a better academic performance.

Discussion

By setting a target and by creating the competitive environment, the academic performance of students got better as the mean of module 2 was more than module 1 which showed that competitive environment had positive impact on academics (as shown by Statstics1)

A research of[8] Alfredo Corell et al, 2018, is consistent with ours. It was found that results of competitive group were higher than control group students. Competitive learning improved their results. It was found that competitive environment also enhances the motivation level, learning strategy and anxiety level of students. It was seen that girls had higher motivation levels than boys. It was also seen that girls had enhanced learning strategies and also got more anxiety attacks than boys (As shown by Correlation 1). A research of[9] Mimi Bong, 2005 is consistent with ours. In that research it was found that Korean school girls have more motivation level in learning environment. In another research of[10] Andrew J Martin,2003, it was found that girls score more than boys and have more learning focus and study management. It was found that study hours and sleep hours were also affected by competitive environment and had effect on academics. Students with fewer sleep hours and more study hours had better academic results. (As shown by Correlations 2) A research of[11] Andrew J Howell et al, 2004, showed that sleep quality and sleep propensity have effect on student's GPA. Students with poor sleep quality performed less well. Another research of[12] Megan L Zeek et al, 2015, showed that sleep hours were positively associated with grades. By the correlations 1, we found that relation between motivation, learning strategy and anxiety was significant whereas the relation between anxiety and learning strategy was not significant which meant although anxiety levels were high but it had no effect on learning outcomes.

Conclusion

The competitive environment in institutes is good for better and improved academic performance. However, it enhances student's motivation, anxiety and learning strategy. Having fewer sleep hours and more study hours results in better academic performance.

Conflict of Interest *None*

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Authors Contribution

ANK: Conceptualization of Project
NN: Data Collection
NN: Literature Search
BN: Statistical Analysis
HAC: Drafting, Revision
HAC: Writing of Manuscript

Effect of COVID-19 Pandemic on Presentation and Outcomes of Gallstone Disease

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Abstract

Objective: To determine the effect of Covid-19 pandemic on presentation and outcomes of gallstone disease and to compare them with the pre-covid time.

Methods: it is a retrospective observational study conducted in surgical emergency department of holy family hospital, Rawalpindi. Data of all the patients presented to emergency department (ED) from April to August 2020 (Group I) and in the same months of 2019 (Group II) was collected retrospectively. More patients presented with complicated gallstone disease in emergency department during COVID'19 than in pre-covid time. Covid'19 is an independent risk factor for presentation of patients in emergency department with complications.

Results: There were 108 (53%) patients in Group I and 95 (47%) patients in Group II retained in emergency department (ED) of General surgery, holy family hospital, Rawalpindi. There were more patients admitted through ED in Group I than in Group II (63[58%] vs 40[42%] p-value 0.003). In Group I patients, duration of symptoms was prolonged before reaching ED than Group II (3.55+1.45 vs 2.86+1.32 days, p-value 0.001). Moreover, patients presented with more severe disease assessed by Tokyo criteria and number of patients with complicated gallstone disease in Group I were also higher (p-value 0.01).

Conclusion: During covid-19 pandemic, patients were reluctant to attend hospitals for elective surgeries as a result of fear of the COVID'19. Moreover, due to cancellation of elective procedures during lockdown, there were more patients admitted through Emergency Department with severe and complicated gallstone disease. Hence COVID19 is an independent risk factor for presentation of patients in ED with complications.

Keywords: Covid-19, gallstone disease, complicated gallstone, surgical emergency.

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Introduction

All community members have been affected by the Corona virus Disease 2019 (COVID-19) outbreak, which has caused significant disruption in all spheres of life.[1] On January 7, 2020, Chinese authorities identified this viral strain.[2] The healthcare system had to expand its capacity to handle the influx of patients, preserve the maximum amount of hospital resources, and reduce infection risk as much as possible during the COVID-19 pandemic. In this regard, the healthcare system agreed to reduce elective surgical treatments globally in March 2020.[3,4]

To stop the spread of the corona virus infection, the nations enacted preventative measures like lockdown and movement restrictions. This had an effect on the population's mental health and, as a result, made many reluctant to seek medical treatment for their problems.[5] This led to increase the morbidity in even manageable diseases. By June 30, 2020, an estimated 41% of U.S. people had postponed or avoided medical care, including urgent or emergency care (12%) and routine care (10%), due to worries about COVID-19 (32 percent). Unpaid caregivers for adults as well as people with underlying

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medical conditions were more likely to avoid urgent or emergency care.[6]

One of the most common medical problems that necessitates surgery is still gallstone disease. About 20% of people over the age of 40 and 30% of people over the age of 70 have biliary calculi. The ratio of women to men in reproductive years is around 4:1, with the gender disparity narrowing to almost equality in the proportion of senior persons.[7] The symptoms of gallstone disease range from being asymptomatic to being symptomatic, the latter of which includes both acute pain bouts and severe disease. There is a high likelihood that symptomatic sickness may return and require cholecystectomy. Although sex, age, BMI, and the characteristics of gallstones detected by ultrasonography are all factors that affect the progression of disease from an asymptomatic to a symptomatic state, pandemic conditions and patients' reluctance to visit hospitals for follow-up also contributed to progression and compilations.[8] The 30-day overall mortality, length of hospital stay, conversion rates to open surgery, and medical costs were all substantially correlated with the TG13 severity grading for acute cholecystitis, which is frequently used to grade the severity of gall stone illness.[9]

The most effective method of treating benign gallbladder diseases is laparoscopic cholecystectomy. To finish the process securely in some situations, the protocol must be changed to open cholecystectomy. The three most frequent intra-operative findings resulting in conversion were inflamed gall bladder, adhesion, and anatomic difficulties. Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic biliary sphincterotomy and stone extraction is the gold standard for the treatment of common bile duct (CBD) stones as part of complication[11].

The objective of our research is to see how COVID-19 affects the presentation or severity of presentation and outcomes of gall stone disease, which is a prevalent reason for patients to wind up in the surgical emergency department. The goal of the study is to document the impact so that public awareness campaigns can be launched to reduce the number of emergency room visits.

Materials and Methods

A retrospective observational study was conducted at surgical emergency department, Holy family hospital, Rawalpindi. After endorsement from the ethical committee, data of all the patients with diagnosed gall stone disease, presented to emergency department (ED) from April to August 2020 (Group I) and in the same months of 2019 (Group II) was collected retrospectively. Data of all the patients including their demographics, clinical findings and duration of symptoms was retrieved and filled out on the form. Outcomes noted were number of admissions, severity of disease, number of complicated gallstones and total length of hospital stay were all reviewed and entered into the respective form. Data entry and analysis were all done using SPSS vs 26. Descriptive analysis was performed. The relative risk of complicated gall stone disease presentation among patients in COVID'19 durations was calculated.

Results

There were 203 patients retained overall in surgical emergency department (ED) of holy family hospital, Rawalpindi. There were 108 (53%) patients in Group I (between April – July 2020) and 95 (47%) patients in Group II (between April – July 2019). Median age was 48 (18 – 66) years with a female predominance of 63%. There was no difference with respect to age, gender, BMI, co-morbid and presenting symptoms between two groups as shown in **table I**.

Group II patients presented earlier in ED while Group I patients presented late (2.86+1.32 vs 3.55+1.45 days; p-value 0.001). There were higher number of admissions through ED in Group I as compared to Group II (63 [58.3%] vs 40[42.1%]; p-value 0.003). Moreover, patients presented with more severe and complicated gallstone disease assessed by Tokyo criteria (p-value 0.01) as shown in **table II**.

Out of 203 patients, 137 (67.5%) patients were managed conservatively by giving iv antibiotics and analgesics; 19(9.4%) patients underwent ERCP for cholangitis and choledocholithiasis; 33 (16.2%) patients were admitted for laparoscopic cholecystectomy due to empyema gallbladder and acute cholecystitis; 14(6.9%) patients were admitted for laparoscopic cholecystectomy but later converted to open cholecystectomy due to dense adhesions with surrounding structures and intraoperative bleed. Seven (3.5%) patients developed complications postoperatively; 5 patients had wound infection and 2 patients had intraabdominal collection which were managed conservatively by iv antibiotics and ultrasound guided aspiration of the collection. There was no statistically significant difference in terms of management and length of hospital stay as shown in table II.

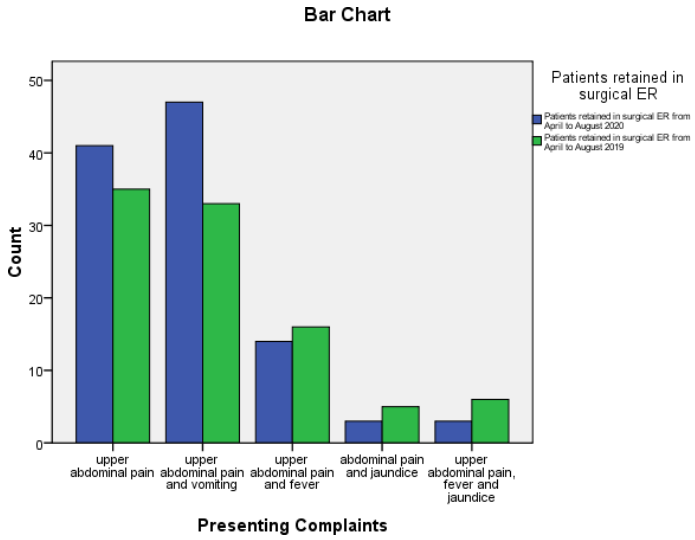

Table 1: *Groups Comparison on the Basis of Demographics, Commorbids And Symptom Complex:*

Patients retained inER		Group I (n= 108)	Group II (n= 95)	P-value
Age (yrs)		41.08±11.37	40.73±11.09	0.82
Gender	Female	69	59	0.79
	Male	39	36	
BMI (kg/m^2)	18.5-24.9	11	13	
	25-29.9	68	60	0.82
	30-34.9	27	21	
	35-39.9	2	1	
ASA	I	66	62	
	II	31	26	0.7
	III	11	7	
Diabetes mellitus		30	25	0.81
Hypertension		41	34	0.75
IHD		13	8	0.49
COPD		2	1	0.64
Symptoms of Disease	Upper abdominal pain	41	35	
	Upper abdominal pain and vomiting	47	33	
	Upper abdominal pain and fever	14	16	0.4
	Upper abdominal pain and jaundice	3	5	
	Acute cholangitis	3	6	
Duration of Symptoms before ER consultation (days)		3.55±1.45	2.86±1.32	0.001

Discussion

The dynamics of practically every area of our civilization have been dramatically altered by the corona virus pandemic, let alone the healthcare industry. Surgery has an impact on both acute and elective surgical care, affecting benign, slowly developing, and readily curable illnesses like cholelithiasis as well as urgent pathologies. Our retrospective cohort analysis shows how the severity and side effects of gallstone disease varied between Covid-19 and before. During the pandemic, patients with gallstone disease had more severe symptoms. The patients who presented to the surgical ER during the times of COVID-19 had disease severity of grades 2 and 3, in contrast to those who presented at the same time a year before to COVID-19. This was obvious using the Tokyo criteria. The delay and interruption of surgical procedures at surgery departments as well as a lack of presentation to surgical outpatient departments due to a preventative fear of contracting Covid-19 could be the plausible explanation for this striking difference in the severity of the disease between the two groups. Additionally, since the patient influx was on the rise, the majority of resources, including ICU and other healthcare institutions, were devoted to fighting Covid-19. In a related study, the department of surgery at Stanford University School of Medicine discovered that, as measured by higher Tokyo criterion scores, more patients presented with severe cholecystitis during Covid-19 as compared to pre-covid periods. (mean SD = 1.39(0.56) vs 1.16 (0.44); p=0.02)1.

Table 2: *Comparison of Different Parameters Between*

Parameters		Group I (n= 108)	Group II (n= 95)	P-value
Outcomes	Admitted cases	63 (58%)	40 (42%)	0.003
Preoperative diagnosis	Complicated gallstones	63	40	0.01
Severity of disease	Grade 1	47	60	
	Grade 2	61	35	
	Grade 3	8	2	0.01
Management	i.v antibiotics and fluids	71	66	
	Underwent ERCP	11	8	
	Lap cholecystectomy	17	16	0.8
	Lap converted to open cholecystectomy	9	5	
Inpatient complications		5	2	0.32
Total length of hospital stay (days)		7.15±4.6	7.01±4.5	0.83

As evidenced by the higher number of patients kept in

the ER during COVID-19 than during 2019, the surgical ER was overrun with patients with serious gallstone disease during 2020. Furthermore, Group I had a higher prevalence of the complex condition than did Group II. As noted by Harnett and Wong, we believe that this is likely the result of a delay in presentation brought on by worry about getting the pandemic and the use of painkillers and over-the-counter treatments to ease gallstone-related abdominal pain.[12,13]

Our work has also emphasized and contrasted the surgical methods necessary for the main treatment of gall stones in the two research groups, as demonstrated by Gabriel Sandblom's work, which was published in the Scandinavian journal of surgery. It was discovered that Group I performed more laparoscopic cholecystectomies than Group II. In order to combat the pandemic, resources were reallocated and planned surgeries were postponed, which led to an increase in the number of acute procedures.[14]

It's interesting to note that Group I required more open cholecystectomies than Group II did (9.3% vs. 5.3%), perhaps as a result of the higher incidence of complications in that group. During COVID'19, a notably greater number of patients had their laparoscopic cholecystectomy procedures converted to open cholecystectomy procedures. This result also invalidates a related study by Franziska Koch, Sven Hohenstein, and Jorg-Peter Ritz in Germany, which showed that the number of cholecystectomies decreased significantly during the first lockdown but increased during the second lockdown due to a rise in patients presenting with complicated disease, necessitating open surgery to remove the gallbladder.[15]

Hospital discharge rates were yet another important factor that supported the results of our study. Similar studies were out at the Department of Surgical Sciences, University of Rome Tor Vergata, Italy, revealed that treatment delays were unavoidable for benign hepatobiliary illnesses like gallstones. It was observed that cohort 1 had a discharge rate from ER of 29% while cohort 2 had a discharge rate of 52%. Surprisingly, during the months of April through December 2020, 14 out of 63 patients who were admitted through the emergency room were discharged with a follow-up procedure, as opposed to 6 out of 40 patients during the previous year.[16]

Recommendations are that "Mass campaigns and Telemedicine" to be made more common and information to be disseminated regarding risk factors and complications to masses associated with gall stone diseases around the clock so that worse case scenarios can be avoided. More and more patients to be registered via online ways and to be approached on regular basis to analyze the disease progression so that timely decisions can be made. This also is the lesson to combat future pandemics and targeted steps to be taken in time for the benefit of patients. National and international policies to be made to overcome such scenarios where patient suffers from partial closure of health system as we saw in case of Covid.[19]

Conclusion

Patients were hesitant to go to hospitals for elective surgery during the COVID-19 pandemic out of dread of the pandemic. Furthermore, more patients with severe and difficult gallstone disease were admitted through the ED as a result of the cancellation of elective treatments during the lockdown.

Conflict of Interest: *None*

Funding Source: None

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Authors Contribution

SMD: Conceptualization of Project
HZ: Data Collection
MKB: Literature Search
SMD: Statistical Analysis
UQ, GR: Drafting, Revision
JSK: Writing of Manuscript

Evaluation of Helicobacter Pylori Infection Prevalence in Patients with Portal Hypertensive Gastropathy in Pakistani population-A single centered study

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Abstract

Objective: To evaluate the prevalence of Helicobacter pylori in patients with portal hypertensive gastropathy in the Pakistani population.

Method: A descriptive cross-sectional study was performed on ninety patients presenting with PHG. A gastric biopsy was taken from each patient followed by histopathology for the presence of H. pylori infection.

Results: Out of ninety patients, H. pylori was found in thirty (33.3%) patients while sixty (66.7%) patients were negative for H. pylori infection. A significant prevalence of H. pylori was found in patients aged more than 50 years OR=3.50, 95% CI=1.372-8.926, (p=0.007). Moreover, gender and BMI were found insignificantly associated with H. pylori infection.

Conclusion: In conclusion, the present study revealed a significant prevalence of H. pylori infection in patients with PHG and the prevalence rises in elderly age patients in the local Pakistani population.

Keyword: H. pylori, Peptic Ulcer Disease, Portal hypertensive gastropathy, Liver cirrhosis

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Introduction

The most common pathogen causing peptic ulcer disease declared to be due to Helicobacter pylori (H. pylori), gram-negative microaerophilic bacterium that affects approximately half of the world's population, although substantial regional variation exists.[1] Generally, the prevalence of H. pylori infection tends to be high in regions of world that are underdeveloped but varies in different regions and increasing age predisposes one's to this infection. In individuals below the age of 30 years and those with an average age of 60 years, the sero-prevalence of H. pylori is approximately 30% and 63%, respectively.[2] Better living standards improve the decline in the incidence of infections in most of the developed countries where the incidence is less than 40% in the total population.[3,4] In the early stages of life, various stomach-related diseases including gastric cancer, peptic ulcer, and mucosa-associated lymphoid tissue disorder are risk factors associated with H. pylori infection while duodenal involvement is the mainly present in the later course of the disease.[5,6] Fecal-oral and oral-oral pathways are the most common route of transmission of the disease.[6] Living conditions that facilitate intimate contact between persons, such as crowded conditions and bed-sharing, are some physical risk factors for transmission.[2]

About 20 to 80% patients with portal hypertension have PHG, presented as upper gastrointestinal hemorrhage as a result of bleeding varices due to PHG.[7,8] Like other developing countries, more than 80% of the Pakistani population is also affected from H. pylori.[9] Knowing the frequency of H. pylori infection in local population with peptic ulcer disease might impact the management of the disease with poor sanitation in the form of prevention. As the gastro-intestinal complications associated with H-Pylori infection not always observed in patients with PHG.[10]

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The study rationale was to determine the prevalence of H. pylori in patients with Portal hypertensive gastropathy presenting in a tertiary care hospital. Literature data have shown that these patients have more susceptibility to H. pylori infection but some researchers have shown debatable findings. Data regarding the H. pylori infection in patients with Portal hypertensive gastropathy in the Pakistani population is scanty. The current study aimed to find the prevalence and risk of H. pylori infection with different demographic features in cases with portal hypertensive gastropathy from the Pakistani population.

Material & Methods

This cross-sectional study was conducted in Department of Gastroenterology, Jinnah Hospital, Lahore, and was dully approved by the Ethical Review Board of the institute in accordance with the declaration of Helsinki. For the study, ninety patients (42 males, and 48 females; mean age 48.87 years), diagnosed as infected with H-pylori infection detection in stool specimen were recruited. Patients of age 20-70 years either gender presenting with portal hypertensive gastropathy were included while patients having prior treatment for H. pylori eradication despite infection with HCV, HIV, and HBV viruses were excluded from the study. Informed consent was taken from each participant before his/ her enrolment while maintaining the confidentiality of the data record. Demographic information including age, gender, BMI, duration of cirrhosis, and duration of portal hypertension was recorded followed by endoscopy and biopsy for diseases presence/absence of H. pylori.

Data was presented as descriptive statistics i.e. Mean & Standard Deviation (SD) for vari-ables; age, gender, BMI, duration of cirrhosis, and dura-tion of portal hypertension. All statistical analysis was performed using SPSS version 21.0. The frequency and percentage were calculated for the qualitative variable gender and H. pylori. Post-stratification, the chi-square test was applied to compare H. pylori in stratified groups taking p-value ≤ 0.05 and odd ratio (OR) with a 95% confidence interval (CI) was considered as statistically significant.[11]

Results

The demographic and clinical information were calculated and summarized in (Table. 1). Amongst the enrolled cases, 53.33% were females and 46.67% were males (Figure. 1A) with a mean disease duration of 11.47

Table 1: *Demographic and Clinical information of the patients. [SD: Standard deviation; BMI: Basal metabolic index]*

Variables	Subjects (n=90)
Gender n (%)	
Male	42 (46.7)
Female	48 (53.3)
Age mean ±SD years	48.86±7.76
Elderly (n=)	
(20-49 years)	45 (50%)
Male	21
Female	24
(50/more than 50 years)	45 (50%)
Male	21
Female	24
Disease Duration mean ±SD years	11.46±5.02
1-5 years	15 (16.7%)
6-10 years	33 (36.7%)
More than 10 years	42 (46.7%)
BMI mean± SD kg/m2	22.86±1.86
22 or below n (%)	33 (36.7%)
More than 22 n (%)	57 (63.3%)
Frequency of disease presence on biopsy n (%)	
Present	30 (33.3%)
Absent	60 (66.7%)

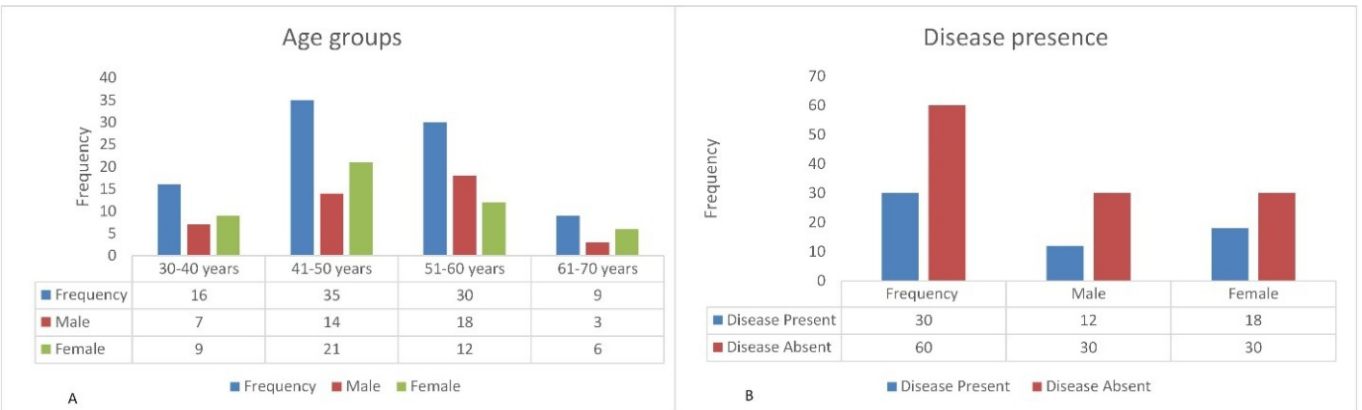

Fig-1. *Bar chart represent the age group with gender (A); Bar chart represents the disease presence in patients (B)*

years and the majority of the patients having a disease duration of more than 10 years. The age ranges (from 38 to 64) with a mean age of 48.87 years. The average BMI was observed at 22.87 with a range (from 19 to 26) kg/m^2. The frequency of H. pylori in patients with PHG was measured n=30 (33.3%) while 60 (66.7%) patients with absent disease (Figure. 1B). The relationship between demographic and H. pylori infection revealed that patients more than the age of 50 years have more susceptibility OR=3.50, 95%CI=1.372-8.926, (p-value=0.007) while gender and BMI show insignificant association OR=0.667, 95%CI=0.274-1.621, (p-value=0.370); OR=1.238, 95%CI= 0.502-3.054, (p-value= 0.643) respectively, with H. pylori infection **(Table. 2)**. Logistic regression analysis revealed that both age and BMI might be a risk factor for the disease i.e. with the increase in age (OR=1.083, 95% CI= 0.977-1.202) and BMI (OR = 1.189, 95%CI=0.900-1.571) of the patients, the risk of having the diseases is also increased **(Table. 2)**.

Discussion

PHG remains a least common cause of significant upper GIT hemorrhage in people with portal hypertension, but hemorrhage is the most detrimental consequence. A large number of individuals (2–12%) experience acute upper gastrointestinal hemorrhage due to PHG.[8] More than 2% of individuals with PHGs reportedly experience significant bleeding, and 10% of PHGs cause anemia as a result of constant blood loss.[12] On the other hand, the relevance of H. pylori on liver cirrhosis and PHG is remain unclear.[13,14]

PHG can be identified with the help of endoscopes, with the characteristic features including angiodysplasia-like lesions, mucosal edema, pigmented black-brown spots, flat red spots, mucosal granularity, and mucosa with a reticulated mosaic-like pattern.[15,16]

The aimed of our study was to determine the prevalence of H. pylori infection in patients with PHG. There was 33.3% frequency for positive H. pylori infection while 66.7% patients of PHG were negative for H. pylori infection in biopsy sample after endoscopy. In terms of positive H. pylori infection, 12 males (13.3 %) and 18 female (20 %) were found affected. Our findings are in similar direction with the studies of Abbas et al.[17] Safwat et al.[18] and Eid et al.[14] where they found less than 50% infection rate in patients with PHG with no association of H. pylori infection with disease severity. Contrary to these finding, the study of El-Toukhy et al.[19] and Kim et al.[20] had reported the significant association of H. pyloric infection with diseases severity of PHG. Furthermore, multi-variant analysis was performed and results showed PHG patients with age more than 50 years have more susceptibility towards H. pylori infection (p=0.07) while gender and BMI doesn't show the association with H. pylori disease presence (p > 0.05). These findings are in agreement with the study of Hammad et al. where H. pylori infection was found associated with PHG patients with elder ages. [21] Assessment of patients with PHG for H. pylori infection is necessary for the diseases cure. PHG patients showed better recovery after H. pylori treatment that is because after the removal of H. pylori there is decrease in pro-inflammatory cytokines (TNF-α) synthesis thus imp-rovement in mucosal inflammation and PHG severity. To the best of our knowledge, this is the first study that revealed the frequency of H. pylori's infection on PHG patients. These findings have important relevance for our understanding of the etiology of PHG and how frequent H. pylori affects the PHG and susceptible to the elderly patients.

This study has several significant limitations, including

Table 2: *Comparison of variables with susceptibility of H. pylori infection [OR: odds ratio; CI: confidence interval; p-value is considered as statistically significant when ≤0.05 (in bold)].*

Variable	Category	Disease Present	Disease Absent	Crude OR (95% CI)	Crude p-value	Adjusted OR (95%CI)	Adjusted p-value
Gender	Male	12 (13.3%)	30 (33.3%)	0.667	0.370	0.565 (0.212-1.505)	0.253
	Female	18 (20%)	30 (33.3%)	(0.274-1.621)			
Age	Less than 50 years	21 (23.3%)	24 (26.7%)	3.50	0.007	1.083 (0.977-1.202)	0.130
	50 or more than 50 Years	09 (10%)	36 (40%)	(1.372-8.926)			
Disease Duration	1-5 years	9 (10%)	6 (6.7%)	0.52	0.056	0.95 (0.845-1.173)	0.955
	6-10 years	9 (10%)	24 (26.7%)	(0.38- 1.240)			
	More than 10 years	12 (13.3%)	30 (33.3%)				
BMI	22 or below	12 (13.3%)	21 (23.3%)	1.238	0.643	1.189 (0.900-1.571)	0.224
	More than 22	18 (20%)	39 (43.3%)	(0.502-3.054)			

the fact that it was conducted in a single tertiary hospital, involved less sample cohort, and had a limited follow-up duration. Therefore, more extensive multicenter trials with a large population size, would be necessary to validate the current investigation findings.

Conclusion

In conclusion, our study demonstrated that patient with portal hypertensive gastropathy has susceptibility to infection with Helicobacter pylori with a frequency of 33.33%. Moreover, patients above age of 50 years have a significant association with H. pylori susceptibility. However, H. pylori infection in patients is independent of gender and BMI. Therefore, it is suggested that PHG patients infected with H. pylori must have eradicated the H. pylori infection to combat the serious sequel of the diseases, with additional use of local protective agents like sucralfate.

Conflict of interest *None*

Funding Source *Yes*

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Authors Contribution

AP: Conceptualization of Project
SN, AP: Data Collection
FT: Literature Search
AP, SB: Statistical Analysis
HS, AP: Drafting, Revision
AP: Writing of Manuscript

Factors and Morbidities Associated with the Delayed Diagnosis of Congenital Heart Disease in Children Under 5

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Abstract

Objective: The aim of this study is to highlight the factors associated with the delayed diagnosis of Congenital Heart Disease and the resultant probability of developing life-threatening co-morbidities.

Method: A retrospective, population-based study was performed, consisting of 500 children with undiagnosed CHD, at Pediatric Medical Emergency, Children Hospital Faisalabad, from June 2021 to December 2021.

Result: According to the results, male predominance was observed (M: F = 1.3:1) with age ranging from 1 to 60 months. Most of them developed symptoms of CHD at or before the age of 1 month (n= 233; 47%) Only 62% were diagnosed at the age ranging between 2 to 6 months. Main factors for the delayed diagnosis of CHD were delayed first medical visit (n=230) and socioeconomic restraints (n=227). Main complications of CHD at the time of presentation were Hypovolemic shock (n=362; 72%) and Pulmonary Hypertensive Crisis (n=52; 10%).

Conclusion: The delayed diagnosis of CHD is associated with life-threatening complications and co-morbidities, which can be prevented with early diagnosis. The need of an hour is trained medical personnel, general public awareness, and easy access to specialized, well-equipped healthcare facilities.

Keywords: Congenital heart disease, pediatrics, morbidity, delayed diagnosis, complications

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Introduction

Congenital Heart Disease (CHD) is the most common congenital malformation worldwide.[1] In Pakistan, over 60,000 children are diagnosed with CHD every year.[2] However, the number of undiagnosed patients is much more. According to a study, 86 of 1000 Pakistani children with CHD die before they turn 5, about 44 die before the age of one month, accounting for 11% of total neonatal mortality rate.[3] The estimated prevalence of CHD is approximately 8 per 1000 live births.[3,4] Globally, the mortality rate of CHD patients has significantly declined and their quality of life is remarkably improved. But still, it accounts for a major portion of medical emergencies and pediatric health problems, worldwide.[1,4,5] By definition, CHD is structural or functional abnormality of the heart and/or the great blood vessels, that persists after birth.[6] There are over thirty-five types of CHD with variable clinical presentations. CHD is commonly divided into two sub-categories; This is a type of CHD where there is mixing of oxygenated and de-oxygenated blood.[6] The prominent presenting complaint is bluish discoloration of skin or Cyanosis due to low oxygen blood in the circulation, including Tetralogy of Fallot (TOF), Transposition of great vessels, Pulmonary Atresia, etc. It usually presents as medical emergency with obvious signs of CHD and cardiac de-compensation such as cyanosis, clubbing, respiratory distress, and congestive cardiac failure.[7,8] In this case, there will be no mixing of oxygenated and deoxygenated blood. The

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oxygen saturation in the blood will be adequate but the heart defect will result in the failure to supply the oxygenated blood efficiently throughout the body. It includes, Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD), Patent Ductus Arteriosis (PDA), Aortic Valve Stenosis, Pulmonary Valve Stenosis, and Coarctation of Aorta.[7] Usually asymptomatic at the beginning but reveals itself at a certain age with the presenting complaints similar to that of lower respiratory tract infections, indigestion/neonatal colic, or asthma. These types of CHD can be easily misdiagnosed by general physicians, require expert evaluation followed by confirmative/diagnostic echocardiography.[6,7] Delayed diagnosis of congenital heart disease is prevalent globally whether it is high, middle, or low-income countries.[9] The accurate, early diagnosis of congenital heart disease can significantly control and manage the symptoms with decreasing the risks of long term complications and multi organ involvement.[10,11] Late diagnosis is associated with otherwise preventable morbidity, mortality, and disabilities. For example, most of the unattended or undiagnosed TOF patients later present with stroke, hemiparesis or hemiplegia. In that case, even if the CHD gets corrected, the associated morbidity will compromise the quality of life for a longer period of time or may be throughout the life.[11-14]

Patients with the suspicion of Congenital Heart Disease (previously un-diagnosed) confirmed with Echocardiography from CH & ICH, Cardiology Department Faisalabad.

Only those cases are included in the study where the attendants are the caregivers of the patient, to ensure the credibility of the collected data. Caregivers/Mothers not willing to participate in the study. Previously diagnosed cases of Congenital Heart Disease. This study aims to highlight the socioeconomic, perceptual, and behavioral factors that cause delay in CHD diagnosis and the resultant complications in the form of CHD associated morbidities. The results of this study can provide a basis for social education about the congenital heart diseases which may aid in its early diagnosis and prompt treatment. It also draws attention to the significance of prenatal screening to rule out CHD, which is currently not available to the women in Pakistan, especially in the rural areas.

Materials and Methods

The Concordat and the Outline of this study was approved by the Children Hospital Faisalabad's Ethical Review Board before the commencement of the study. To ensure the authenticity of the patient's history and collected data, only those children were included in the study where the attendants are the caregivers of the children. In the majority of the cases, the caregivers were mothers. After taking the verbal consent, detailed demographic history and relevant data was recorded. Statistical Analysis was performed using Statistical Package for Social Sciences Version 20 (SPSS-20).

Results

Over the period of six months, 500 undiagnosed CHD patients were enrolled in this study. Later on, the provisional diagnosis of CHD was confirmed by echocardiography. The results showed male predominance in CHD patients with male to female ratio 1.3:1, accounting for males n=299; Mean= 42.71; SD= 16.89 and females n=201; Mean= 28.71; SD= 11.68. Most of the patients presented at the age of 1 to 2 months comprising of 72 males (14.4%) and 55 females (11%). All the patients presented in pediatric medical emergency with the complications of congenital heart disease. In most of

Table 1: *Relationship between Age at the time of presentation at tertiary care hospital a frequency of confirmed cases of Congenital Heart Disease.*

Age Groups	Gender		Frequency	Valid Percent	Mean		Standard Deviation (SD)	
	Male	Female			Male	Female	Male	Female
1-2 Months	72	55	127	25.4%	42.7142857	28.7142857	16.89221533	11.68288474
2-6 Months	60	33	93	18.6%				
6-12 Months	46	21	67	13.4%				
12-24 Months	36	25	61	12.2%				
25-36 Months	38	27	65	13.0%				
37-48 Months	27	23	50	10.0%				
49-60 Months	20	17	37	7.4%				
Total	299	201	500	100.0%				

the cases, patients developed diarrhea associated with rapidly progressive, severe dehydration that precipitated the symptoms of CHD. Other documented complications of CHD were Cardiogenic Shock, Pulmonary Hypertensive Crisis, Infective Endocarditis, Recurrent Respiratory tract infections, Cerebrovascular Accident CVA.

Table.3 concludes all the possible factors that potentially caused delay in the diagnosis of Congenital Heart Disease in the selected patients. The most common factors among them were delayed first consultation with a doctor by guardians (n=230; 46%; p<0.001) and socioeconomic restraints (n=227; 45.4%; p<0.001).

Table 2: *Active complications of CHD documented at the time of their presentation*

	Active Complications	Frequency	Valid Percent
Due to delayed Diagnosis of CHD	Cardiogenic Shock	52	10%
	Recurrent RTI	12	2%
	Hypovolemic Shock due to severe dehydration	362	72%
	Pulmonary Hypertensive Crisis	52	10%
	CVA	3	1%
	Infective Endocarditis	19	4%

Table 3: *Frequency of the factors influenced the delayed diagnosis of CHD*

Possible Factors of Delayed Diagnosis of CHD	Present	Absent	Percentage
Socioeconomic Constraints	227	273	45.40%
Lack of Trained Health System	133	367	26.60%
Delayed First Consultation with a doctor by Guardians	230	270	46.00%
Delayed Diagnosis by Medical Professionals	124	376	24.80%
Delayed Referral to a Pediatric Cardiologist	118	382	23.60%
Social Taboos	212	288	42.40%
Most Children were delivered outside the Hospital	215	285	43.00%
Siblings more than 2	115	385	23.00%

Other include, delivery of children outside the hospital setup, social taboos, lack of trained health system, delayed diagnosis by medical health professionals, delayed referral to a cardiologist/ pediatric cardiologist, and more than 2 siblings.

Discussion

More than 80% of childbirths in rural areas occur at home by formal birth attendants (Daies).[15] Therefore, at the time of presentation, most of the mothers are unable to provide any documents regarding birth events of the child and/or unable to recall birth history.[16] Without proper history and expert's clinical examination, the signs and symptoms of CHD can be easily confused with respiratory tract infection.[17] Most of the children with congenital heart disease are misdiagnosed and mistreated in their early ages till they get access to tertiary healthcare center.[16-18] For cyanotic heart disease, delayed diagnosis is when an affected newborn is sent home after delivery without being diagnosed. For acyanotic heart disease, the delayed diagnosis is labeled when the patient is diagnosed after the age of elective surgical correction or after developing the hemodynamic instability as a complication of CHD.[19] All the patients included in this study were diagnosed at the time of their presentation in the Pediatric Medical Emergency, Children Hospital Faisalabad. Almost all types of congenital heart defects can be accurately diagnosed with pre-natal screening and in-utero fetal echocardiogram.[20] However, the misdiagnosis of CHD is still a major concern worldwide.[21] With the complex web of symptoms, vague history, co-morbidities, and lack of proper medical/ birth record makes it very difficult for a physician to diagnose CHD at the first visit. So the early diagnosis of CHD is a challenge for the primary healthcare physicians with their limited exposure, knowledge, and resources. Unfortunately, this relevant delay causes not only the morbidity and mortality of the patient but also the psychological and socioeconomic burden to the family.[22]

There are multiple factors that contribute to the delayed diagnosis of CHD. It mainly includes delay in the first consultation to a doctor by the guardians of the patient, socioeconomic restraints as people from rural areas have to travel far to access the specialized healthcare facility, and social taboos.[23] The social factors were defined as personal, cultural, and spiritual beliefs that hindered in seeking medical attention or being compliant with the CHD treatment.[21] These factors are more relevant to the acyanotic heart disease where patient is mostly asymptomatic or mildly symptomatic and do not develop obvious and more serious signs and symptoms such as peripheral and central cyanosis, apnea spells, etc. Other factors include lack of trained health system, delayed diagnosis by medical professionals, and delayed referral to a pediatric cardiologist.[22] These

delays transform into injudicious hospital admissions for symptomatic treatment resulting in the mismanagement of their medical condition as well as adding to the economic and psychological burden to their attendants or caregivers.[23-25]

The study shows that the patients with fewer siblings, 2 or less, had better chances to get access to the medical facilities and were diagnosed earlier than those with more than 2 siblings. This factor also justifies the socioeconomic restraints contributing to the limited resources and poor prognosis of affected children.[24-25]

Conclusion

Congenital Heart Disease is one of the most common congenital anomaly. Early diagnosis is the key factor to enable timely management of the disease and its associated complications. Unfortunately, the facility of prenatal screening is not available to the most of the pregnant females in developing countries like Pakistan. However, detailed history taking, careful clinical examination and timely referral to cardiologist for diagnostic echocardiography can remarkably control the disease and its adverse outcomes.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

HSK: Conceptualization of Project
HSK, MA: Data Collection
ZZ, MA: Literature Search
MA, ZM: Statistical Analysis
MA, ZM: Drafting, Revision
ZA, MA: Writing of Manuscript

Comparison of the Local Anesthetic Effect of Two Doses of Dexmedetomidine , 5µg and 10µg added to Intrathecal Hyperbaric Bupivacaine

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Abstract

Objective: To Ascertain the optimum intrathecal dose of dexmedetomidine along with local anesthetic.

Method: Prospective randomized study, Place and Duration of Study was in the Department of Anaesthesia, FMH College of Medicine & Dentistry, Lahore from1st. February to 31st. July (6 months) 2021. Ninety patients posted for urological, lower abdominal and pelvic general surgical procedures selected for the study were distributed in three groups. All groups comprised 30 patients each. Our facility is providing treatment to infertile males and that was our main study population. We selected ASA1&2 patients between 20 and 60 years. The first group [Control (C)] received only local anesthetic (2 ml. of hyperbaric bupivacaine 0.75%) plus 0.5 ml normal saline. The second group [Dexmedetomidine (D1)] received in addition to local anesthetic 5 micrograms of dexmedetomidine. The third group [Dexmedetomidine (D2)] received in addition to local anesthetic 10 µg of dexmedetomidine. The duration of surgical anesthesia, motor blockade and severity of side effects (hypotension and bradycardia) were noted for all patients in all the three groups. All the groups received 2.5 ml intrathecal injection.

Results: The onset of the blockade was similar in all groups. The duration of block was maximally prolonged in (D2) group. The duration was in between in (D1) group. It was minimum in (C) group.

Conclusion: Intrathecal use of dexmedetomidine with local anesthetic prolonged the sensory and motor blockade and 5 µg was found to be the optimal dose.

Keywords: α2-adrenergic agonist, Dexmedetomidine, Bupivacaine, Lower abdominal surgery

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Introduction

Spinal anesthesia is very popular these days due to its relative safety and economy as compared with general anesthesia. It is especially useful in infraumbilical general surgical, urological, orthopedic, obstetric and gynecological operations. The availability of blunt bevel needles has markedly reduced the incidence of post spinal headache. The problem with spinal anesthesia is its relatively short duration. To overcome this, various adjuvants namely ketamine, clonidine and buprenorphine have been used with local anesthetics intrathecally to cause prolongation of effect. At higher intrathecal doses opioids can cause side effects like pruritus, drowsiness, nausea and vomiting. Ketamine and clonidine also have bad side effects. Nowadays a relatively new drug dexmedetomidine is in use to prolong the duration of effect of intrathecal local anesthetics. It is a specific α2 adrenergic agonist relatively free from these side effects though hypotension and bradycardia can occur.[1]

Dexmedetomidine has been used as a premedicant, and can be used as a sedative in intensive care unit (ICU)

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setting.[1,2] It causes prolongation of all types of nerve blockade (sensory and motor) and ameliorates both visceral and somatic pain.[3]

There are very few studies in the literature regarding the optimum intrathecal dose of dexmedetomidine.[4] Gupta R et al. used 5 mcg dexmedetomidine along with ropivacaine ,in their study, and found prolonged sensory as well as motor block with minimal hemodynamic change and decreased requirement for rescue analgesics for 24 hours , in comparison with fentanyl.[1] Abdelhamid and El lakany used 5 mcg of dexmedetomidine with local anesthetic intrathecally and encountered prolonged postoperative analgesia and decreased shivering. Those studies depict that usually dexmedetomidine given intrathecally along with local anesthetic prolongs the sensory as well as motor block but increasing the dose more can exhibit troublesome hemodynamic depression. Therefore, we decided to study at our setup the optimum dose producing prolongation of sensory and motor blockade, meanwhile causing negligible hemodynamic disturbances.

Materials and Methods

This prospective randomized study was done in a tertiary care hospital affiliated with medical college. IRB (Institutional Review Board) approval was taken. Sample size was calculated in reference to the study done by Shagufta Naaz et al[(4)]. J Clin Diagn Res 2016 Apr; 10(4): UC 09-UC13. They calculated the sample size using a power analysis of @=0.05 and B=0.8. We selected 90 patients for the study and distributed them randomly in three groups. All the groups comprised 30 patients each. Most of our patients were male by chance as our facility caters for the treatment of infertile males. All the patients had to undergo mainly urological procedures plus some lower abdominal and pelvic general surgical operations.

Inclusion criteria was male and female patients aged 20-60 years and American society of anesthesiologists class 1 and 2. Extremes of ages and BMI were avoided in the study. In similar studies, similar demographic profiles were encountered.[4] Exclusion criteria was patients with hypertension, cardiac disease, coagulation disorders and β blocker therapy etc. Computer-generated random number sequencing was used for randomisation. All the groups received 2.5 ml volume intathecally. This comprised 2ml of 7.5% bupivacaine plus 0.5 ml normal saline. The arrangement was made that in groups D1 and D2, after adding dex. the volume of normal saline was such that total volume of the injectate was 2.5ml. The first group (C) received only 15 mg of heavy bupivacaine intrathecally only. The second group (D1) received the same amount of heavy bupivacaine plus 5 μg of dexmedetomidine. Third group received the same amount of heavy bupivacaine plus 10 μg of dexmedetomidine.

All the patients fasted for 6 hours for solids but were allowed clear fluids upto 2 hours before surgery. On arrival in the operation theatre, intravenous access was taken and all the patients received lactated ringer's solution 10ml/kg. Patients, wellbeing was monitored using non- invasive blood pressure, pulse oximetry, and ECG. Under strict aseptic precautions, using 25-gauge pencil point blunt bevel needle, subarachnoid block was established in the sitting position at 3-4 lumbar interspace. Hyperbaric bupivacaine was taken in 3cc. disposable syringe (2ml= 15mg) and dexmedetomidine in the insulin syringe 5 or 10 micrograms according to the group allocation. The available ampule of dexmedetomidine over the counter contains 200 micrograms in 2 ml. Dexmedetomidine was added to the 3cc.syringe of heavy bupivacaine. 2.5 ml volume was ensured in all the patients in all the groups by adding normal saline. The intrathecal injection time of the drug was labeled zero time and subsequently all the time calculations were done in reference to that. Sensory checking with the pin prick method was done with 23 G hypodermic needle, every minute, to find out the time for the onset of block, for the maximum block and the highest dermatomal level until all were recorded. Hemodynamics were checked every 2 minutes initially, for 10 min. then every 5 min. thereafter. Analgesia was checked every 30 min. until patient started feeling pain, both intra and postoperatively. Modified bromage scale was used for motor blockade assessment. This scale assesses the intensity of motor block by the patient's ability to move his lower extremities. Bromage score 1 is complete block (unable to move feet or knees). Bromage 2 is almost complete block (able to move feet only). Bromage 3 is partial block (just able to move knees). Bromage 4 is detectable weakness of hip flexion while supine (full flexion of knees). Motor blockade grossly coincided with the duration of analgesia. It was taken as hypotension if the fall in SBP 30% or more from the pre-induction level and treatment was done with intravenous crystalloids, colloids and ephedrine. It was labelled bradycardia if heart rate decreased to<50 beats per minute and was treated with intravenous glycopyrrolate 0.4 mg. Anal-

gesic fortification with other drugs was not done. Anxious patients were given 1mg. of Midazolam. Analgesia time was considered from the time of intrathecal injection to the first dose of the rescue analgesic due to pain. Nalbuphine 4 mg intravenous, was our rescue analgesic until the pain subsided to an acceptable level.

Results

Most of our patients were males (88 males as compared to 2 females only). The age of the patients ranged from 20 to 60 years. The weight of most of the patients ranged from 75–80 kilograms (Table 1). Most of our patients had microsurgical varicocelectomy operation.

The onset of the sensory block was almost 5 minutes or less in all the groups. Maximum block established in 10 minutes or even less in all the groups. Duration of analgesia/motor blockade was maximum (more than 200 min.) in the D2 group. It was least (less than 100 min.) in the control (C) group and in between in the D1 group (133 min.). Hemodynamic stability was more in the control group where only 1 patient became unstable, i.e. either had bradycardia or hypotension. In the D1 group 26 patients (28.9%) remained stable and only 4 patients (4.4%) became unstable. In the D2 group 23 patients (25.6%) remained stable and 7 patients (7.8%) showed either bradycardia or hypotension (Table 2). Data was analyzed using SPSS-23. The first table shows descriptive statistics of the patients. As regards gender, frequency and percentages are given whereas mean and standard deviation are used to illustrate age and weight. In the second table, Kruskal Wallis H test was used for the variables barring hemodynamics where Chi Square test was used.

Table 1: *Descriptive statistics of the patients (n=90)*

Variable	Group C	Group D1	Group D2
Gender			
Male	30 (100%)	30 (100%)	28 (93.3%)
Female	-	-	2 (6.7%)
Age (years)	36.53±10.96	36.66±8.47	36.26±8.40
Weight (kg)	78.53±12.62	77.36±7.95	78.23±10.47

Table 2: *Characteristics of sensory and motor blockade (Time in min.)*

Characteristic	Control (C)	D1	D2	P Value
Onset of sensory block	4.43±1.16	3.36 ± 1.12	3.30± 0.79	0.0001
Maximum block (sensory+motor)	8.63±2.73	6.50±1.19	6.36 ± 1.27	0.0001
Highest sensory level	T8 (T6-T8)	T8 (T6-T8)	T6 (T4-T8)	
Duration of analgesia/ Motor blockade	95.3±35.0	133.6±35.6	214.8 ± 31.4	0.0001
Rescue analgesia (minutes)	104.0± 44.3	153.5±38.9	235.6 ± 38.3	0.0001
Highest pain score	3.1±1.5	2.3±0.7	2.0 ± 0.6	0.013
Haemodynamics				
Stable	29 (%)	26	23	0.056
Unstable	1	4	7	

Discussion

To prolong the analgesia and anaesthesia in operations done under spinal anaesthesia has been hitherto a difficult proposition. Dexmedetomidine is presently of tremendous help in this regard. Very little amount (5-10 µg of dexmedetomidine added to the local anesthetic, say Bupivacaine) can literally double the duration of analgesia.

Dexmedetomidine is a highly specific α2adrenergic agonist.[1] The sedative cortical analgesic effects of dexmedetomidine are caused by the hyperpolarization of noradrenergic neurons. Norepinephrine release is inhibited in the medullospinal noradrenergic pathway.[5-7] This triggers the formation of new neurotransmitters that consequently decrease histamine secretion producing hypnosis that resembles normal sleep, making dexmedetomidine a promising and efficient sedative.[8] The decreased activation in the descending noradrenergic pathway, which regulates nociceptive transmission, stops passage of pain signals and analgesia is produced.[7] At spinal cord level, increased activity in both α2-C and α2 – A adrenergic receptors, present in the dorsal horn neurons, especially lamina II, produces effective analgesia.[6,9,10] The sympatholytic effect due to stimulation of central α2 adrenergic receptors resulting in hypotension and bradycardia is beneficial in the attenuation of stress response of surgery.[10,11]

Recent studies have demonstrated that intrathecal dexmedetomidine significantly decreases postoperative analgesic requirements.[12] Different dose finding studies,[13,14] have been conducted in the past to find the optimal dose. The studies evaluating intrathecal dexmedetomidine do not demonstrate any neurological deficits produced by it, in the dose range 2.5 – 100 mcg. Some studies, however have shown that dexmedetomidine could have adverse effects on myelin sheath in human beings.[15] Kanazi et al. used 3 mcg of dexmedetomidine intrathecally with local anesthetic and found quicker onset of

motor block and prolongation in the duration of sensory and motor block with hemodynamic stability. Al - Mustafa et al. used 5 & 10 mcg of dexmedetomidine with bupivacaine intrathecally in urological cases and found prolonged analgesia and motor blockade in a dose dependent manner. Hala EA Eid et al. in their study using 10 and 15 mcg of dex. with 3ml of 0.5% heavy bupivacaine encountered good and prolonged analgesia.[16] Shagufta Naaz et al. in their study even used 20 mcg dose of dexmedetomidine. In our study, in agreement with previous studies, the control group, i.e. that without dexmedetomidine had the shortest time of anesthesia and analgesia. Onset of sensory and motor blockade was somewhat delayed as compared to dex. groups (study groups). In study groups, the onset of blockade was quicker with 10 mcg dex. dosage as compared to that with 5mcg dex. respectively D2 and D1 groups in our study. Time to reach maximum blockade was also less whereas the height of the block was more in dex. groups especially in D2 group (10 mcg dex. group). Hemodynamics remained stable in the control group whereas there was some bradycardia &hypotension in the D1 and D2 groups, more in the later. All this complies with the findings of the previous studies. Presently, more research is required to establish the safety, efficacy and optimum dosage of intrathecal dexmedetomidine.

Conclusion

The addition of 5µg of dexmedetomidine to 15 mg of hyperbaric bupivacaine for the subarachnoid block has caused a significant increase in the duration of the block in patients undergoing urological and lower abdominal surgery without causing adverse effects on cardiovascular stability.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

KA: Conceptualization of Project
KJS: Data Collection
MAK: Literature Search
MA: Statistical Analysis
MA: Drafting, Revision
RK: Writing of Manuscript

Family History – An Indicator For Developing Type 2 Diabetes At Earlier Age

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Abstract

Objective: Positive family history is an indicator for developing diabetes. Data are needed to determine if it effects age at onset of diabetes.

Method: This cross-sectional study was conducted at Ghurki Trust Teaching Hospital (GTTH) Lahore, in Diabetic And General Medical OPD. Enrollment for study began on January 1st 2020, and ended on March 31st, 2020.We conducted a Cross-sectional study. 933 diabetics and 396 non diabetics were interviewed regarding family history and age at onset of diabetes. Patients were then categorized into three groups based on their familial risk as average, moderate and high.

Results: In the diabetic group 487 (52.2%) had an average familial risk of developing diabetes, while 299 (32%) and 147 (15.8%) had moderate and high familial risk respectively. Conversely, similar groups among the non-diabetic population had 312 (78.8%), 69 (17.4%) and 15 (3.8%) familial risk of developing diabetes. Relation of family history with the age at the time of diagnosis of diabetes was statistically significant (P<0.0001). In average risk diabetes group the average age at time of diagnosis of DM was found to be 43.9 years, whereas, with average, moderate and high familial risk the average age of the onset of diabetes was 46.04, 41.70 and 41.28 years, respectively. The individuals with a family history of diabetes are 2.83 times (95% CI: 2.19-3.65) more likely to get diabetes as compared to those with no family history of diabetes. Females were found to be 1.6 times more likely to have an early onset of diabetes and there are 1.88 times (95% CI: 1.18-2.99) more chances of having diabetes if the mother is diabetic (P<0.05).

Conclusions: Family history is a strong independent predictor of diabetes. Patients with moderate to high risk of diabetes develop diabetes at an earlier age. Diabetic mothers confers more risk of early development of diabetes than any other relative.

Key Words: Type 2 Diabetes, Family History, Age at diagnosis

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Introduction

Diabetes Mellitus is the current century's pandemic. Developing world including Pakistan, being most effected. Diabetes patient number is on the rise and is diagnosed at an earlier age. Now more people are living with diabetes in their productive years. This translates into increased number of lost work days, more spendature on health and morbidity. Type 2 accounts for more than 90% of all cases of diabetes.[1] Guidelines for management of diabetes not only focus on early detection, life style modification as well as early intensive glycemic control to prevent or delay complications once diabetes has set in.[2] Early detection depends on identification of risk factors so as to implement strategies which may help in delaying the disease onset. This study evaluated the use of self-reported family history of diabetes as a potential, independent screening tool to identify people at risk for developing the disease. The association of

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age at onset of diabetes with the number of first or second-degree family members having diabetes was studied. Few studies globally, but none in Pakistan have compared the age of onset of diabetes and their relationship with diabetic relatives.

Materials and Methods

This cross-sectional study was conducted at Ghurki trust teaching hospital (GTTH) Lahore, in diabetic and general medical OPD. Enrollment for study began on January 1st, 2020, and ended on March 31st, 2020. A total of 1329 patients (933 cases and 396 controls) were included. Patients were considered to be diabetic based on ADA 2020 criteria.[3] A parent, brother, sister, or child was considered as First Degree Relatives (FDR). A second-degree relative is someone who shares 25% of a person's genes. It includes uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings, and double cousins and third-degree relatives constituted the extended family i.e. first cousins, great grandparents and great grandchildren. Lineage is the line of descendants of a particular ancestor. All type 2 diabetics who were previously or recently diagnosed and agreed to participate in the study and render the required information were included. Type 1 diabetics were excluded. Controls were selected from general medical OPD. They were not known diabetics and agreed to get blood sugar levels checked and to render the required information. After being selected, a survey form was filled by the patient or some helper. This included the number of family members with diabetes, relationship to the patient, and age of the patient at the onset of diabetes. Using the number and type of affected relatives, participants were classified into average, moderate, or high familial risk.[4] High: At least 1) two first-degree relatives with diabetes from the same lineage; 2) one first- and two second-degree relatives with diabetes from the same lineage; or 3) three second-degree relatives with diabetes from the same lineage. Moderate: Only 1) one first- and one second-degree relative with diabetes from the same lineage; 2) one first-degree relative with diabetes; 3) either mother or father with diabetes, or 4) two second-degree relatives from the same lineage with diabetes. Average: Only 1) one second-degree relative with diabetes from one or both sides of the family; or no family history of diabetes. The data was processed using SPSS version 21 and STATA. The validity of family history as a screening tool was examined by calculating sensitivity, specificity, positive and negative predictive values. Logistic regression analysis was applied with and without adjustment for risk factors and Odds ratio was calculated. Association of age at onset of diabetes was evaluated with the number of family members having the disease and the effect of any particular relation to the patient with age at onset of diabetes.

Results

Of the 1329 patients inquired regarding the status of diabetes, 933 had a self-reported diagnosis of diabetes whereas the other 396 (29.8%) were non-diabetics. The demographic and baseline characteristics in both groups are depicted in Table-1. Both sample populations were stratified according to their familial risk into average, moderate and high risk groups. In the diabetic patients group 487(52.2%) had an average familial risk of developing diabetes, while 299 (32%) and 147 (15.8%) had moderate and high familial risk respectively. Conversely, similar groups among the non-diabetic population had 312 (78.8%), 69(17.4%) and 15(3.8%) familial risk of diabetes. (Fig-1). The individuals with a family history of diabetes are 2.83 times (95% CI: 2.19-3.65) more likely to get diabetes as compared to those participants with no family history of diabetes (Prob>χ2 <0.0001, R2=0.0423). When gender was taken into consideration, it was found that females are 1.6 times more likely to have an early onset of diabetes with high familial risk as compared to males however this difference was statistically non-significant. Logistic regression analysis was applied for the age at onset of diabetes with and without any adjustment for risk factors like age, gender, and family history. The average age at onset of diabetes was 43.90 years. The analysis showed that in patients with no or average risk, the age of onset of diabetes was 48.5 years (OR: 2.79, 95% CI:3.77-1.83), with moderate risk it was 41.90 years while it decreased to 41.28 years if familial risk was high (P<0.0001) (Table-2) . By using logistic regression analysis, odds ratio was calculated by keeping negative family history as reference. For this, two models were derived, Model-1 did not have any variable adjusted whereas, and the model-2 was adjusted by gender. Model 1 showed that the diabetic population of our sample was having higher familial risk than the non-diabetic population (OR: 2.63, 95% CI: 2.12-3.27, P<0.0001), while model 2 when adjusted for gender did not show any statistical significance (Table-3). Model 1: No adjustment for any variable; Model 2: adjusted with family history and gender. Prob>χ2: the probability of obtaining chi-square, OR: odds ratio, CI: confidence interval. Association between familial risk and relationships (mother, father,

brother, sister and other distant family members) were also estimated using multiple logistic regression. The results showed that there are 1.88 times (95% CI: 1.18-2.99) more chances of developing diabetes if the mother is diabetic (P<0.05) while in case of father having DM, chances of developing diabetes was doubled if CI was set at 90% while it had non-significant relationship if CI was set at 95%. Furthermore, if both parents are diabetics then there is 33.5% more chance of having diabetes in the next generation (P<0.05). On the other hand, if a brother(s) and sister(s) are having a history of diabetes then the likeliness of having diabetes would be 32.0% (CI 95%: 18.9%-54.0%) and 57.9% (95% CI: 34.3%-97.6%) high, respectively (P<0.05). If all siblings are having diabetes then there is 19.0% higher chance of getting diabetes. On contrary, if any other relative does have a history of diabetes then there is a non-significant chance of getting diabetes. Moreover, if parents and siblings have diabetes then the percentage of getting diabetes is 58% higher than non-diabetic population (P<0.05). There are absolute chances of getting diabetes if parents, siblings, and children are diabetics (P<0.05). **(Table-4)**

Table 1: *Demographics of the study population.*

		Patients (n=1329)					
		Non-Diabetics (n=396)			Diabetics (n=933)		
		Familial Risk Stratification			Familial Risk Stratification		
		Average (n=312)	Moderate (n=69)	High (n=15)	Average (n=487)	Moderate (n=299)	High (n=147)
Gender	Female	241 (60.9)	47 (11.9)	8 (2.0)	340 (36.4)	211 (22.6)	101 (10.8)
	Male	71 (17.9)	22 (5.6)	7 (1.8)	147 (15.8)	88 (9.4)	46 (4.9)
Family History	No	286 (72.2)	-	-	447 (47.9)	-	-
	Yes	26 (6.6)	69 (17.4)	15 (3.8)	40 (4.3)	299 (32.0)	147 (15.8)
Age at presentation	<18	18 (4.5)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)
	18-34	111 (28.0)	37 (9.3)	9 (2.3)	22 (2.4)	27 (2.9)	13 (1.4)
	35-54	133 (33.6)	22 (5.6)	4 (1.0)	274 (29.4)	185 (19.8)	88 (9.4)
	>54	50 (12.6)	10 (2.5)	2 (0.5)	188 (20.2)	87 (9.3)	46 (4.9)
Age group at time of diagnosis	<18	-	-	-	4 (0.4)	1 (0.1)	0 (0.0)
	18-34	-	-	-	64 (6.9)	69 (7.4)	38 (4.1)
	35-54	-	-	-	298 (31.9)	190 (20.4)	95 (10.2)
	>54	-	-	-	121 (13.0)	39 (4.2)	14 (1.5)
Family members having diagnosis of diabetes	Mother	0 (0.0)	29 (74.4)	10 (25.6)	0 (0.0)	181 (63.7)	103 (36.3)
	Father	0 (0.0)	6 (60.0)	4 (40.0)	0 (0.0)	56 (53.3)	49 (46.7)
	Brother	0 (0.0)	26 (70.3)	11 (29.7)	0 (0.0)	46 (36.8)	79 (63.2)
	Sister	0 (0.0)	26 (81.3)	6 (18.8)	0 (0.0)	55 (35.9)	98 (64.1)
	Children	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	6 (27.3)	16 (72.7)
	Other relatives	26 (81.3)	0 (0.0)	6 (18.8)	39 (47.0)	0 (0.0)	44 (53.0)

Table 2: *Age at Diagnosis of diabetes*

	Overall (N=933)	Familial Risk Stratification			Odds Ratio (95% CI)
		Average (n=487)	Moderate (n=299)	High (n=147)	
Age at time of diagnosis years)	**43.90 ± 11.30**	**46.04 ± 11.77**	**41.70 ± 10.10**	**41.28 ± 10.66**	**2.79** (95% CI: 3.77-1.83)
<18	5 (0.5)	4 (0.8)	1 (0.3)	0 (0.0)	
18-34	171 (18.3)	64 (13.1)	69 (23.1)	38 (25.9)	
35-54	583 (62.5)	298 (61.2)	190 (63.6)	95 (64.6)	
>55	174 (18.7)	121 (24.9)	39 (13.0)	14 (9.5)	
P<0.0001					

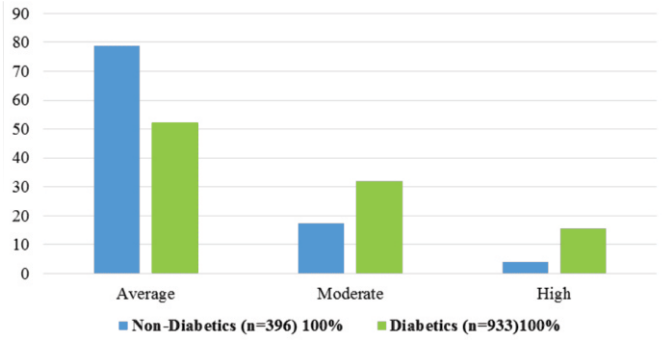

Fig-1: *Distribution of risk according to family history*

Table 3: *Association between family history and risk of diabetes*

	Prob>χ^2	Odds Ratio (OR)	95% CI	P-value
Model 1	<0.0001	2.63	2.12 – 3.27	<0.0001
Model 2	<0.0001	1.23	0.93 – 1.62	>0.05

Table 4: *Association of relationship to patient with chances of getting diabetes*

Relationship to patient	Chance of getting Diabetes	CI	P Value
Mother Alone	1.8 Times	95%	<0.05
Father Alone	-	95%	>0.05
Father Alone	2 Times	90%	<0.05
Mother + Father	33.5%	95%	<0.05
Brother	32%	95%	<0.05
Sister	57.9%	95%	<0.05
All Siblings	19.0%	95%	<0.05
Parents + Siblings	58%	95%	<0.05
Parents+Siblings+Children	100%	95%	<0.05
Other Relatives	-	95%	>0.05

Discussion

This study evaluated the use of self-reported family history of diabetes as a potential screening tool to identify people at risk for diabetes. The study showed that individuals with a family history of diabetes have a higher risk of developing diabetes as compared to the subjects with no family history and also at an earlier age.[1] Family history in fact is a stronger independent predictor of diabetes when compared to other anthropometric, genetic, and lifestyle factors.[5] Although, this study did not take into consideration other anthropometric and genetic factors but did show that familial risk of diabetes is unaffected by gender stratification. Hence, the risk of type 2 diabetes is equally present in both genders. However, other biological and socioeconomic factors associated to each gender may result in higher familial risk of diabetes.[6,9] An early onset of diabetes is strongly associated with a high familial risk of diabetes. In cases with no or average risk of diabetes, the mean likely age of diabetes at time of diagnosis was found to be 46.04 years and decreased to 41.70 and 41.28 years respectively in patients with moderate and high risk of disease. Average age at diagnosis of diabetes was found to be 43.9years whereas in another study by us in 2014 showed that average age at diagnosis was 44.1years.[10] This downward trend was observed in other studies too.[5,11] The early onset of diabetes results in the impaired quality of life and early appearance of chronic complications giving rise to immense healthcare and economic burden. Therefore, family history may be used as an effective tool to ascertain the probability of occurrence of diabetes and may help in monitoring at earlier age and adopt life style modification at appropriate time. Study also showed that there is twice as much chance of developing type 2 diabetes if the mother is diabetic, while a weaker correlation is present if the father is diabetic[12,13] again helping to adopt life style modification at earlier age. This might be due to the occurrence of maternal dysglycemia drastically affecting intra uterine environment during gestational diabetes hence, an elevated risk of diabetes is present in the child.[5,14-16] Similarly, the likelihood of getting diabetes also relies upon siblings where we observed that the chances of diabetes are comparatively higher if the sister is diagnosed with diabetes as compared to brother. The exact mechanism of familial transmission of diabetes is still debatable though impaired secretion of insulin or resistance may be the mechanism involved.[17-20] The scope of our study was limited to assess the association of familial risk to predict type 2 diabetes mellitus. To our knowledge, this study was the first of its kind in Pakistani population and it concludes that family history is a strong independent predictor of diabetes. Patients with moderate to high risk of diabetes develop diabetes at an earlier age. Diabetic mothers confers more risk of early development of diabetes than any other relative. Family history may be employed as a valuable and inexpensive tool for the early detection of diabetes. This will help in early screening and adoption of healthy lifestyle including diet, exercise and weight control.

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Authors Contribution

WA, SS: Conceptualization of Project
SSQ: Data Collection
JZ, SSQ: Literature Search
SSQ, WA: Statistical Analysis
BMB, SSQ: Drafting, Revision
SS, WA, JZ: Writing of Manuscript

Seroma Formation Between Flap and Non-flap Fixation Following Mastectomy in Term of Age and Type of Surgery in Breast Cancer Patients in A Tertiary Care Hospital

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Abstract

Objection: To compare the adequacy of flap fixation and non-flap fixation for preventing seroma formation, depending upon age and type of surgery in patients undergoing mastectomy, at RMU Allied Hospitals following mastectomy.

Method: Randomized controlled trial setting of this study was Surgical units of Rawalpindi medical university (RMU) & Allied Hospital. Duration of this study was conducted from October 2019 to April 2020. Sample size of 114 cases was enlisted in the study. Non probability, consecutive sampling. Patients were equally randomized to flap-fixation (Group A) and non-flap fixation (Group B). Patients of both groups were followed up 48 hours postoperatively for seroma formation as evident by palpation and aspiration. Results were analysed using SPSS software and p-value ⩽0.05 considered significant.

Results: In group A (Flap Fixation), seroma formation was noted in 22.8% (n=13) patients, while in group B (Non-Flap Fixation) it was noted in 45.6% (n=26) patients only (p-value 0.010). In group A, mean aspired fluid found to be 28.46 ml ±15.19SD while it was noted as 30.00 ml ±13.78SD in group B.

Conclusion: The patients undergoing modified radical mastectomy and above 50 years of age are significantly (p-value ⩽0.05) associated with seroma formation following mastectomy. Whereas, flap fixation is more useful technique than non-flap fixation for minimizing post mastectomy seroma formation.

Keywords: seroma, modified radical mastectomy, flap fixation

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Introduction

Breast carcinoma is one of the commonest malignancy in Pakistan. According to an estimate, about 1 in every 9 Pakistani women develops breast cancer at some part of her life.[1] As most patients present late, the commonest surgical procedure performed is Modified Radical Mastectomy (MRM). In MRM, two approaches can be used for wound closure i.e. Non-Flap Fixation or conventional approach and Flap fixation. In the Non-Flap fixation, skin flaps are sutured using interrupted skin sutures while in flap fixation approach the subcutaneous tissue of skin flap is first sutured to the underlying pectoral muscle and then skin is closed conventionally. One of the common complications associated with MRM is seroma formation. Seroma is defined as the accumulation of serous fluid at the site of surgery. The frequency of seroma ranges between 15 and 81%.[2] As a result of its accumulation, many post-op complications including surgical site infection (SSI), delayed healing and skin flap necrosis occur.[3] Many factors contribute in the formation of seroma like age, body mass index and use of electrocautery.[4] In a recent systemic review, chances of forming seroma can be reduced by aspirating the collection along with fixing the skin flaps to underling structures.[5] It is hypothesized that flap fixation reduces seroma formation by reduction in dead space.

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In a study carried out by James Van Bastelaar et al, incidence of seroma formation was 35.9% in patients who underwent flap fixation as compared to 59.1% in patients in whom flap fixation was not done; with a p-value of 0.0023. Similarly, in a retrospective study, incidence of seroma formation reduced to 80.5% in non-flap fixation group as compared to 22.5% in flap fixation ($p< 0.01$).[6] The objective of this research proposal is to opt better surgical procedure among Flap Fixation and Non-Flap Fixation to reduce post-operative complication mainly in terms of forming seroma in patients undergoing mastectomy at RMU and allied hospital.

Material and Methods

Randomized controlled trial setting of this study was Surgical units of Rawalpindi medical university (RMU) & Allied Hospital. Duration of this study was conducted from October 2019 to April 2020. Sample size of 114 cases was enlisted in the study. Non probability, consecutive sampling. After permission from the concerned authorities and ethical committee total of 114 patients with the diagnosis of breast cancer were selected from the surgery outpatient department of RMU and Allied Hospital. These patients underwent mastectomy, mastectomy & sentinel node procedure or MRM having age between 18 to 60 years were selected in this study after the informed consent from every patient. Patients with history of diabetes mellitus, regular steroid intake, and immunocompromised status were excluded. The diagnosis was confirmed by detailed history, thorough clinical examination and relevant investigations. Hospital registration numbers and informed consent were taken from all patients. Pre-anaesthesia workup was completed. Appropriate same intravenous antibiotic prophylaxis (inj. Amoxicillin/Clavulanic Acid 1.2 gram) was given to all patients before surgery. Patients were randomly divided into two groups Group A and Group B by lottery method. All surgical procedures were done under standard general anaesthesia. In group A, surgeries were performed by Flap Fixation while in group B with Non Flap Fixation. After the operation all of the patients will be kept NPO for 06 hours and received two doses of antibiotic, 8 hours apart. The analgesic inj. Ketorolac 30mg (intramuscular, every 8 hours) was used. All patients were discharged after tolerating soft diet. Patient were advised to follow-up in OPD after 48 hours of drain removal and observed for seroma formation as evident by palpation and aspiration.

Results

Mean age of the total study population found to be 45.47 years ±9.49SD. In group A, mean age of patients was 45.35 years ±10.15SD while it was noted as 45.60 years ±8.85SD in group B. 22.8% (n=26) of total study population were belonged to age group less than 35 years, 49.1% (n=56) were of age 36-50 year while 28.1% (n=32) patient were presented with age more than 50 years. Group wise distribution of age groups is presented in table 1. Frequency of seroma formation was noted as 34.2% (n=39) in total study population. In group A (Flap Fixation), seroma formation was noted in 22.8%

Table 1: *Distribution of study population in different age groups.*

Age Groups	Study Group		Total
	Flap Fixation (A)	Non-Flap Fixation (B)	
18-35 Years	14	12	26
	24.6%	21.1%	22.8%
36-50 Years	27	29	56
	47.4%	50.9%	49.1%
>50 Years	16	16	32
	28.1%	28.1%	28.1%
Total	57	57	114
	100.0%	100.0%	100.0%

Table 2: *Seroma formation in both groups (stratification based on age groups)*

Age Groups	Seroma Formation	Group		Total	P-Value
		Flap Fixation (A)	Non-Flap Fixation (B)		
18-35 Years	**Positive**	4	4	8	0.793
		28.6%	33.3%	30.8%	
	Negative	10	8	18	
		71.4%	66.7%	69.2%	
	Total	14	12	26	
		100.0%	100.0%	100.0%	
36-50 Years	**Positive**	6	12	18	0.125
		22.2%	41.4%	32.1%	
	Negative	21	17	38	
		77.8%	58.6%	67.9%	
	Total	27	29	56	
		100.0%	100.0%	100.0%	
>50 Years	**Positive**	3	10	13	0.012
		18.8%	62.5%	40.6%	
	Negative	13	6	19	
		81.3%	37.5%	59.4%	
	Total	16	16	32	
		100.0%	100.0%	100.0%	

(n=13) patients, while in group B (Non-Flap Fixation) it was noted in 45.6% (n=26) patients only. Chi-square test was employed to assess the significance of observed difference in both groups. P-value was found to be 0.010 (<0.05), indicating there was a significant difference in seroma formation among both groups with Group A (Flap Fixation) showed better results. Results are shown in table 2 and 3. Furthermore, mean value of the aspired fluid was noted as 29.49ml ±14.08SD among

Table 3: *Seroma formation in both groups (stratification based on type of surgery)*

Type of Surgery	Seroma Formation	Group		Total	P-Value
		Flap Fixation (A)	Non-Flap Fixation (B)		
Mastectomy	Positive	2	0	2	0.076
		18.2%	0.0%	7.4%	
	Negative	9	16	25	
		81.8%	100.0%	92.6%	
	Total	11	16	27	
		100.0%	100.0%	100.0%	
Mastectomy + SNE	Positive	0	1	1	0.248
		0.0%	50.0%	25.0%	
	Negative	2	1	3	
		100.0%	50.0%	75.0%	
	Total	2	2	4	
		100.0%	100.0%	100.0%	
MRM	Positive	11	25	36	0.000
		25.0%	64.1%	43.4%	
	Negative	33	14	47	
		75.0%	35.9%	56.6%	
	Total	44	39	83	
		100.0%	100.0%	100.0%	

the total study sample who were positive for seroma formation. In group A, mean aspired fluid found to be 28.46 ml ±15.19SD while it was noted as 30.00 ml ±13.78SD in group B. Effect modifiers like age was controlled by the stratification. Post stratification chi-square test was applied. Results reflected that statistically significant difference (p-value ≤0.05) for seroma formation was noted only in >50 years of age group.

Discussion

Seroma formation is one of the commonest complication seen after breast surgery with a frequency of 3% to 85%.[7] Gonzalez et al. in their research analysed cases who underwent MRM (modified radical mastectomy) along with WLE (wide local excision) for breast carcinoma and found that the only predictor of formation of seroma was the type of procedure performed; however tumour size, age, weight of patient, involvement of axillary lymph nodes and use of chemotherapy were not significantly associated with the seroma formation[8]. Whereas our study showed that as the age is a significant contributor of seroma; as age advances, the percentage of seroma in non-flap fixation increases i.e. 33.3% in 18-35 age group, 41.4% in 36-50 year age group and 62 5% in above 50 years age group respectively. The rate of seroma formation declined with flap Fixation as the age group increases.

Management of breast cancer has been adapted from mastectomy to breast conservation surgery during the last decade. It is now concluded that radical mastectomy including MRM increases the incidence of forming seroma as compared to simple mastectomy[9,10]. Moreover, probability of its accumulation is lesser in breast conservation surgery (BCS)[11]. Since there are conflicting results in the literature, this study was conducted to assess the efficacy of flap fixation for preventing seroma formation in comparison with non-flap fixation, so that better treatment may be recommended to our local population.

Mohammed A et al[12] in his prospective interventional study found that the quantity of serous fluid drained after MRM was greater in patients who were not managed with flap anchoring technique (p-value < 0.001). Moreover drains of the flap fixing patients were removed earlier than the control group (p-value <0.001). Similar study was conducted by Arafa et al[13] and found that 22 patients develop seroma in suture group while 39 in the control group (p-value < 0.001).

Hashemi et al conducted a retrospective observational study and found that type of breast surgery has significant impact in forming seroma as it was two and a half times higher in patients of MRM[14]. Moreover the rate of seroma was two and a half times greater in non-flap fixing technique. This is consistent with our results where rate of seroma formation is significantly higher after MRM.

Ten Wolde and Kuroi in their study found that the span of anatomical planes formed during surgery play a vital role in seroma formation, therefore during mastectomy, occlusion of dead space is an essential tool. This was not be achieved by wearing pressure garments or bandages however, quilting of the skin flaps or skin flap fixation was much more effective[15,16].

Coveney et al, evaluated the effect of closing dead space on seroma formation after mastectomy. The complication rate was lower in the flap fixation group, two patients (10%) developed cellulitis; in the control group,

2 patients developed cellulitis and 2 developed partial flap necrosis (20%).[17]

Larsen et al, found that this technique not only fastened the recovery process but it also enhanced the range of shoulder motion among patients underwent MRM[18].

Chilson TR et al, in their publication described that the flap anchoring procedure reduced the frequency of seroma (p value < 0.03). As a result, the number of office visits were also markedly decreased by the patients (p-value < 0.0001).[19]

In another study, Ahmed M et al evaluated the outcomes of anchoring flaps to anterior chest wall for abutting space with drainage as an alternative to the classic form of mastectomy closure with closed suction drain for MRM. Sixty patients of breast cancer after completing metastatic workup, underwent modified radical mastectomy (MRM). Patients were segregated into two groups; group A (n=30) were flap fixing group and group B (n=30) were non flap fixing group. All patients were presented with breast cancer with age range of 32 to 75 years. Postoperative patients were followed and their data was collected and compared. Patients' demographics were not different in the two groups. They reported less overall complication in group A than group B, also reduced total seroma volume in group A and reduced number of drain days in group A than B. They concluded that anchoring skin flaps to chest wall lessens the formation of seroma.[20]

In summary, most of the carried out RCTs indicate that flap fixation prevents seroma formation. The limitation of this study is that it is conducted on a small scale. Moreover, association of many comorbid conditions like hypertension and diabetes are not assessed with outcomes of both of the procedure. A large scale study of our local population is recommended to overcome these limitations.

Conclusion

The patients undergoing modified radical mastectomy and above 50 years of age are significantly (p-value ≤ 0.05) associated with seroma formation following mastectomy. Whereas, flap fixation is more useful technique than non-flap fixation for minimizing post mastectomy seroma formation.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

AZ, SS: Conceptualization of Project
AZ, RS: Data Collection
SMD: Literature Search
SMD: Statistical Analysis
JSK: Drafting, Revision
SS: Writing of Manuscript

Original Article

Prevalence of Diagonal Earlobe Crease (DELC) in General population of Lahore and its Association with Various Ailments, as a Marker of Forensic Significance

Muhammad Kashif Butt,[1] Sundus Mona,[2] Saad Adhami,[3] Fawad Ahmad,[4] Areesha Fatima,[5] Muhammad Maqsood,[6] Muhammad Zahid Bashir[7]

Abstract

Objective: To find prevalence of Diagonal Earlobe Crease (DELC) in general population of Lahore and its association with different medical ailments

Method: It is a cross-sectional study carried out at Department of Forensic Medicine and Toxicology, Shalamar Medical and Dental College, Lahore. Convenient sampling technique was used and the participants included were the residents of different parts of Lahore city. 277 participants were studied, demographic profile was recorded on structured questionnaire and ear lobes were examined for the presence and absence of earlobe crease.

Results: The prevalence of bilateral DELC in our study was found to be 29.6%. There were 167 males (60.3%) and 110 (39.7%) female participants in the study. The Bilateral DELC was more prevalent in males 36% than in females which came to 20%. The male dominance of the crease was found to be statically significant (P = 0.004). There was significant association found between earlobe crease and with ailments like coronary artery disease, hypertension and diabetes.

Conclusion: The prevalence of the DELC is found to be 29.6% in general population with male predominance. The DELC showed statistically significant association with various body ailments including CAD, DM and HTN.

Keywords: Diagonal earlobe crease (DELC), Coronary artery disease (CAD), Hypertension (HTN), Diabetes mellitus (DM), ailments, prevalence

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Introduction

The earlobe consists of robust areolar and fatty connective tissue, lacking the firmness and stretchability that the remainder of the pinna has. The earlobes are usually smooth however, sometimes exhibit creases.[1] Diagonal earlobe crease is a crease that proceeds diagonally at an angle of nearly 45° from the point of tragus to the edge of the earlobe.[2] The crease within the skin of the earlobe was considered first to be linked with coronary artery disease (CAD) in 1973 by Frank and later this crease was known as Frank's sign.[3] The crease manifests as a deep wrinkle, which may present either bilaterally or unilaterally, and extends backwards from the intertragic notch to the auricle.[4] Literature reveals that the DELC could be one of the non-invasive indicators involving the skin. This dermatological marker also correlates with the various internal diseases like coronary artery disease, cerebrovascular diseases and diseases involving peripheral vessels.[5] Among these, coronary heart disease is the major cause of mortality globally, claiming 17.3 million lives a year worldwide.[6,7] It is also thought to be linked with other risk factors for hypertension, hyperlipidemia, occipital baldness and with increased intima

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media.[8] After the original work of Frank, many studies based upon the clinical, histopathological, and autopsy-based examinations revealed the association between ELC and CAD.[9,10] Regarding forensic aspects, DELC is significantly associated with underlying CAD, and can be a strong cutaneous marker for making a prediction regarding the cause of sudden death. In forensic settings medicolegal examiners often come across with the cases of sudden death in which there is no evidence suggesting the criminal involvement. In these circumstances this dermatological marker may be included in external examination considering the underlying coronary heart disease, as it may act as corroborative evidence to comment upon the cause of sudden death. Although the DELC is considered as an important dermatological sign which may be the predictor of the various life endangering morbid conditions, a little work is there as far as subcontinent part of the world is concerned. Even in Pakistan, to best of our knowledge, little research work is there, and the papers published are handful in numbers, seeking the association of DELC with coronary atherosclerosis.[11] At the same time there is literature gap regarding the prevalence of DELC in general population and seeking its association with various ailments. In these circumstances it is imperative to conduct a study to determine the prevalence of DELC in general population.

Material and Methods

A cross-sectional study was carried out at Shalimar Medical and Dental College in the department of Forensic Medicine and Toxicology from 20th to 27th of September 2022. Study participants were residents of different parts of Lahore city. Adults of both genders were included and with age ranging from 20 to 70 years irrespective of socioeconomic status. Sampling was done by convenient sampling technique. All the patients with normal anatomy of earlobes without acquired ear modifications and ailments of external ears (acute and chronic) were included in the research. Patients with ear lobe alterations like surgical modifications and heavy piercings in one or both ears and those whose pinna was distorted due to some diseases were excluded. Sample size was calculated by using prevalence of DELC (25%) as obtained from a pilot study. Calculated sample size was n=277 with 95 % confidence interval.

A well-designed questionnaire as per the need of study was developed to collect and record the data of the participants. The questionnaire was pretested and used for pilot study also. Students being supervised by senior faculty were given training by investigator with the help of power point presentation for identification, classification of DELC into mild and severe, and for the collection of data by using the questionnaire. Trained persons were also provided with the photograph of DELC to help them in explaining about the study to participants.

The informed consent was obtained from the participants of the study. The demographic profile was recorded on a structured questionnaire and participants were asked about history of three medical ailments namely CAD, DM, and HTN, ear lobes of both ears were examined for the status of ear lobe crease and the answers were recorded. The ethical approval was obtained from the institute review board.

The ear lobe creases were scored according to extent and depth and location as

1. No earlobe crease, Score 0
2. Ear lobe crease not touching both borders of ear lobes Score 1
3. Ear lobe crease touching or extending to both borders of an ear lobe and deep Score 2. Both ears will be observed in similar way.[12]

Total scoring

Absent ear lobe crease 0
Mild ear lobe crease 1-2
Severe ear lobe crease 3-4

Statistical analysis was done by using SPSS 22 software (IBMCorp, Armonk, New York, USA). Prevalence and percentages were calculated. The categorical variables were expressed in percentages and quantitative characteristics expressed as means +/- standard deviation Chi-square test was applied to find out the association between DELC and diseases, namely CAD, DM, and HTN.

Results

The prevalence of bilateral DELC in our study was found to be 29.6% (Fig-1). There were 167 males (60.3%) and 110 (39.7%) female participants in the study. The Bilateral DELC was more prevalent in males 36% than in females 20%. The male dominance of the crease was found to be statically significant. (P=0.004) Table-2. Mean age of participants was 40.02 years with standard deviation ±13.174. Diagonal crease was more prevalent

in older age group (49%). Table-1. The prevalence of mild and severe bilateral DELC was 89% and 11% respectively Table-3 -. The 57 patients (20.6%) had history of HTN while the history of Diabetes was present in 19.1% patients. 3.6% patients had the history of CAD respectively. Among the 10 patients having the history of CAD 70% had bilateral crease. Similarly in 57 patients presenting with the history of HTN 49% patients had bilateral ear lobe crease, while in 53 patients with diabetes 45% had earlobe crease respectively. Significant association was observed between bilateral DELC and DM (p = 0.005), HTN (P = 0.001) and CAD (P=0.004). Table-4.

Table 1: *Frequency of DELC*

Age Group	Frequency Of DELC	Percentage %
20 to 35	14	17
36 to 50	28	34
51 to 70	40	49
Total	82	100

Table 2: *Gender distribution of diagonal earlobe crease*

DELC	Sex		Total	P Value
	Female, n (%)	Male, n (%)		
Yes	22(20%)	60 (36%)	82(29.6%)	0.004
No	88(80%)	107(64%)		
Total	110(100)	167(100)		

Table 3: *Grade of BDELC*

Grades	Freq	%
Mild	73	89%
Severe	9	11%
Total	82	100%

BDELC= Bilateral Diagonal earlobe crease

Table 4: *Association between diagonal earlobe crease and medical ailments*

Association between DELC and CAD				
DELC	**CAD**		**Total**	**Significance**
	Yes, *n* (%)	**No, *n* (%)**		
Yes	7 (70)	75(28)	82(29.6)	
No	3(30)	192(72)	195(70.4)	P= 0.004
Total	10 (100)	267(100)	277(100)	
Association between DELC and DM				
DELC	**DM**		**Total**	**Significance**
	Yes, *n* (%)	**No, *n* (%)**		
Yes	24(45.3)	58(26%)	82(29.6)	P= 0.005
No	29(54.7)	166(74%)	195(70.4)	
Total	53(100)	224(100)	277(100)	
Association between DELC and HTN				
DELC	**HTN**		**Total**	**Significance**
	Yes, *n* (%)	**No, *n* (%)**		
Yes	28(49)	54(24.5)	82(29.6)	P= 0.000
No	29(51)	166(75.5)	195(70.4)	
Total	57(100)	220	277(100)	

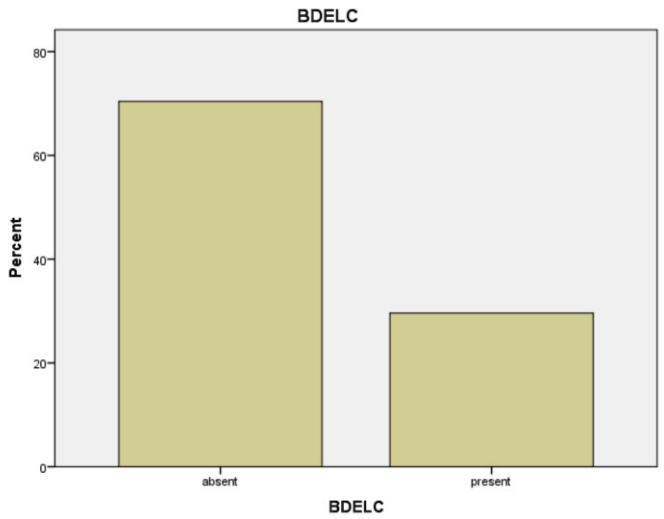

Figure 1. *Prevalence of BDELC*

Discussion

Diagonal ear lobe crease is thought to be a cutaneous marker of generalized atherosclerosis. It has been stated already that both earlobes and heart are supplied by "end arteries" and the chances for development of collateral circulation are minimum. Significant research work involving the histopathology from earlobe in cases of DELC have revealed some characteristic premature variations, like degeneration of elastin, atrophic elastic fibers, and the thickening of anterior artery wall.[13] The presence of diagonal ear lobe crease as a noninvasive marker is an important marker that could result in increase in pretest probability.[14] Most of the studies conducted in clinical settings or on findings on angiogram and postmortem study reports suggest that DELC may be associated with CAD and can be used as a valuable sign which can be identified easily clinically.[15,16]

A meta-analysis from literature review revealed around 5 times increased likelihood of having CAD in the presence of DELC (OR 4.61 P<0.00001) and the association between these categorical variables was independent of different conventional cardiovascular risk factors including the age. In this regard, it can be conceived that DELC may be an important risk marker for CAD.[17]

Majority of the studies determining the "prevalence" of DELC was conducted in hospital settings while our study is a community-based study. The prevalence of

DELC is found to be 29.6% in our study which is higher than a study conducted in India showed the prevalence of 2.7%.[12] The prevalence of DELC was found to be significantly higher in males. This finding of male preponderance matches with the other studies though the studies were hospital based.[15] It was observed that prevalence of DELC was mainly present in the older age and similar findings were noted by other investigators.[12,19] Another theory regarding the pathophysiology of atherosclerosis is telomeres shortening during a period when somatic cells undergo replication. This attrition in the length of telomere represents the progression in the biological age. Telomere length in addition to the oxidative stress and inflammatory processes involving the circulatory system of an individual during his life has been reported to be a useful marker of biological aging of the cardiovascular system. A study carried out in Japan on Japanese population with metabolic syndromes revealed that DELC was associated with telomere shortening, which is an indicator for accelerated aging and associated atherosclerosis.[18]

It has already been discussed that this cutaneous noninvasive marker is significantly associated with coronary artery disease which is a leading cause of sudden death. The death which occurs without any preceding symptoms is regarded as sudden death and from medico-legal perspectives it provokes the suspicion of foul play. So in theses situation this cutaneous sign might be helpful while framing opinion regarding the cause of death.[20]

DELC was also observed to be significantly associated with DM, HTN and CAD in our study. DM and HTN are independent risk factors for CAD, and patients with DM and HTN are vulnerable to atherosclerosis. This fact may explain a significant association between DELC, DM, and HTN. These findings are in accordance with the study conducted and are in contrast with other studies.[21]

Keeping in view all the discussion, it is suggested that as there is close association between diagonal ear lobe crease (DELC) and CAD which in turn is the leading cause of the death worldwide, this cutaneous marker may be of forensic concern as forensic experts often come across with the cases of sudden deaths occurring in suspicious circumstances. In these scenarios the ear lobes can be examined for the presence or absence of ear lobe crease and emphasis should be given to complete and meticulous dissection of heart and related vessel including histopathological findings. But still, it requires further research work on larger samples and while conducting autopsies on the victims of sudden death the ear lobe examination may be included as a part of external examination.

Conclusion

The prevalence of the DELC is found to be 29.6% in general population with male predominance. The DELC showed statistically significant association with various body ailments including CAD, DM and HTN.

Conflicts of interest *None*

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Authors Contribution

MZB, MKB: Conceptualization of Project
SM, FA, AF, SA: Data Collection
MKB, MM: Literature Search
MKB, SA: Statistical Analysis
MKB, SM: Drafting, Revision
MKB: Writing of Manuscript

Demographic and Clinical Correlates of Deliberate Self-harm in Patients with Substance Use Disorder

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Abstract

Objective: To evaluate the demographic and clinical correlates of deliberate self-harm in patients with substance use disorder.

Method: Correlational research design, the study was conducted in out-patient Department of Psychiatry, Services Hospital, Lahore. 75 male participants gave their consent to participate in the study. Demographic form comprised of information i.e. age, education, marital status, type and years of substance use, no. of hospitalization and relapses, history and means of self-harm etc were gathered. The participants with self-harm history were then given an Inventory of Deliberate Self-Harm to assess the means of self-harm. Descriptive analysis i.e. means, standard deviation, frequency and percentages were calculated for relevant variables. Pearson's Correlation was employed to assess the association between scale variables.

Results: The frequency of self-harm was 45.3% in the present study. The findings were significantly associated with being unemployed, long standing history of substance use, and opioid use disorder.

Conclusion: Keeping in view the high frequency of self-harm in substance use disorder, practical consideration should be taken by health care system to manage this issue at immediate level.

Keywords: Deliberate Self-Harm, Substance Use Disorder, Epidemiology

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Introduction

Suicide is the fourth leading cause of death among 15-19 years-old.[1] Strongest risk factor for suicide is deliberate self-harm, and it is applied on young as well as older people. Single episode of self-harm, in the following year, increases the risk of suicide to 60 to 100 times.[2] According to Keith Hawton, in his prospective study of 20 years duration of Deliberate self-harm (DSH) in young people, 57.4% of all deaths during study period were due to suicide.[4] The prevalence of DSH is 23.6% in age range 12-19 years.[5] Psychiatric disorders and use of multiple substances also increase the risk for greater severity.[6]

Substance use disorder has been considered to be an important risk factor that is significantly associated with self-harm.[7] In another study, deliberate self-harm is the most common condition associated in substance use disorder i.e. 27.1% in substance users,[10] and recently 20% patients reported substance use at the time of self harm[3].

In Pakistan, substance use has reached to the alarming situation. About 5.8% or 6.45 million, of the population aged 15 to 64 used drugs in 2012.[8]

The severity and intent of attempting self-harm vary among the sub groups of substance use disorder from passive wish to death, imprecise plan to precise plan of action and to actively attempting self-harm.[7] Keeping in view the difference of severity or intent, socio-demographic and clinical correlates must be considered in

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evaluating the risk factors leading to self-harm in substance use disorder. The purpose of this study was to assess frequency and determinants of self-harm behavior in patients with substance use disorder. Secondly, to explore demographic and clinical correlates of increased rates of deliberate self-harm in substance use disorder in Pakistani context. This study may serve to highlight the issue, leading to further research in preparing effective management plans for patients of substance use disorder.

Material and Methods

Correlational research design was used to conduct this study in out-patient department of Psychiatry, Services Hospital, Lahore. An inclusion criterion was followed while recruiting include: male, age 15 years and above with history of any substance use disorder as per Diagnostic and Statistical Manual of Mental Disorders criteria. The process of data collection was started after approval from the ethical committee of hospital. Non-probability purposive sampling technique was used for data collection. Patients from outpatient department of Psychiatry, Services hospital, Lahore, strictly fulfilling the inclusion criteria were included. Informed consent was taken after explaining the purpose and method of study. Demographic information (age, education, birth order, marital and educational status, occupation and monthly income, type of family system ete) clinical information (age of onset of substance use, substance of use at time of data collection, no. and reason of relapses, attempts to withdraw, no. of hospitalization, history of self-harm etc) were recorded. Details about means and actions of self-harm were recorded by using 17-Item inventory named Deliberate Self-Harm Inventory.[11] The collected data was entered to IBM SPSS v21 for descriptive and correlation analysis.

Results

A total of 75 participants were enrolled in study after fulfilling the inclusion criteria. Demographic details of the sample are mentioned in **Table-I**. The mean age of patients were (31.5±9.02), majority were married (n=40; 53.3%), were employed (n=53; 70.7%), living in nuclear family system (n=43; 57.3%). Frequency of deliberate self-harm in substance use disorder was (n=34; 45.3%). Clinical details of sample are mentioned in **Table-II**. The mean of substance use in years were (8.09± 6.99), Majority of the patients were dependent on opioid i.e. heroin (n=40;53.3%), with cause of relapse was craving (n=21; 28%) and reason behind self-harm attempt was mental or financial stress (n=31;41.3). Correlation analysis of sample was mentioned in **Table-III**. Results revealed negative relationship with employment status and self-harm. Whereas, positive relationship with dura-

Table 1: *Demographic characteristics of patients (n=75).*

Demographic Variables	M±*SD* or *f*(%)
Age (years)	31.5±9.02
Education (years)	8.10±4.56
Marital status	
Unmarried	30(40)
Married	40(53.3)
Divorced	5(6.7)
Employment Status	
Unemployed	22(29.3)
Employed	53(70.7)
Family System	
Nuclear	43(57.3)
Joint	32(42.7)
Self-harm	
Yes	34(45.3)
No	41(54.7)

Note. M= mean, SD= Standard Deviation. f= frequency

Table 2: *Clinical details of patients (n= 75).*

Clinical variables	M±*SD* or *f*(%)
Duration of Abuse (years)	8.09±*6.99*
Type of substance use	
Opioid use disorder	40(53.3)
Cannabis use disorder	14(18.6)
Alcohol use disorder	7(9.3)
Stimulus use disorder	6(8)
Tobacco use disorder	5(6.6)
Sedative, hypnotics or anxiolytics use disorder	3(4)
Causes of relapse	
Craving	21(28)
Peer Pressure	17(22.7)
Stress	14(18.7)
Reason of self-harm	
Intoxification	3(4)
Mental/financial stress	31(41.3)
In remission	1(1.3)

Note. f = Frequency, % = Percentage

Table 3: *Association between self-harm attempts with demographic variables (N=75)*

Measures	1	2	3	4	5	6	7	8	9	10
1.age	-	.05	.01	.0 5	.07	-.02	.454**	-.08	-.01	-.01
2.Employment status		-	.09	.01	.11	-.09	-.16	-.19	-.04	-.401**
3.Education			-	.22	-.17	-.08	-.18	.03	.335**	.04
4.Religiousinclination				-	-.15	.23	.01	-.14	.05	-.01
5.No. of addicts in family					-	-.10	.17	-.17	.001	.143
6.Family system						-	.07	.251*	.05	-.05
7.Duration of abuse							-	.01	-.02	.349**
8. No. of hospitalization								-	.290*	.09
9. No. of relapses									-	.13
10.Total self-harm score						-				-

Note.*.p < .05; **.p< .01; ***.p< .001

tion of abuse with self-harm.

Discussion

The present research was carried out to evaluate the demographic and clinical correlates of deliberate self-harm in patients with substance use disorder in Pakistani population because substance use has increased in recent years in Pakistan[8] and according to international literature the most common condition associated with substance use disorder is DSH.[10] This work has not been done on Pakistani population at large. The findings suggest that self-harm is frequently present in patients with substance use disorder and the findings also revealed several demographic and clinical correlates including middle age, married/un-married, employed, living in nuclear family system, severity of substance use disorder with shorter duration of abuse, opioid dependence, with peer pressure being the most common cause of relapse and mental/financial stress being the reason being attempting self-harm. Duration of substance use and unemployment were significantly correlated with self-harm attempts. Conflicts with family and psychosocial stressor were also identified in another Pakistani study[9]. The mean age of substance use patients who attempted self-harm was 31.5+9.02. Previous researches carried on demographic profiles suggests that patients with substance use disorder in their early thirties are going through severe emotional pain i.e. anger, frustration, sadness and lack healthy coping skills to manage their emotional pain.[7,12]

Demographic profiles of sample revealed that majority of the patients are married/unmarried, employed and living in nuclear family system. These findings were in line with previous researches carried out in India[7,12,13] suggests that lack of poor social support, day to day life stressors and financial instability can be viewed as risk factor for continued use of substance leading towards repeated attempts of self-harm. A Pakistani study reports the most common reason for attempting SH was inter-personal relationship issues (54.3%).[15]

The frequency of deliberate self-harm in substance use disorder was 45.3%. The findings of our study are in agreement with previous studies showing deliberate self-harm is the most common condition associated in substance use disorder i.e.44.8%,[14] 32.7%,[7] 23.6%[5] and 27.1%.[10] Williams and Hasking[15] suggest that both substance use and self-harm are associated with poor impulse control. There is extensive research evidence linking impulsivity with substance use.

The clinical profile of the sample revealed that majority of the patients who attempted self-harm has longer duration of substance abuse and are opioid depended. Patients with longer and consistent use of substance use, attempts self-harm as an alternative method. People who usually harm themselves with cutting, burning etc may shift to other drugs as an alternative method.[16]

The presence of opioid dependence is significantly associated with self-ham attempts. Previous researches[7,16] revealed that opioid substances release endorphins i.e. associated with positive feelings and reduction in pain, the same is true for self-harm thus increasing the risk of attempting self-harm in patients with opioid dependence.

The most common method of attempting self-harm was cutting self with sharp instruments.

Results from correlation analysis revealed significant relationship of self-harm and employment. Unemployed

person has greater chances of attempting self-harm as compared to employed one. The correlation analysis further revealed significant positive relationship with duration of abuse. The longer the duration the higher rate of attempting self-harm.

This study served to highlight the issue and leads to further research in preparing effective management plans for patients of substance use disorder.

Conclusion

We concluded that the frequency of deliberate self-harm is higher in substance use disorder in Pakistani population. Demographic as well as clinical profile should be taken into account when dealing with risk of self-harm attempt so that further chances of attempting self-harm can be minimized.

Conflict of Interest: None

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Authors Contribution

NA, RRH: Conceptualization of Project
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AB: Drafting, Revision
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Diagnostic Accuracy of CT Scan in Necrotizing Pancreatitis Taking Surgical findings as Gold Standard

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Abstract

Objective: To find out diagnostic accuracy of computed tomography (CT) for necrotizing pancreatitis in comparison with surgical findings (gold standard).

Method: This cross-sectional study was conducted in Department of Radiology, Jinnah Hospital, Lahore from January 2019 to December 2019. 165 patients clinically suspected to have necrotizing pancreatitis aged 30-70 of either gender constituted the study population. After taking informed consent, pre and post contrast CT scans of the abdomen were performed. These studies were then assessed by experienced consultant radiologist for presence or absence of necrotizing pancreatitis. These findings were then compared with surgical findings.

Results: Mean age of the study population was 47.45 with standard deviation of 8.34 years having male: female ratio of 1.5:1. Among patients diagnosed with necrotizing pancreatitis on CT, 82 turned out to be True Positive and 11 False Positive. On the other hand, there were 06 False Negative and 66 True Negative patients in those not diagnosed with necrotizing pancreatitis by CT (p=0.580). The diagnostic accuracy of computed tomography (CT) in necrotizing pancreatitis came out to be 89.70%.

Conclusion: Computed tomography (CT) has dramatically improved our ability of accurate detection of necrotizing pancreatitis and can improve patient care by guiding pre-operative management plan of these patients.

Keywords: acute pancreatitis, computed tomography, necrotizing pancreatitis

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Introduction

Acute pancreatitis starts with damage to acinar cells of pancreas. This releases activated enzymes into the pancreatic interstitium and surrounding tissue.[1] The ensuing inflammation can lead to a process which can be classified as either edematous or necrotizing, each of which has different morphological features, disease course, management and prognosis.[2] The importance of differentiating between these 2 entities can be gauged from the fact that reported mortality rates of 1.5% in patients with mild interstitial pancreatitis[3] jump to 15%–40% in patients with necrotizing pancreatitis.[4] Not only does necrotizing pancreatitis carry a grave prognosis in comparison with interstitial pancreatitis, but within the subset of patients with necrotizing variety, the rate of organ failure and mortality also depends on the degree of necrosis.[5] Necrosis occurs in a sizeable proportion of patients with pancreatitis seen in upto 20-30% of cases.[6]

Role of imaging in pancreatitis ranges from confirmation of diagnosis to grading the disease severity, detecting complications as well as therapeutic purposes. Albeit its limited diagnostic value, the first imaging undergone

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by most patients is ultrasound.[7] However, CT scan is standard imaging modality for acute pancreatitis.[4] Its most important role is in diagnosing necrosis, establishing its extent and detecting complications.[8] Recently, pancreatic necrosis volume as calculated on CT has been shown to have a prognostic value as well, predicting the chances of readmission and re intervention in these patients.[9] Takahashi Net al[10] have shown sensitivity and specificity of CT scan in diagnosing necrotizing pancreatitis as 80.0% and 82.2% respectively. On searching the previous literature, we found limited data for using this non-invasive imaging modality in general practice for diagnosing necrotizing pancreatitis particularly in our part of the world. Thus, we planned this study to determine utility of computed tomography in diagnosing necrotizing pancreatitis.

Materials and Methods

This descriptive, cross-sectional study was conducted at Department of Diagnostic Radiology, Jinnah Hospital, Lahore from January to December 2019. Sample size of 165 cases was calculated keeping 95% confidence level, 7% margin of error for sensitivity and 9% margin of error for specificity and taking expected percentage of necrotizing pancreatitis i.e. 70.0%[11] with sensitivity 80.0%[12] and specificity 82.2%[10] of computed tomography in diagnosing necrotizing pancreatitis. After taking permission from Ethical Committee, patients who ful-filled the inclusion criteria were selected through non-probability, consecutive sampling. All patients of either gender and aged 30-70 years who presented with clinical suspicion of necrotizing pancreatitis [presence of sudden onset abdominal pain (epigastric pain radiating to the back) and serum amylase > 400 U/L] with duration of symptoms <14 days were included. Patients with history of abdominal trauma or surgery, pregnant patients, those with chronic renal failure and those unwilling to undergo surgery were excluded. Furthermore, those patients who improved on conservative treatment and did not undergo surgery were subsequently excluded from the study.

After taking informed consent, patients underwent CT scans of the abdomen with administration of intravenous contrast on 16 slice CT scanner. All studies were read by a consultant radiologist having 5 years' experience of interpreting CT scans. Presence of pancreatic necrosis was specifically documented - this was defined as the presence of non-enhancing areas within the pancreatic parenchyma, having density of less than 30 HU on post contrast images (Figures 1 and 2). Pancreatic necrosis was further graded as less than 30 % or more than 30% based on the extent of percentage of parenchyma showing density less than 30 HU. The patients were then followed up and those who did not undergo surgery were excluded. Those who underwent surgery according to the management decision based on their clinical status, were followed for their per operative findings. Then CT scan findings of patients were compared with surgical findings. Collected data was analyzed through computer software SPSS 20.0. Frequency and percentages were tabulated and used to calculate sensitivity, specificity and diagnostic accuracy.

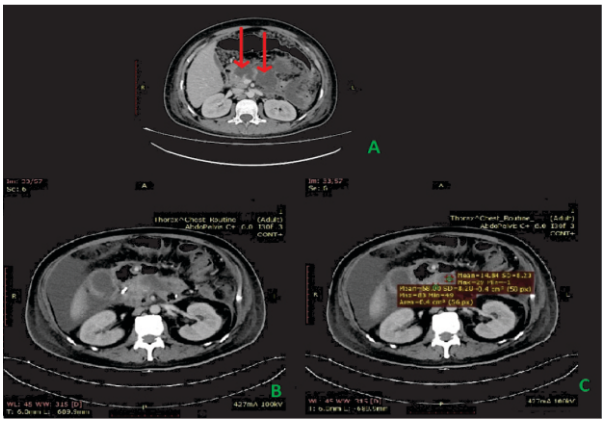

Fig-1: A) *Axial CT scan section showing typical findings of non-enhancing areas in pancreas in necrotizing pancreatitis (red arrows)* **B)** *Axial CT scan in another patient shows areas of non enhancing pancreatic parenchyma in pancreatic head and neck which on drawing ROI show density of 14 HU as compared to 68 HU of normal enhancing pancreatic parechyma (E)*

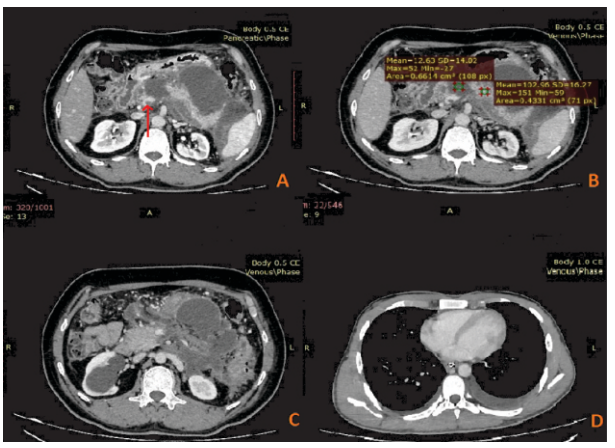

Fig- 2: *Axial CT sections in another patient show non enhancing areas in pancreas in a patient with necrotizing pancreatitis show* **A)** *thrombosis in portal vein* **B)** *non enhancing pancreatic parenchyma having density of*

12 HU as compared to 102 of normal enhancing pancreas **C)** *Extensive peripancreatic collections* **D)** *Bilateral pleural effusions*

Results

The mean age of patients was 47.45 years with standard deviation of 8.34 years and range of 30-60 years. Majority (40.61%) were aged 41 to 50 years. 100 (60.61%) of them were male and 65 (39.39%) were females. Mean duration of disease was 6.76 ± 3.29 days. 68 (41.2%) had less than 30 % pancreatic necrosis while 97 (58.8%) had more than 30% pancreatic necrosis. CT scan findings favoured diagnosis of necrotizing pancreatitis in 93 (56.36%) patients. Surgical findings confirmed necrotizing pancreatitis in 88 (53.33%) cases. Considering the findings on CT scan, there were 82 True Positive, 11 False Positive, 06 False Negative and 66 True Negative (p=0.580) (Table 1). Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of computed tomography (CT) in diagnosing necrotizing pancreatitis was 93.68%, 85.71%, 88.17%, 91.67% and 89.70% respectively. Further analysis revealed no significant effect of age, gender, duration of disease or extent of pancreatic necrosis on the sensitivity, specificity, PPV, NPV and diagnostic accuracy of CT scan (p value ≥ 0.05).

Table 1: *2 x 2 table comparing the findings of CT scan and surgery.*

	Positive on CT	Negative on CT	Total	P-value
Positive on surgery	82	06	88	
Negative on surgery	11	66	77	
Total	93	72		0.580
	Sensitivity = 93.68% Specificity = 85.71 % PPV = 88.17% NPV = 91.67% Accuracy = 89.70%			

Discussion

The diagnosis of pancreatitis requires a combination of clinical assessment and laboratory investigations particularly measurement of serum amylase and lipase levels. Once the diagnosis of acute pancreatitis has been established, role of imaging comes into play which further confirms the diagnosis, helps in detecting complications and assesses the disease severity. This includes classification of the disease into necrotizing and non-necrotizing or interstitial edematous subtypes. It is an established fact that presence and extent of necrosis directly correlates with mortality rate in acute pancreatitis.[13] The mortality rate has been shown to increase by 10-25 % if necrosis develops as compared to non-necrotizing acute pancreatitis. If this necrosis becomes secondarily infected, the mortality rate increases further. Hence there is a need for establishing the presence of necrosis as early as possible. Patient management, disease course and progression, therapeutic strategies all depend on presence and extent of necrosis. Assessment of necrosis has prognostic implications as well since there is an incidence of 2%–10% potentially lethal attacks in acute necrotizing pancreatitis.[8] Thus, the early detection of pancreatic necrosis is crucial for this as well. Noninvasive investigations for pancreatitis have evolved rapidly in the last decade. An ideal test should be able to detect necrosis early, provide rapid results with high sensitivity, be easily available and be cost effective[14] Different clinical criteria and laboratory investigations satisfy this criterion to a variable extent, each having its own advantages as well as limitations. With the advancements in imaging technology, it has come to the forefront for diagnosis of pancreatitis, particularly necrotizing variety. The role of imaging is not only limited to establishing diagnosis of necrotizing pancreatitis but also to determine underlying cause, grade the disease severity and identify complications. Additionally, therapeutic interventions can also be performed under image guidance.[15] The decision to perform intervention in initial uncomplicated necrotizing pancreatitis is based on clinical condition, CT imaging or laboratory investigations.[16]

CT is the main diagnostic tool in acute necrotizing pancreatitis since it can determine the extent and severity of necrosis.[17] Furthermore it is a prognostic tool because its findings have been shown to correlate well with outcome[18] CT severity index established by Balthazar et al[19] and later on modified by Mortele et al[20] have been found to correlate well with disease outcomes. Nevertheless, a CT scan performed earlier than 72 hours has limited accuracy in delineating necrotic areas.[21] However, CT scan has a role in follow up too as well as for planning therapy.[22] In a series,[12] length of hospital stay and development of complications showed an excellent correlation with pancreatic necrosis as detected on CT. Morbidity rates in necrotic vs non necrotic pancreatitis as defined on CT were 82 % and 6 % respectively. Similarly, there was 23 % mortality in case with necrosis

in comparison with no death in those without necrosis. Not only this, but extent of necrosis also correlated well with prognosis. Other investigators[5,18] later confirmed the validity of these findings.

While it has been found that presence of necrosis correlates with prognosis, it does not predict percutaneous intervention success or failure.[23] Yet, it has been established that imaging modalities should be employed for detecting necrosis and pancreatic ductal disruption before minimally invasive procedures.[24] Infact, in certain special situations, CT has been found to detect pancreatitis even before serum lipase levels.[25] This study provided similar results showing that CT is a highly accurate technique for establishing diagnosis of necrotizing variety of acute pancreatitis.

Conclusion

This study concluded that computed tomography (CT) can dramatically improve our ability to accurately detect necrotizing pancreatitis and improve patient care by pre-operatively planning the proper management of patients.

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Conflict of Interest *None*

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Authors Contribution

RS, AM: Conceptualization of Project
RS, AM, SA: Data Collection
ZI, AA: Literature Search
ZI, AA: Statistical Analysis
RS, AM, SA: Drafting, Revision
AM, SA, MM: Writing of Manuscript

Determination of Clinical Patterns of Onychomycosis in Patients presenting with Nail Disorders to a Tertiary Care Hospital

Ayesha Sarwar,[1] Asma Kanwal,[2] Hira Tariq,[3] Muhammad Shahid,[4] Faria Asad,[5] Salman Haseeb[6]

Abstract

Objective: To determine the clinical pattern of onychomycosis among patients of nail diseases at Faisalabad

Method: This cross-sectional survey was done over a period of six months, at Outpatient Department of Dermatology, Allied/ D.H.Q Hospitals, Faisalabad Medical University. 210 cases with clinical diagnosis of onychomycosis were included. Patients taking treatment for fungal infection were excluded. Detailed history and examination was done. Type of onychomycosis was noted. Co morbidities like diabetes, hypertension and immunosuppression (determined on history and medical record) were noted.

Results: A total of 210 patients were included with mean age 47.14±13.71 years. Males were 113 (53.81%) and females were 97 (46.19%). Distal lateral subungual onychomycosis (DLSO) was seen in 112 (53.33%), Total dystrophic onychomycosis (TDO) in 56 (26.67%), proximal subungual onychomycosis (PSO) in 27 (12.86%) and white superficial onychomycosis (WSO) in 15 (7.14%) patients.

Conclusion: It is seen that onychomycosis is a frequently seen nail disorder at a tertiary care setting. Distal lateral subungual onychomycosis was the most frequently encountered clinical pattern.

Keywords: Pattern, Onychomycosis, Nail disorders, Tertiary care hospital

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Introduction

Finger and toenails are frequently infected by dermatophytes and yeasts causing onychomycosis.[1] Increasing age, immunosuppression and repeated trauma contribute to more cases of onychomycosis presenting to health care settings.[2] Other contributing factors include increased sweating, swimming, diabetes, etc. It is not a life-threatening condition, however, it significantly impairs quality of life of sufferers.[3]

Onychomycosis is caused by dermatophytes, non-dermatophyte moulds (NDM) and yeasts.[4] Diseases that may mimic onychomycosis include inflammatory diseases like psoriasis, lupus erythematosus, lichen planus, bacterial paronychia and nail apparatus tumors.[5] KOH examination can provide immediate and accurate information in the diagnosis of onychomycosis.[6]

Predominantly observed patterns of onychomycosis are Distal or lateral subungual Onychomycosis (DLSO), which is the commonest pattern seen; Total dystrophic subungual Onychomycosis (TDO); Proximal Subungual Onychomycosis (PSO); Superficial white Onychomycosis (SWO).[7] White superficial onychomycosis (WSO) is characteristic in immunocompromised patients. Onychomycosis in diabetes generally indiactes complicated disease.[8]

Owing to latest therapeutic advances, prognosis of disease has significantly improved.[9] Therefore, it is expected that the frequencies of various patterns of onychomycosis have changed over time. There is no updated local data available regarding the frequency and clinical pattern of onychomycosis in our population.

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This study will provide data about the magnitude of the disease so that preventive steps can be taken to avoid or better manage the condition. Unfortunately, due to lack of resources mycological confirmation couldn't be attempted. Our data however, may help other researchers base their analyses of mycological species and drug resistance on pattern of disease presenting in patients of various ages and risk factors.

Materials and Methods

This cross-sectional survey was done at Dermatology unit, DHQ hospital Faisalabad from 15th January 2021 to 14th July 2021. Patients of both genders presenting with clinical diagnosis of onycomycosis, aged 18 to 80 years were included after taking written informed consent. Patients already taking treatment for fungal infections or having nail diseases that closely mimic onychomycosis (psoriasis, eczema) were excluded.

Detailed history and clinical examination was done. Type of onychomycosis was noted. Fungal scrapping was done to confirm diagnosis of onychomycosis in cases where diagnosis was not confirmed. Data was entered in predesigned proforma.

Data was entered and analysed using SPSS Vs 27. Mean and standard deviation were used to present quantitative variables. Qualitative variables were expressed as frequency and percentages. Role of effect modifiers like age, gender, diabetes, hypertension, immunosuppression and duration of disease were addressed through stratification of data. Post-stratification, results were analysed using student t-test. A p-value of ≤ 0.05 was considered significant.

Results

After taking written informed consent, 210 patients of onychomycosis were enrolled. Their ages ranged from 18 to 80 years with mean age of 47.14 ± 13.71 years. Majority of the patients (138/ 65.71%) were between 18 to 50 years of age as shown in Table 1. 113 patients (53.81%) were male and 97 (46.19%) were female with male to female ratio 1.25:1. Effect modifiers like age, gender, diabetes, hypertension, immunosuppression and duration of disease had statistically significant association with clinical patterns seen (Table 2).

In our study, clinical pattern of DLSO was observed in 112 (53.33%), TDO in 56 (26.67%), PSO in 27 (12.86%) and WSO in 15 (7.14%) patients (Fig 1).

Table 1: *Descriptive Demographic Data of Patients*

		Number of Patients	Percentage %
Age	18-50	138	65.71
	51-80	72	34.29
Gender	Female	97	46.19
	Male	113	53.81
Immunosuppression	Yes	101	48.10
	No	109	51.90
Contributing Factors	Yes	130	61.90
	No	80	38.10
Diabetes Mellites	Yes	103	49.05
	No	107	50.95
Hypertension	Yes	131	62.38
	No	79	37.62
Duration of Disease (months)	⩽6	145	69.05
	>6	65	30.95

Table 2: *Stratification of Clinical Pattern with Respect to Effect Modifiers*

		DLSO	TDO	PSO	WSO	p-value
Age	18-50	65	36	23	14	0.006
	51-80	47	20	04	01	
Gender	Male	57	31	21	09	0.011
	Female	55	25	06	11	
Duration	⩽6	78	29	25	13	0.001
	>6	34	27	02	02	
Diabetes Mellitus	Yes	47	30	12	14	0.002
	No	65	26	15	01	
Hypertension	Yes	80	28	19	09	0.001
	No	32	28	08	11	
Immuno-suppression	Yes	49	21	20	11	0.002
	No	63	35	07	04	

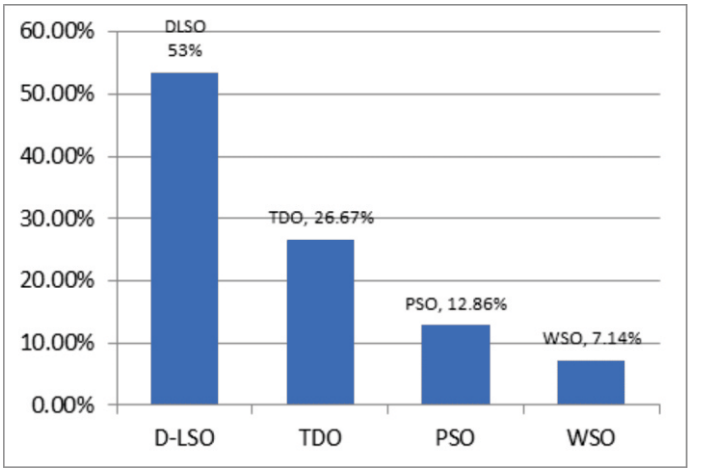

Fig 1: Frequency of various patterns of Onchomycosis

Discussion

In our study, DLSO was the commonest clinical pattern seen in 112 (53.33%) patients, followed by TDO in 56 (26.67%), PSO in 27 (12.86%) and WSO in 15 (7.14%) patients. Similar results have been reported in a number of studies.10-12 Ma Y et al. studied dermoscopic findings in onychomycosis in Chinese patients and found DLSO pattern in 59 (67.82%), TDO in 19 (21.83%), PSO in 6 (6.90%) and WSO in 3 (3.45%) patients.[10] Grover S observed various clinical patterns of onychomycosis in Indian population and found DLSO as the commonest pattern seen while WSO was least commonly seen. They too observed that the disease was commoner among younger population, probably because of being physically active and prone to trauma and infections. They seek medical advice earlier due to cosmetic reasons.[12,13]

Elderly men with diabetes were found to be particularly prone to the development of onychomycosis. It is not fully known whether this is due to decreased immunity or diabetes itself.[14] More involvement of male patients was also highlighted by Vijaya et al.[15] This can be attributed to outdoor activities, being more prone to trauma and sports activities. Most of the patients in our study had disease duration of less than 6 months. This is contrary to other studies,[12-14] probably because of cosmetically conscious young population in our part of the world.

Onychomycosis is a common nail disorder associated with significant cosmetic and physical disability due to pain, discoloration and brittleness involved. Due to slow growth of nails, treatment is also troublesome and prolonged, leading to further aggravation of misery of patients. With advancement in treatment strategies, clinical patterns of onychomycosis may vary over time. Therefore, knowledge of these patterns are of utmost importance especially in our part of the world where no such studies have been conducted on this topic. This will lead to improved management plans and predictability of treatment and may help us in further increasing our knowledge about the causative agents too. Our results will further help researchers to plan mycological analysis of causative fungi along with drug resistance analysis in susceptible population.

Conclusion

Onychomycosis is a frequently seen disease of nails caused by dermatophytes. Knowledge of its clinical pattern is very helpful in dealing with the disease properly. We found Distal lateral subungual onychomycosis as the commonest pattern seen while white superficial onychomycosis was the least common.

Conflict of interest *None*

Funding Source *None*

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Authors Contribution

AS: Conceptualization of Project
AK: Data Collection
AS: Literature Search
SH: Statistical Analysis
MS, FA: Drafting, Revision
HT: Writing of Manuscript

Reasons for Delay in Presentation of Vesicovaginal Fistula Patients at Tertiary Health Facility

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Abstract

Objective: To explore the factors that lead to the delayed presentation of VVF in our circumstances.

Method: This is a retrospective case series study which was conducted in department of Urology Services Hospital Lahore from January,2021 to March,2022. Patient name, age and possible factors that can lead to delayed presentation of VVF to the tertiary care hospital were entered in pre designed Proforma. All data was analyzed with SPSS 25.

Results: Total 82 patients with diagnosis of VVF were included in this study. The mean age of patients was 38.50 years. The average period from the onset of symptoms to presentation at Services Hospital Lahore was 23.34 months. Approximate distance from the hospital was 34.1% patients from within 50km, 30.5% from 50 to 100 km, 17.1% patients from 100 to 200km and 18.3% patients were more than 200km. Regarding educational status, 30(36.6%) patients were uneducated, 30(36.6%) studied up to primary level and 22 (26.8%)were educated to secondary level. Out of 82 patients, 18 (22%) had a monthly income of 10000 to20000 Rupees, 45(54.9%) had a monthly income of 20000 to 30000 thousand Rupees, and 19(23.2%) had a monthly income of more than 30000 Rupees. All the patients in this research were initially treated by a local health care practitioner i.e. GP, Quacks, Homeo dr, RHC doctor and Hakeem etc.

Conclusion: Vesicovaginal fistulas patients present late at specialized centers because most of them are poor, illiterate, from far furlong areas and also because they get initial treatment from untrained practitioners.

Keywords: Obstetric fistulas, Vesicovaginal fistula, VVF, delayed presentation,

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Introduction

Genitourinary fistula is a serious public health challenge in areas where women have inadequate access to qualified professional emergency obstetric and gynecological care.[1] Due to the closeness of the bladder, ureters, uterus, and vagina, genitourinary fistulas can develop after obstetric or gynecologic surgery and result in an abnormal communication between the bladder or ureter and the uterus, cervix, or vagina.[2] Contrary to the previous trend, a significant shift has been observed regarding the etiology of female urogenital fistula. Recent studies have shown a growing incidence of iatrogenic fistula while doing pelvic surgeries i.e. caesarian section, hysterectomies for obstetric as well as gynecological reasons. In under developed nations, still prolonged obstructed labor constitutes the most common etiology of VVF (>90%), especially in Sub-Saharan African countries.[3] Pathology of VVF in case of obstructed labor is pressure necrosis which develops as a result of compression of bladder between symphysis pubis and fetal head. So any instrumentation in this area can lead to VVF formation.[4] Simple vesicovaginal fistulas are isolated, tiny (0.5 cm), and seen in patients who have not been exposed to radiation. They do not show any signs of malignancy involvement. A vesicovaginal fistula is categorized as intermediate if its size

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ranges from 0.5 to 2.5 cm. Large (>2.5 cm), complex vesicovaginal fistulas are linked to chronic illness, radiation, or failed fistula repairs in the past.[5] WHO classification of VVF is as mentioned in table1.[6] Trend that observed in various studies conducted over a period of 13 years in Pakistan show a significant increase in iatrogenic fistula.[7] Among all Genitourinary fistulas, vesicovaginal fistulas(VVF) are more common.[8] Vesicovaginal fistula is an abnormal communication between bladder and vagina that usually presents with continuous incontinence of urine.[9] The true incidence of VVF is difficult to estimate because of social stigma i.e. continuous wetness, odor, attached with this disease.[3] It is estimated that at least three million women in poor countries have unrepaired VVF and that 30 thousand to 130 thousand new cases develop each year in Africa.[9] Poor socioeconomic status, malnutrition, early marriages, low literacy rate contribute to high prevalence of VVF in under developed countries.[3] The objective of this article is to explore the factors that lead to delayed presentation of VVF in our circumstances.

Material and Methods

This is retrospective case series study which was conducted at department of Urology Services Hospital Lahore from January, 2021 to March, 2022. All patients with preoperative diagnosis of VVF who were admitted in ward were included this study. Name of patient with age and possible factors that can lead to delayed presentation of VVF to the tertiary care hospital i.e. time from symptoms to presentation at this tertiary care hospital, distance, monthly family income, educational status of patient, primary health care taker who treated her initially were entered in pre designed proforma. All data was analyzed with SPSS 25.

Results

Total 82 patients with diagnosis of VVF included in this study. The mean age of patients was 38.50 years (Range 22 to 59 years). The average period from the onset of symptoms to presentation at Services Hospital Lahore was 23.34 months (3 to 170 months). Patients came from periphery all around Lahore. The estimated distance was recorded, as given in Table 2. In terms of educational status, 30(36.6%) patients were uneducated, 30(36.6%) patients were educated up to primary school level, and 22(26.8%) patients were educated up to secondary school level. The patients' family income was also tracked on a monthly basis. Out of 82 patients, 18 (22%) had a monthly income of 10000 to 20000 Rupees, 45 (54.9%) had a monthly income of 20000 to 30000 thousand Rupees, and 19(23.2%) patients had a monthly income of more than 30000 Rupees as mentioned also in Figu-1. All the patients in this research were initially treated by a local health care practitioner, as shown in Table 3.

Table 1: *Type of Fistulas.*

SIMPLE FISTULA (GOOD PROGNOSIS)	COMPLEX FISTULA (UNCERTAIN PROGNOSIS)
• Simple Fistula < 4cm • Vesicovaginal fistula • Closing mechanism not involved • Minimal tissue loss • Ureter not involved • First attempt repair	• Fistula >4cm • Multiple fistula • Rectovaginal, mixed, cervical fistula • Closing mechanism involved • Scarring • Circumferential defect • Extensive tissue loss • Intravaginal ureters • Failed previous repair • Radiation fistula

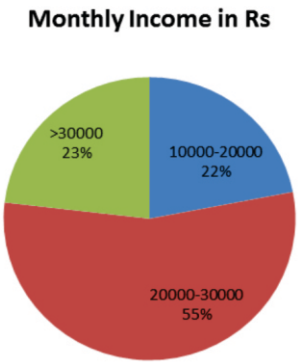

Fig -1: *Monthly family income.*

Table 2: *Distance from hospital.*

Distance(km)	Number of Patients	Percentage %
0-50	28	34.1
50-100	25	30.5
100-200	14	17.1
>200	15	18.3
Total	82	100.0

Table 3: *Primary health care provider*

	Number of patients	Percentage%
GP	22	26.8
Quack	24	29.3
Homeopathic dr	20	24.4
RHC dr	9	11.0
Hakeem	7	8.5
Total	82	100.0

Discussion

Where females are still second degree citizens especially in rural areas these people hesitate to spend money for cure of disease. This gender discrimination becomes more visible when females are poor, illiterate and unemployed. This gender inequality and its effect on female population in seeking treatment in India are well mentioned in article by Milind Deogaonkar, MD.[10] In Indian society, men typically make critical family decisions, but women abstain from making any decisions, not even those pertaining to their own health. It is well documented in this study that delayed in reaching tertiary care facility by pregnant women is because of lack of autonomy in decision making even in emergency situation by pregnant women.[11] Poverty plays major role in hindering women for seeking treatment in vesicovaginal cases. Another factor which is well mentioned in article by Muhammad Anka Nasiru is positive behavior of health care professional towards the sick is very important. Positive attitude goes long way in promoting communication between sick and health care provider and ultimately it leads to quality health care.[12] All factors which we have mentioned i.e. distance from tertiary care hospitals, lack of education, poor family income, and initial treatment from quacks contribute somehow in delaying presentation at tertiary care hospitals. Delay in seeking treatment is defined as: if a woman has incontinence of urine and/or feces and does not seek medical help for more than 3 months then this is considered as a delay to seek medical help (WHO 2006).[13] In our study we have noticed almost all age group adult female patients with mean age 38.50 (Age ranges from 22 to 59) and mean presentation time was 23.34 months. Most of our patients travelled from far-flung areas 35.4% patients in our study travelled from more than 100 km away to reach to services hospital Lahore among which 18.3% travelled from even more than 200 km. This shows how much shortage of tertiary care facilities at periphery hospitals. Literacy ratio which we have documented and that is 36.6% patients were illiterate and same percentage of patients were educated just up to primary level education. A similar study was conducted at medical college in Udaipur Rajisthan by CP Sharma et all documented education status of patients were as 41.5% illiterate, 37.5 %just educated up to primary level like our study.[14] It is worth mentioning most of our patients from poor socio economic status with average monthly income in76.9% of patients less than 30000 rupees. It is already mentioned in many studies that vesicovaginal fistula is problem of poor population and countries with poor resources.[15] And it is also documented that 29.3% patients still were under treatment initially from quacks at areas where they were living. This shows still even in this modern era patients having difficulty in reaching to qualified medical personals who can manage such complications at periphery hospitals. It is also mentioned in study done at Patna Medical College and Hospital Behar that emergency obstetric hysterectomy is one marker of obstetric morbidity. Although it is life-saving procedure in life threatening catastrophes i.e. uterine rapture, densely adherent placenta, uncontrollable hemorrhage but it is also associated with complications like hemorrhage, shock, iatrogenic bladder injury and later VVF.[16] According to statistics from throughout the world, the incidence rate of emergency obstetric hysterectomy in developing and wealthy nations differs dramatically.[17] All this high prevalence rate of such complications i.e VVF among our women because factors like high parity, early marriages, lack of family planning, inadequate qualified maternity services at rural areas, prolonged labor, illiteracy, lack of proper referral system for complicated cases.[18]

Conclusion

As mentioned in detail already that vesicovaginal fistula patients present late at specialized centres because most of them are poor, illiterate and from far furlong areas, get initial treatment from untrained practitioners. To reduce the incidence of obstetric fistulas, adequate antenatal health services, timely identification of high-risk cases, public awareness, interconnected close relationships between primary health services and tertiary hospitals, early referral with backup system, and improvement of existing health facilities in a teaching hospital with involvement of seniors, skilled, and experienced per-sonnel in the management of obstetric emergencies should be implemented.

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Authors Contribution

AM: Conceptualization of Project
MF: Data Collection
AAS: Literature Search
SG: Statistical Analysis
HF: Drafting, Revision
MSA: Writing of Manuscript

A Review of Ocular Surgeries Performed in 2020 and 2021 at Tertiary Care Hospital

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Abstract

Objective: To review the types and total number of ocular surgeries performed at Tertiary Care Hospital in two consecutive years i.e.,2020 & 2021. This study will also indicate the pattern of ophthalmic diseases in the catchment area of the hospital.

Methods: It was retrospective study. Study center was Tertiary Care Hospital. Study duration was two years i.e., 1-1-2020 to 31-12-2021.Data was obtained from eye department of Tertiary Care Hospital. Collected data was analyzed by using SPSS version 25. Tables and graphs were made which presented total number and percentage of all data.

Results: Only one ocular surgery i.e., enucleation was carried out in 2020 upon a female 31 years of age. In next year total number of ophthalmic surgeries performed was 60. 66.6 % surgeries were performed due to cataract. 60% of males were operated for cataract and 40% were females. 53.3 % of total surgeries were performed upon females . 10% of total surgeries were performed for squint, predominantly in females, 83.3 % of total squint surgeries. 60% of patients belonged to age group of 60-75years.

Conclusion: Number of surgeries carried out in 2020 was only one. In 2021 it increased upto 60 surgeries.

Keywords: Tertiary Care Hospital, cataract, glaucoma

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Introduction

The incidence of various eye diseases differs in different months of the year. But most commonly occurring diseases of eye prevailing in different areas are cataract, glaucoma, NLD blockage, trachoma[1]. A world wide data about various eye diseases occurring was collected in 2015. According to which thirty-six million people had lost their power to see things permanently. Two hundred and sixteen million people had got permanent disability due to eye diseases. That survey also concluded that pattern of eye disease occurrence differed in various areas of the world. Females more suffered than the males[2]. Multiple factors effect upon incidence of different ophthalmic diseases. These include financial condition, availability of health facility, literacy and health education[3]. Ophthalmic diseases cause a lot of financial burden upon society as well as country[4]. Most of the ophthalmic diseases are influenced by weather.[5] Ophthalmic conditions like pain, itching and decreased visual acuity are more common in women.[6] Pakistan is one of the thickly populated country in the globe. According to a survey of 2017, presbiopyia was a most prevalent disease followed by retinal detachment and cataract. The incidence of all these were more in women than men.[7] People from villages suffer with cataract more than persons living in cities.[8] The patients with diabetes and hypertension present with retinal complications. Diabetes leads the hypertension in causing retinal comlications.[9,10] Ophthalmic health improvement can be studied by looking critically the eye health indicators. Ocular surgeries were decreased in 2020 as compared to 2019.[11]

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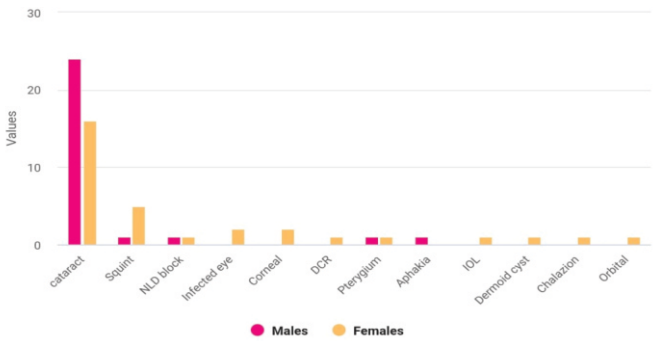
Material & Methods

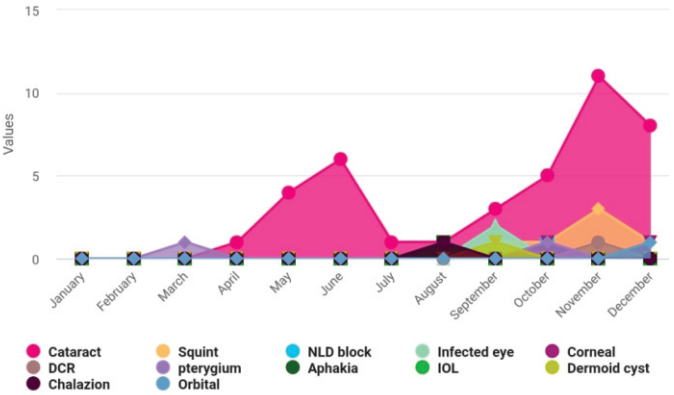
Study center was Tertiary Care Hospital. It was retrospective study. Data regarding diseases, surgery performed was obtained from eye department. The data was collected for 2 consecutive years i.e., 2020 & 2021. SPSS version 25 was used to perform statistical analysis. Tables & graphs regarding number, percentage were formed.

Results

Only one surgery of tumor of eye was performed in 2020. In 2021, 60 ophthalmic surgeries were performed. Their description is shown in table no 1.



Graph No 1: *Frequency of different ophthalmic conditions in different months of year 2021*



Graph No 2: *Frequency of different surgeries in different age groups*

Discussion

Among the ophthalmic surgeries, surgery for the opacity of the lens has been maximally performed throughout the world. Its number will go on increasing day by day[12]. In the current study surgery for squint was second to cataract surgery. Squint is an ocular condition leading to binocularity. It also effects negatively upon beauty and may lead to depression, shyness, social avoidance and inferiority complex[13]. In current study cataract surgery was maximally carried out. 66.6% of total ocular surgeries were that for cataract. This percentage is in accordance with a previous study carried out in Karachi[12]. Another

Table1: *Descriptive data indicating ocular surgeries with their percentage in both sexes.*

Ocular surgeries	Males	Percentage	Females	Percentage	Total	Percentage
Cataract	24	60%	16	40%	40	66.6%
Squint	1	16.66	5	83.33	6	10%
NLD Block	1	50%	1	50%	2	3.3%
Infected Eyes	0	0%	2	100%	2	3.3%
Corneal	0	0%	2	100%	2	3.3%
DCR	0	0%	1	100%	1	1.7%
Pterygium	1	50%	1	50%	1	3.3%
Aphakia	1	100%	0	0%	1	1.7%
IOL	0	0%	1	100%	1	1.7%
Dermoid cyst	0	0%	1	100%	1	1.7%
Chalazion	0	0%	1	100%	1	1.7%
Orbital	0	0%	1	100%	1	1.7%
Total	28		32		60	100%

Table 2: *Descriptive data indicating number of patient in different age groups*

Age	1-15	15-30	30-45	45-60	60-75	Total	Percentage
Male	2	1	3	2	20	28	60%
Female	6	4	5	1	16	32	40%
Total	8	5	8	3	36	60	
Percentage	13.3%	8.4%	13.3%	5%	60%		100%

study conducted in India among 560, 348 were patient of cataract[14]. 60% Males underwent cataract surgery and 40 % females got rid of cataract. Although in a previous study this percentage is tilted to females[15]. Another study performed in Rawalpindi 92% of overall patients was females who underwent ophthalmic surgeries[16]. In a study in Egypt this percentage was 52% for males and 48% for females[17]. Age group which most commonly got the surgery belonged to 60-75 years (60%). This result was in accordance with a study carried out in Nigeria[18]. Most of the cataract surgeries were performed in October, November and December 2021. In 2020 only one surgery was performed in the hospital. That was a tumor surgery. Comparative study indicates huge increase in the number of surgeries performed during 2021. In Punjab people enjoy four seasons ranging from very warm to very cold. This variation in season effects human life and disease incidence[19].

A scholarly work performed at Lahore show that 3rd, 10th and 11th months of the calendar were the months having the most number of cataract patients[20]. Glaucoma also shows different incidence rate in different months[21]. The results of another study carried out in Lahore indicate that glaucoma was the second most common disease causing visual impairment preceded by cataract[22]. Health care facilities related to ophthalmic surgeries has a lot been increased with altered improvement for the last decade. But the credence related to undergo ocular surgeries in specific months especially in March and October, has not been altered[23]. Ocular injuries are one of the leading causes of low vision[24,25] but in current study only one case of eye trauma was operated.

Conclusion

The most common ocular surgeries carried out in Tertiary Care Hospital in the African region. 2017. McCormick I, Mactaggart I, Resnikoff S, Muirhead D, Murthy G, Silva JC, et al. Eye health indicators for universal health coverage: results of a global expert prioritisation process. British Journal of Ophthalmology. 2022;106(7):893-901.

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SAB, MA: Conceptualization of Project
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Comparison of Ventricular Late Potentials in Patients with Ischemic and Non-Ischemic Cardiomyopathies

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Abstract

Objective: Our study aim was to compare the ventricular late potentials in patients with ischemic and non-ischemic cardiomyopathy.

Method: It was a comparative cross sectional study conducted at Cardiac Electrophysiology unit in Armed Forces Institute of Cardiology, Rawalpindi from February 2019 to August 2019. Thirty individuals with ischemic cardiomyopathy as well as thirty with non-ischemic cardiomyopathy were nominated through non-probability purposive sampling. Patients with hypertension, bundle branch block, diabetes mellitus, heart failure, stroke and those on antiarrhythmic therapy were omitted from the study. Mortara ELI 350 Electrocardiograph was used to attain Signal Averaged ECG (SAECG). Data was analyzed using SPSS-23.

Results: Total sixty subjects were recruited. Out of these, 30 were diagnosed cases of Ischemic cardiomyopathy and 30 were diagnosed cases of non-ischemic cardiomyopathy. Among those with ischemic cardiomyopathy 8(26.7%) had VLPs, while 6 (20.0%) non-ischemic patients had VLPs present. This difference was statistically insignificant. VLPs were absent in 22 (73.3%) patients with ischemic cardiomyopathy and 24 (80%) patients with non-ischemic cardiomyopathies.

Conclusion: As proven through literature, ventricular late potentials have a higher negative predictive value in comparison to their positive predictive value. Hence their absence in signal averaged ECG along with other cardiac tests helps us screen high risk population for ventricular arrhythmias.

Keywords: Ventricular late potentials, ischemic cardiomyopathy, non-ischemic cardiomyopathy, Signal Averaged ECG.

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Introduction

Cardiovascular diseases have posed high burden on health care system of Pakistan. In accordance to the Universal health coverage report Pakistan 2019, cardiovascular diseases have shifted from 5th in year 2000 to 2nd in year 2019 as disease ranking in Pakistan.[1] Latest WHO data published in 2020 stated coronary heart disease deaths in Pakistan have reached 16.49% of total deaths.[2] Hence risk stratification is crucial to decrease incidence of sudden cardiac death.

The yearning to find non-invasive cardiac screening markers from arrhythmogenic sudden cardiac death in increasing by the day. Signal Averaged ECG (SAECG) is being used universally as a non-invasive technique to record micro voltage changes in the electrical impulses of heart by uncovering high frequency low voltage activity at end of QRS complex. These electrical activities are labelled as ventricular late potentials. SAECG can help identify at risk individuals for malignant ventricu-

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lar arrhythmias and help prevent sudden cardiac death.[3]

Delayed conduction through the diseased myocardium leads to altered electrical activity that appears as positive potential at end of QRS complex on SAECG. SAECG is specialized non-invasive high resolution ECG machine. Appearance of VLPs on SAECG may indicate underlying anatomical and electrophysiological changes that may contribute to chance of having fatal ventricular arrhythmias in susceptible individuals. VLPs arise as a results of slow activation and conduction from diseased myocardium leading to delayed ventricular depolarization and as a result predisposes to reentry arrhythmias. Their amplitude is often too small to show on normal ECG. When multiple QRS complexes (consecutive 250 QRS complexes) are averaged while filtering random noise, late potentials show up. Such a recording is called signal averaged ECG.[4,5]

Anatomical disturbances like ischemic, dilated or hypertrophic cardiomyopathies and physiological disturbances like abnormalities in distribution and function of cardiac gap junctions contribute to the pathophysiology of VLPs. Ventricular arrhythmias are common in patients with cardiomyopathies. They may range from asymptomatic ventricular premature beats, sustained ventricular tachycardia or ventricular fibrillation ending in sudden cardiac death. Dysfunctional alteration in structure or conductive pathway of myocardium leading to heart failure are categorized as cardiomyopathies. They can be genetic myofibrillar disarray or acquired i.e. secondary to disease. One of the most common acquired cause is ischemic cardiomyopathy where coronary artery disease leads to impaired left ventricular function. Here the scarred myocardium acts as area of slow conduction. This structural change acts as substrate for arrhythmias mainly ventricular tachycardia. Moreover, myofibrillar disarray or gap junction dysfunction results in histological changes rendering a suitable medium for reentry arrhythmias. In non-ischemic cardiomyopathies, causes like viral myocarditis, drug reactions, inflammation, autoimmune reactions, amyloid and sarcoid infiltrations are some of the leading causes that predispose a patient to ventricular arrhythmias.[6]

VLPs assessment in signal-averaged ECG offers a rational and low-cost solution to an otherwise fatal undetected ventricular arrhythmia. Our study was designed to appraise Ventricular late potentials in patients with two different types of cardiomyopathy i.e. ischemic and non-ischemic cardiomyopathy. Outcomes of the study will not only help isolate patients endangered of developing ventricular arrhythmias but also impart understanding about the conceivable pathophysiologic mechanism for the deranged electrical activity within their myocardium. Furthermore, they can be subjected to additional investigations for enhancement of arrhythmia risk and for starting appropriate therapeutic measures in order to avoid sudden cardiac death.

Material and Method

It was a comparative cross sectional study conducted at Cardiac Electrophysiology unit in Armed Forces Institute of Cardiology, Rawalpindi from February 2019 to August 2019. Age and gender matched thirty patients with non-ischemic cardiomyopathy and thirty with ischemic cardiomyopathy patients were recruited. The probability purposive sampling was applied to recruit patients. Diagnosed cases of ischemic and non-ischemic cardiomyopathy were included in the study after taking written consent. Brief history, general physical examination, standard 12 lead ECG and echocardiogram were implied, excluding those having cerebrovascular accidents, bundle branch blocks, heart failure, systemic arterial hypertension, diabetes mellitus and anti-arrhythmic drugs. The chosen individuals were requested to come to electrophysiological department of AFIC. Signal averaged ECG (SAECG) using Mortara ELI 350 machine was obtained for each patient. IBM SPSS version 23 was employed to analyze the data. Mean and standard deviation were estimated and independent t-test was applied to compare mean values of signal averaged ECG parameters between non-ischemic and ischemic cases. Chi-square test was employed to compare frequency of ventricular late potentials in non-ischemic and ischemic patients. Confidence interval of 95% with a p-value of 0.05 was considered significant.

Results

Out of 60 selected individuals, 30 (50%) had diagnosed non-ischemic and 30 (50%) had ischemic cardiomyopathy. Among the ischemic, 7 (23%) were females and 23 (76.7%) were males. Their mean age was 51.27 ± 12.65 years. Among the non-ischemic, 10(33.3%) were females and 20 (66.7%) were males. Their mean age was 51.23 ± 16.28 years. Comparison of frequency of presence or absence of ventricular late potentials among both groups is shown in Table 1. Out of 30 individuals with ischemic cardiomyopathy 8 (26.7%) had VLPs, while 6 (20.0%) non-ischemic patients had VLPs. This difference was statistically insignificant. Whereas, VLPs

were absent in 22 (73.3%) patients with ischemic cardiomyopathy and 24 (80%) patients with non-ischemic cardiomyopathies, as shown in Table 1. Table 2 shows comparison of various specification of Signal Averaged

Table 1: *Frequency comparison of individuals with and without ventricular late potentials between ischemic and non-ischemic cardiomyopathies*

		VLPs		p-value
		Present	Absent	
Group	Ischemic cardiomyopathy	8 (26.7%)	22 (73.3%)	0.54
	Non-ischemic cardiomyopathy	6 (20.0%)	24 (80%)	

Table 2: *Comparison of SAECG variables between ischemic and non-ischemic cardiomyopathies*

		Mean ± SD		p-value
		Ischemic cardiomyopathy	Non-ischemic cardiomyopathy	
SAECG variable	fQRS	105.07±37.34	110.00±38.52	0.62
	RMS	21.73±12.32	30.43±16.89	0.02*
	LAS	37.00±20.83	31.64±13.20	0.24

**p-value significant (<0.05)*

ECG between patients with ischemic and non-ischemic cardiomyopathies. The difference was significant only for mean values of RMS (p=0.02).

SAECG parameters:- fQRS: filtered QRS, LAS: Low amplitude signals, RMS: Root mean square.[7]

Discussion

Being a multifactorial disease, causes of cardiomyopathy range from genetic abnormalities to those secondary to myocardial ischemia and other cardiovascular diseases. They can be broadly classified into ischemic and non-ischemic cardiomyopathies. In our study we divided the patients into two categories based on the same classification and assessed them for ventricular late potentials' presence or absence. Presence of VLPs were slightly lower in ischemic patients in comparison to non-ischemic but the difference was statistically insignificant (p= 0.54). As shown in the table, VLPs were absent in 73.3 % (n=22) of ischemic and 80% (n= 24) of the non-ischemic among our study population. As shown through literature, VLPs have a greater importance due to their negative predictive value.i.e. if VLPs are absent in patients, indicating decreased likelihood of future arrhythmic episode. Santangeli P states in his article that although VLPs have a weakness regarding their low positive predictive values particularly when they are used as a single diagnostic tool, but their negative predictive value is very high making them an affordable and practical tool for screening of future arrhythmic events.[5,8] An international research mentioned 94.1% sensitivity, 72.3% specificity, 13.6% positive predictive value and 73.2% negative predictive value of ventricular late potentials with sudden cardiac death in 385 patients.[9] Bobkowski W conducted a follow-up research on children with mitral valve prolapse and looked for ventricular late potentials. He found out that sensitivity of VLPs was low i.e. 52% (ppv of 50%) but specificity was high i.e. 90% (npv of 91%) for development of ventricular tachycardia in children with mitral valve prolapse. He concluded that SAECG alone is a specific but not sensitive tool for prediction of development of ventricular tachycardia in these diseased children.[10] Middlekauff et al evaluated VLPs in 62 patients, 31 with ischemic and 31 with non-ischemic cardiomyopathy. He assessed efficiency of multiple non-invasive tools to screen out patients who were at high risk of developing ventricular arrhythmias. He settled that existence of ventricular late potentials may distinguish between occurrence and absence of ventricular tachycardia irrespective of the cardiomyopathy type.[4,9] Mancini et al recruited 114 patients having cardiomyo-pathy and observed them up for 5 years. He concluded that among 20 patients having abnormal SAECG, 4 developed ventricular tachycardia, 5 ended up with sudden cardiac death and 2 died of progressive heart failure.[4,11] Amino et al assessed the value of signal averaged ECG in Japanese patients suffering from cardiomyopathy. He calculated the mean value for fQRS complex as 111.4± 28.9 ms nearly similar to our study (107.53±37.7 ms). This could be ascribed to the fact that their patients' mean age was closer to ours i.e. 51.25 ±14.4 years and 55±6.7 years, sequentially.[12] In another study by Marques and his colleagues, checked ventricular late potentials in 487 healthy French males. Their mean fQRS value came out to be 97±12 ms, mean LAS value was 32±10 ms and mean RMS value was 39±27 µV. Contrary to that, our mean fQRS value was 80.32±24.19 ms, mean RMS value was 31.33±23.24 µv and mean LAS value was 32.02±11.36 ms. This difference could be attributed to the fact that our study comprised of both genders while our total number of patients were also considerably less as compared to Marques study.[13]

Our study in contemporization with other studies as mentioned above shines emphasis on the practical employment of signal averaged ECG and ventricular

late potentials as a low cost empirical non-invasive screening tool for arrhythmia risk assessment.

Conclusion

Ventricular late potentials assessment through a portable bed side ECG machine presents cardiologists with an affordable, practical and easy to manage screening tool for identification of possible electrophysiological substrate that may lead to life threatening arrhythmias. Negative predictive values of VLPs render them their strength whereas when positive, they act as an adjunct for risk stratification of arrhythmias in potential at risk patients.

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HA, AA, SN: Writing of Manuscript

Correlation of Perceived Stress on the Academic Achievement of Undergraduate Nursing Students of KPK

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Abstract

Objective: To identify the impact of stress on academic performance among undergraduate nursing students of kpk.

Method: The design of the study was descriptive-correlational. It was conducted from April to August 2022, having a sample size of 103 and using a convenient sampling technique through an adopted questionnaire perceived stress scale.

Results: In this study, the male students were more (69.9%) n=72 than the female students were (30.1%) n=31. The students of semester 4th were in the majority (45%). Among the participants, (4%) were suffering from high stress, while moderate stress (88%) and low stress only (8%). The majority of the students' academic performance was good (58.3%), average (35%), and poor performance (6.8%). The mean scores of stress were: 8th semester (19.2±4.18), 6th semester (21.3±2.98), 4th semester (20.3±3.67) and 2nd semester (18.2±5.25). The correlation between stress and academic performance was calculated through SPSS. It shows that academic performance is not correlated with stress (p-0.681), while stress was also not correlated with demographic variables like gender (p-0.13) and age (p-0.139).

Conclusion: Stress in the first year is common due to exposure to new and difficult subjects and environments. Through coping strategies, senior students managed stress to avoid problems with the passage of time.

Keywords: Stress, academic performance, nursing students, Khyber pukhtankhwa, undergraduate

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Introduction

The nursing profession is a well-known profession in Khyber Pukhtankhwa Pakistan. The nursing institutes follow the curriculum in academic and clinical skills that is approved by the higher education commission and the Pakistan Nursing Council.[1] Nursing schools enable learners to become employees or as leaders in the future, where they will teach or perform clinical work on behalf of their institution or university.[2] A 4-year nursing degree is a very demanding and tough program. Students worked hard in clinical duties and within the nursing organization to achieve better grades and ranks throughout the semesters. Therefore, they face psychological issues that impact their performance. The intensity of these issues varies from student to student. A psychological, emotional state and situation arose in which the students react when they feel pressured or threatened, called stress. These mental health problems are becoming more common among healthcare workers.[3] Studies have shown that nursing students face stress more than other professions.[4] Nursing students have to complete theoretical exams, tests, and clinical skills assessments within a specific time frame. When the burden increased from the resources of students with

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which they were dealing, stress increased among students.[5] A high level of stress not only affects student performance but also leads to serious mental health illnesses such as depression.[6] Stress has not only a negative impact; it also has a positive impact. For example, low to moderate stress may increase students' motivation, encouraging them to persevere in their studies and achieve their targets.[7] Nursing students not only face stress in theory, but they also face challenges in clinical duties. Nursing students during their initial clinical days become under pressure and nervous about how to face patients and clinical staff. Students' adjustment with the concerned department, health care staff, and patients took some time, so those students who are good at coping strategies overcome this period, but those students who are new to the challenges are affected by psychological stress. The prevalence of clinical stress is higher in nursing students because nursing students spend more time in the clinical areas and come into contact with patients with severe injuries, chronic diseases, and the deaths of patients.[8] Studies have shown that the first and second years of nursing students are the most stressful for nursing students because they are new to the profession and subjects. For other students, the third year is more stressful due to clinical duties.[9] Some of the students are affected by stress in the last year of research projects, nursing seminars, and the transition from nursing institute to clinical training internship. The study of Goff (2011) shows that there is no relationship between stress and academic performance.[10]

Stress is a condition that can't be avoided. Therefore, coping strategies and stress reduction programs could improve the academic performance of students. It is very unfortunate that none of the nursing institutes in Khyber pukhtankhwa have a stress reduction program to engage students in the last period of their degree program to improve their academic performance. The purpose of this study is to explore the perceived stress among nursing students and its impact on their academic performance.

Material and Method

The conducted study was a descriptive correlational study conducted from April 2022 to August 2022 in the different private and public institutes of Khyber pukhtankhwa Pakistan. The inclusion criteria for the study were nursing students who are currently enrolled in any registered nursing college and students who are willing to be part of the study. A formal permission from the nursing institutes was obtained before approaching the nursing students. The sample size of the population was 103 nursing students through a convenient sampling method. All the students were clarified through verbal conversation and in consent form that their participation in the project is purely voluntary, no student will receive any direct benefit from the project, their data will be used only for data analysis, and they can leave the study when they want to ensure the ethical rights of the participants. The data was collected from the participants after permission from the college authorities. A paper was printed that contained a consent form and a perceived stress inventory questionnaire. The aim and objectives of the questionnaire were explained to all the participants.

Perceived Stress scale: An adopted questionnaire of the perceived stress scale (PSS) was used, developed by Cohen, S.(1983).[11] The questionnaire contains two parts: part-a (gender age, year of program, and college status), while part-b contains 10 questions that contain two subscales:

Questions 1, 2, 3, 6, 9, and 10 are perceived helplessness (a feeling of an individual). Questions 4,5,7, and 8 are lack of self-efficacy (measured in reverse) (0 =>4;1=> 3;2 => 2;3=> 1;4 =>0).

The scale contains a 5 point Likert scale (0-never, 1-almost never, 2 sometime, 3-fairly often, 4-often). The validity of the questionnaire was checked by and the test-retest reliability was checked by Lee, E. H. (2012).[12] The academic performance (GPA) of the students were taken from the students directly during data collection and then cross checked with examination record of the college. The study was approved by the institutional review board (IRB) before data collection. The proposal, questionnaire, and consent were submitted and, after the review concluded that there was no harm to the participants, the approval from the IRB was received for data collection.

Results

The total number of the participants in this project was 103. Among these participants, the number of male participants was higher (69.9%) n=72, than the number of female participants (30.1%) n=31. In the age-category, the students aged (20 to 23 years) were in the majority (67%) n=69, followed by those aged 24 to 27 years (30.1%) n=31, and those aged 28 and above (2.9%) n=3. The majority of the students were from private colleges (96%) and (4%) from public nursing colleges. The stu-

dents of 2nd year (3rd and 4th semester) were higher (45%), followed by the 4th year (7th and 8th semester) students (39%), while the students of 3rd year (5th and 6th semester) were (12%), and 1st year (4%) (Table-1). In the questionnaire of the perceived stress inventory, the number of questions was 10 with a 5-point Likert scale (0-never, 1-almost never, 2-sometime, 3-fairly often, 4-often). In (table 2), the mean and standard deviation of each question with the most frequent option of the participants are present; the results of questions 4, 5, 7, and 8 are reverse. ((Table-2).). A cut-off value was set for the level of stress. The majority of the students (88%) n=91 suffered from moderate stress, while (8%) n=8 suffered from a low level of stress, and only (4%) n=4 was identified as high stress. Comparing the male and female students' stress levels, the male students' high stress level was higher (6%) than female students (0%), followed by a higher level of moderate stress in males (89%) compared to females (87%), and low stress was maximum among females (13%) compared to male students (5%) ((Table-3). In 2nd semester nursing students, the stress of moderate level was n=3, compared to high (n=0) and low-stress level (n=1), while in 4th semester nursing students, the moderate level was high (n=41), followed by low stress level (n=3) and high stress (n=2). Among the 6th semester students, the moderate stress level was (n = 13), while the low and high stress levels were the same (n=0). In the 8th semester, the majority of students, n=34, were suffering from moderate stress, while n=4 faced low stress and high stress, n=2 (Fig-1). The mean and standard deviation score of the 2nd semester was (18.2±5.25), 4th semester (20.3±3.67), 6th semester (21.3±2.98) and the 8th semester (19.2±4.18). The values were set in categories with a cutoff score to identify the performance of participants as good, average, or poor performance. (58.3%) had a good performance, then (35%) students had an average performance, and (6.8%)

Table 1: *Demographic characteristics*

Characteristics	Categories	Frequency n=103	Percentage
Gender	Male	72	69.9%
	Female	31	30.1%
Age	20 to 23 years	69	67%
	24–27 years	31	30.1 %
	28 and above	3	2.9%
Institute Status	Public college	4	4%
	Private college	99	96%
Year of BSN Program	2nd semester	4	4%
	4th semester	46	45%
	6th semester	11	12%
	8th semester	40	39%

Table 2: *Perceived stress inventory mean standard deviation and most frequent response (N-never, AN-almost never, ST-sometime, FO-fairly often, O-often)*

S.No	Question	Mean and SD	Most frequent
1	In the last month, how often have you been upset because of something that happened unexpectedly?	2.23 ± 1.23	2-ST (29.1%)
2	In the last month, how often have you felt that you were unable to control the important things in your life?	2.06 ± 1.19	2- ST (35.9%)
3	In the last month, how often have you felt nervous and "stressed"?	2.23 ± 1.21	2- ST (30.1%)
4	In the last month, how often have you felt confident about your ability to handle your personal problems?	1.34 ± 1.23	0-N (33%)
5	In the last month, how often have you felt that things were going your way?	1.60 ± 1.17	2- ST (32%)
6	In the last month, how often have you found that you could not cope with all the things that you had to do?	2.25 ± 1.28	3-FO (29.1%)
7	In the last month, how often have you been able to control irritations in your life?	1.54 ± 1.13	1-AN (35%)
8	In the last month, how often have you felt that you were on top of things?	1.97 ± 1.29	2-ST (30.1%)
9	In the last month, how often have you been angered because of things that were outside of your control?	2.33 ± 1.26	2-ST (33%)
10	In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	2.16 ± 1.10	3-FO (40.8%)

Table 3: *Academic performance and stress among the participants*

Academic performance of the participants			Gender	
Academic performance	**Cutoff values**	**Students performance**	**Male**	**Female**
Good performance	3.41 to 4.0	60 (58.3%)	41(57%)	19(61%)
Average performance	2.81 to 3.4	36 (35%)	27(37%)	9(29%)
Poor performance	Below 2.80	7 (6.8%)	4 (6%)	3(10%)
Stress among the participants				
Low level of stress	0 to 13	8 (8%)	4 (5%)	4(13%)
Moderate stress	14 to 26	91 (88%)	64(89%)	27(87%)
High stress	27 to 40	4 (4%)	4 (6%)	0 (0%)
Correlation of stress with academic performance				
	Academic performance		Gender	Age
Stress (p-value)	0.681		0.139	0.465

of students' performance were poor ((Table-3)). The findings indicate that there is no correlation between academic performance and stress, nor is stress correlated with gender, nor with age, nor with semester ((Table-3).

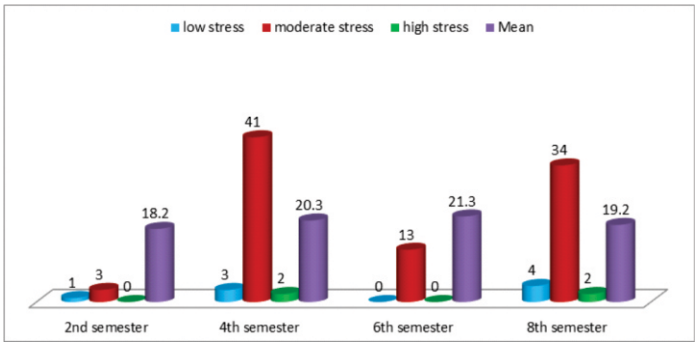

Fig 1: *Stress level and mean score (semester)*

Discussion

In the current study, the total number of participants was 103, where the number of males (69.9%) was higher than female students. The maximum number in 4 categories of semester among the nursing students was moderate, like in the 4th semester the score was (n=3), in the 4th semester it was (n=41), in the 6th semester it was (n=13), and in the 8th semester it was (n=34). The outcomes are similar to the study conducted by Elias, H et al. (2011) found that among undergraduate students, moderate stress is most common due to medical and health sciences.[13]

In this study, the findings reveal that there is no correlation between stress and academic performance. The findings are similar to those of studies conducted by Awofode, A. D. (2011)[14] and Womble, L. P. (2003) that found no significant correlation between stress and academic performance.[15] The findings of our study are opposite to the results of studies conducted by Oketch J. et al. (2018) and Rafidah, K. et al. (2019) that found a significant association between academic performance and stress.[16,17]

Furthermore, the results of our study identify that the 8th semester students' stress mean score (19.2±4.18) is less than the stress level of the 6th (20.3±3.67) and 4th semester (21.3±2.98). The findings are not similar to the study conducted by Elias, H et al. (2011) that reveals that final semester students have a high stress mean score of (1026 ± 267) compared to the mean score of the middle semester (929 ± 317).[13] This study reveals that the mean score of the 8th semester is low (19.2±4.18) compared to the scores of the 4th and 6th semesters. That means that senior students easily manage the stress through coping strategies. Similarly, the study accompanied by Awofode A. D. (2011) found that seniors reduce the impact of stress on their academic performance because these students easily deal with issues.[14] These findings are also supported by the studies of Hara et al. (2014), and Monterio et al. (2014).[18,19]

Our study reveals that the students of the first semester have the lowest mean score of stress (18.2±5.25) compared to middle semester students. The findings are similar to those of Elias, H et al. (2011),[13] but contradict the findings of Wintre MG, (2000).[20]

The results of this study indicate that there is no relationship between gender and stress and academic performance, which is not similar to only the findings of Scott (2009) that show the impact of gender on stress capability,[21] but also the results of Oketch J. et al. (2018) that show statistically significant stress and academic achievement with both male and female.[16]

Conclusion

The study concluded that there is no correlation between stress and academic achievement. Compared to female students, male students have more exposure to stress due to the burden of study and domestic responsibilities. Stress among first-year undergraduate nursing students is common due to exposure to medical and health subjects. With the passage of time, nursing students manage stress with the help of coping strategies.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

AS: Conceptualization of Project
HJ: Data Collection
SA: Literature Search
FA: Statistical Analysis
S, S: Drafting, Revision
AS: Writing of Manuscript

Ethanolic Extract of Azadirachta Indica Seeds and Leaves and its impact on Lipid Profile in Diabetes Mellitus

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Abstract

Objective: To evaluate and compare the outcomes of Azadirachta indica on serum lipids in alloxan induced diabetic albino rats.

Method: Randomized controlled trial (RCT) carried out in Physiology Department of Services Institute of Medical Sciences, Lahore from. November 2018 to April 2019. 120 male albino rats were randomly and uniformly divided into four groups (n=30). The control group is designated as G1 and kept on normal saline only. The Diabetic control (G2) and the other two experimental groups (G3 & G4) were administered with alloxan monohydrate intraperitoneal injections (120mg/kg) to induce diabetes mellitus. While G1 and G2 were used as the normal control and the diabetic control groups, only G3 and G4 were treated with Neem leaves (500 mg/kg body weight once a day) and Neem seeds (500 mg/kg body weight once a day) respectively for 28 days. Subsequently, blood samples (4-5ml intracardiac) were collected from each group member on the 29th day to evaluate the biochemical parameters of serum lipids.

Results: The ethanol-based extracts of Neem leaves and seeds lead to highly significant ($p<0.001$) reduction in lipid profile of G3 and G4.

Conclusion: Azadirachta indica leaves and seeds can significantly contribute in lowering serum lipid parameters.

Keywords: azaditachta indica, lipid lowering effect.

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Introduction

The prevalence of diabetes mellitus is predicted to increase globally from an estimated 382 million in 2013 to 592 million by 2035.[1] Type 2 diabetes has already attained epidemic level, while the incidence of type1 diabetes also increases. It initially emerges as a group of disorders with defective or deficient insulin secretory process culminating in glucose underutilization, hence, leading to hyperglycemia.[2] Patients with diabetes may suffer with wide range of microvascular complications such as as stroke, ischemic heart disease, diabetic retinopathy and nephropathy.[3] Others complications include periodontitis, neural disorders, gastroenteritis, delayed gastric emptying, renal disorders, dermatological manifestation, erectile dysfunction, diabetic retinopathy and diabetic macular edema.[4] Medicinal herbs have played a significant role in treating and preventing a variety of diseases worldwide for centuries. Herbal remedies are tried globally to treat diabetes mellitus proactively or to delay any further complications. They are considered a significant source of antioxidants which help in preventing or delaying many diseases and their adverse outcomes.[5] Such remedies not only seem to increase the insulin secretion and cellular glucose uptake but also decrease the intestinal glucose absorption and hepatic glucose production.[6] One of the conventional herb used to treat diabetes mellitus is Azadirachta indica commonly known as

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neem. It's found in abundance in Asian subcontinent.[20] It has gained worldwide attraction in recent years, owing to its wide range of medicinal properties[7]. Many pharmacological and biological effects are attributed to various parts and extracts of this plant, including antidiabetic, anti-inflammatory, antioxidant, antiplasmodial, antitrypanosomal, anticancerous, antimicrobial, spermicidal, antiheliminthic, antifertility, immunomodulating, nematicidal, immunocontraceptive, insecticidal ,and insect repellant effects.[8,9] The present study is the experimental type and aims to add value to future research in elaborating the protective properties of ethanolic extracts of neem leaves and seeds specifically on serum lipid profile. Although many researches have been carried out that uses neem as their subject of interest to study blood pressure, obesity, and hyperlipidemia but our study is unique in that it uses ethanolic extracts of both seeds and leaves on diabetic grounds to assess the fluctuation in lipid profile.

Materials and Methods

Adult and healthy male albino rats (One hundred and twenty) were housed in groups of 30 per cage for minimally one-week prior the commencement of experiment. Dwelling environment was kept at 26±2°C with 12-hour light/dark cycle10 The rats were categorized in four groups (each group containing 30 rats). Group 1: Normal control provided with normal saline orally. Group 2: Diabetic control was given normal diet. Group 3 (Experimental 1): got treatment with extract of Azadirachta indica leaves orally (500 mg/kg) daily for 28 days. Group 4 (Experimental 2): got treatment with extract of Azadirachta indica seeds orally (500 mg/kg) daily for 28 days. Alloxan monohydrate achieve its diabetogenic results by specifically destroying the pancreatic beta cells, but other endocrine cells and exocrine parenchymal cells were unaffected. The cytotoxic agent exerts its diabetogenic effects by reactive oxygen species which promptly destroys beta cells[11]. To induce diabetes, a single dose of alloxan monohydrate was given to overnight fasting rats of diabetic control and experimental groups before commencement of experiment.[11] At this dose (120 mg/kg), there is incomplete destruction of pancreatic beta cells which results in type 2 diabetes mellitus (NIDDM).[12] As Alloxan can lead to fatal hypoglycemia because of tremendous release of pancreatic insulin, rats were infused with 15-20 ml of 20% glucose solution intra peritoneally after 6 hours. To prevent hypoglycemia for next 24 hours the rats were kept on 5% glucose solution bottles.[13] Blood glucose was evaluated after 72 hours to confirm hyperglycemia.[14] Rats with hyperglycemia (>200 mg/dL) were considered diabetic and incorporated in experiment.[15] Then diabetic rats of group 3 and 4 were treated with leaves and seeds (ethanolic extract) of Azadirachta indica for 28 days.[16] On 29th day, intracardiac blood sample (4-5ml) was obtained to evaluate the effects of plant extract on lipid profile.

Freshly matured leaves and seeds (5kg each) of Azadirachta indica were fetched locally from Lahore. Botanical identification of the leaves and seeds was completed in the Botany Department, Punjab University. An 80% ethanol extract of the air-dried and coarsely ground Azadirachta indica leaves and seeds was obtained via standardized Soxhlet extractor in Applied Chemistry Research Centre, PCSIR Labs, Lahore. The extract thus acquired, was subjected to filtration and ethanol (solvent) evaporation in a rotary evaporator in a vacuum. A blackish-brown concentrate, obtained post-evaporation, was then preserved at 4°C. Preceding to every dose, the crude extract was liquefied in sterilized distilled water and diluted to the required concentration.[17]

Initial blood sample was drawn aseptically from tail vein 72-hours after alloxan injection to confirm hyperglycemia. Sampling was repeated on the 29th day of the experiment after ensuring the animals were fasting overnight. Each rat was anesthetized using ether before drawing 5-milliliter blood from their tail vein. Four ml of each sample was allowed to coagulate at room temperature in the test tube for 30 minutes followed by centrifugation at 5000 rpm for 20 minutes. Post-centrifugation, the serum was collected and preserved in labeled tubes. It was kept at -20°C to be test cholesterol, triglycerides, HDL later on.[18] PASW (formerly SPSS) was used to conduct data analysis. ANOVA test was carried out for descriptive analysis to find the arithmetic mean±SD values of obtained data. Post hoc Tukey's HSD test (multiple comparisons) was applied to find any significant value (p-value less than 0.05) among the four groups existed. The values were appraised highly significant when the p-value was less than 0.001.

Results

In this randomized controlled trail, the effects of Azadirachta indica (neem) leaves and seeds on the serum lipid profile of a total of 120 male diabetic albino rats were evaluated. The serum cholesterol, triglyceride, LDL, and VLDL in diabetic control group was found to be highly significantly (p=0.000) greater than in the control group **(Table-1)**. Similarly, serum HDL level was

also significantly higher in normal controls than in the dia-betic controls **(Table-1)**. After administering neem leaves and seeds extract, the mean difference showed a highly significant (p=0.000) drop in cholesterol, triglyceride, LDL, and VLDL levels (Table 2 and 3); and highly sig-nificant (p=0.000) rise in serum HDL level in treated group compared to the untreated diabetic control group **(Table-2)**. The experimental group treated with neem leaves extract had highly significantly lower (p=0.000) serum triglyceride and VLDL levels than in the experi-mental group treated with neem seeds. However, the decline serum cholesterol and LDL levels in experi-mental group (G3) treated with neem leaves versus the experimental group treated with seeds (G4) did not show such significance. Similarly, Difference of increased serum HDL between the two groups was non-significant **(Table-2)**. Figure 1 shows mean lipid values in normal control, diabetic, and treatment groups.

Table 1: *Comparison of Serum Lipid Profile in Normal Control and Diabetic Control Groups Values are given as Mean ± SD*

Lipids	Normal control	Diabetic control	Mean difference	p-value
Cholesterol (mg/dL)	92.30±28.60	227.77±15.76	135.47	0.000*
Triglyceride (mg/dL)	83.60±7.39	216.20±10.20	132.60	0.000*
HDL(mg/dL)	25.83±1.91	19.47±2.29	6.37	0.000*
LDL(mg/dL)	49.75±29.04	165.06±15.85	115.31	0.000*
VLDL(mg/dL)	16.72±1.48	43.24±2.04	26.52	0.000*

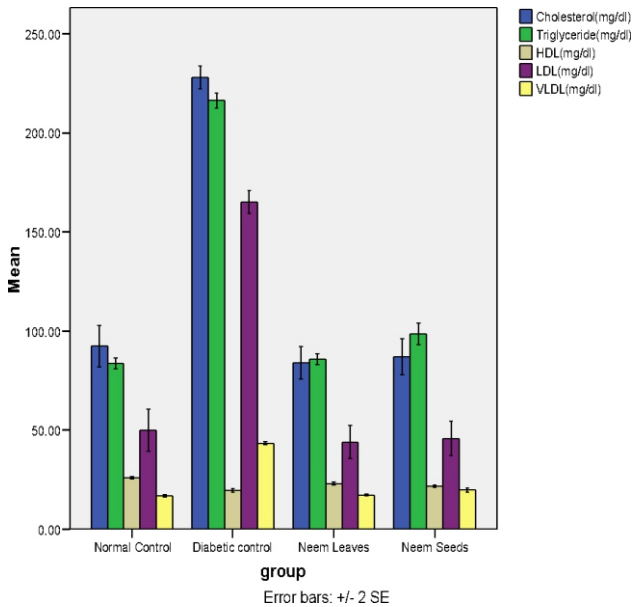

Figure1: *Mean ± SEM lipid profile of the four groups*

Table 2 : *Comparison of serum lipid profile in diabetic control group and group treated with neem leaves. Values are given as Mean ± SD*

Lipids	Diabetic control	Neem leaves	Mean difference	p-value
Cholesterol (mg/dL)	227.77±15.76	83.90±22.68	143.86	0.000*
Triglyceride (mg/dL)	216.20±10.20	85.70±7.32	130.50	0.000*
HDL(mg/dL)	19.47±2.29	22.90±1.81	3.43	0.000*
LDL(mg/dL)	165.06±15.85	43.86±23.00	121.20	0.000*
VLDL(mg/dL	43.24±2.04	17.14±1.46	26.10	0.000*

*p <0.001 highly significant

Discussion

Recently, more research is being focused on unveiling the anti-diabetic properties of neem in search of some harmless herbal alternative to allopathic medicines. For this purpose, meta studies are being carried out to assess the effects of various aqueous, ethanolic, methanolic. and petroleum extracts from all parts of the plant on blood pressure, hyperlipidemia and obesity.[20] The current study is focused to evaluate and compare the lipid lowering outcomes of ethanolic neem leaves and seeds extracts in alloxan induced diabetic rats.

When induced with Alloxan, diabetic rats showed a rise in serum triglyceride, total cholesterol, VLDL- cholesterol, LDL- cholesterol levels (p=0.001) compared to normal controls. Also, serum HDL levels was higher in normal controls (p=0.000) than in the diabetic controls. The serum triglyceride, total cholesterol, & LVDL-cholesterol reduced; and HDL-cholesterol increased in the experimental groups treated with the ethanolic extracts of neem leaves & seeds versus the untreated diabetic controls. Furthermore, the leaves extract was shown to have more potent triglyceride and VLDL lowering effect than the seed extracts (p=0.000). Similar results were obtained by Dholi et al[17], when alloxan induced diabetic rats were administered ethanolic extract of neem leaves for single dose therapy and multiple dose therapy for two weeks both leading to decline of cholesterol and triglyceride levels. Patel et al[18], administered neem extracts among few other herbal extracts for 42 days to diabetic rats that resulted in notable decline in the serum lipids levels. Ashafa et al[19], evaluated effects of ethanolic extract of stem bark extract of Azadirachta indica that seemed to significantly decrease the serum triglyceride and HDL-cholesterol but increased the serum concentration of cholesterol, LDL- cholesterol at all tested doses. Hence, the results of our study indicate the potential lipid lowering benefits of using the

Azadirachta indica in herbal medicine and warrants further research and human trials.

Conclusion

The current research decides; Ethanol based extracts of neem seeds and leaves are potent lipid lowering agents. Leaves of neem may have more potent effects in lowering the serum triglycerides and VLDL than the neem seeds.

Conflict of Interest *None*

Source of Funding *None*

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Authors Contribution

TS: Conceptualization of Project
TS, AS, NK: Data Collection
TS, NZ, AZ: Literature Search
AS: Statistical Analysis
TS, NS: Drafting, Revision
TS, NZ: Writing of Manuscript

Impact of Chewing Cardamom and Fennel Seeds on Salivary Ph: A Hospital-Based Comparative Analysis

Thelma Farast Bashir,[1] Rabia Arshad,[2] Zunaira Khalid,[3] Eman Aslam,[4] Maryam Usman[5]

Abstract

Objective: To compare the changes in salivary pH by chewing fennel and cardamom seeds.

Methods: A factorial randomized controlled trial was conducted in the Department of Oral Diagnosis, Altamash Institude of Dental Medicine, Karachi during February-April 2022. Following trial registration with the clinical trial. gov. (NCT05245019) and IRB approval, 75 subjects attending the Altamash Institute of Dental medicine after informed consent were enrolled and randomized into three groups. Group X as controls, Group A for chewing fennel and Group B for cardamom seeds. Salivary samples from controls once and the other two groups at baseline and immediately after 5 minutes of seed chewing, were determined using calibrated pH meter. Required statistical tests were applied to evaluate the results using SPSS 26.

Results: The mean salivary pH at baseline, and after 5 minutes of chewing seeds were statistically different in groups A (before vs after, p-value<0.01) and B (before vs after, P<0.01 respectively). When we compared the pH for the three groups together (group X control, group A and group B both after seed chewing) the results were statistically significant (p<0.01). Further, after the use of seeds in group A vs group B, the increase in pH was statistically significant; (p< 0.001).

Conclusion: Cardamom and fennel seeds significantly rise the salivary pH when compared to controls. However, cardamom seeds have proven to increase more salivary pH than fennel.

Keywords: seeds, foeniculum, elettaria, saliva, hydrogen ion concentration, oral health.

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Introduction

Dental cavities with caries are the most common infectious disease related to the oral cavity.[1] Although significant advances have been made on a global front to prevent caries, still studies show its incidence is on the rise making it one of the major chronic oral diseases affecting all age groups.[2] It largely affects children and the lower socioeconomic groups hence demanding feasible and inexpensive ways to counter this growing ailment.

Dental caries is a multifactorial disease involving the interaction of the host, agent, and environment.[3] The primary etiologic agent implicated in dental caries is the streptococcus mutans and non-streptococcus species like Lactobacillus, Actinomyces, and Veillonella species.[4] These oral microbes break down carbohydrates content in the diet, producing acids as by-products. Cavities or dental caries are ultimately made worse by acid production because they cause demineralization of enamel and dentine, and lower the pH of plaque and saliva.[5]

The responsibility of saliva in maintaining oral health has been studied extensively over time. Saliva not only competes for a very important role in lubrication by flushing the oral cavity of food remains, and fighting

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off the invading microorganisms but also plays a major task in neutralizing the acids yielded by oral microorganisms.[6] The buffering capacity of saliva prevents the teeth from demineralization by maintaining the pH of the oral cavity thereby declining the possibility of dental caries.[7,8] Since ancient times, medicinal plants and herbs have been used for maintaining oral health. Recent studies have shown fennel seeds and cardamom to play a meaningful role in regulating the pH of saliva and plaque, and ultimately preventing dental caries.[9]

Cardamom (Elettaria cardamomum) is historically identified as the queen of spices. It is used as a flavouring agent in foods as well as for treating various cardiovascular, gastrointestinal, and neural problems. Fennel (Foeniculum vulgare) is a dry seed used in treating many ailments. Known for its anti-inflammatory, anti-spasmodic, and analgesic properties, it is also widely used for treating gastroenteritis and indigestion. It has been used as a breath freshener on its own and in several oral treatments for its antibacterial qualities over antiquity.[10]

Fennel and Cardamom are commonly used economical household ingredients that can affect oral pH, hence having an impact on oral pathogens. The present study was designed and conducted to evaluate the variations in salivary pH at baseline and after 5 minutes of chewing fennel and cardamon seeds. Secondly, to compare the pH changes after chewing fennel and cardamom seeds between both the groups. To the best of our knowledge this work with detailed comparison of two seed in respect to salivary pH has not been reported yet in any study with such prospective.

Material and Method

A factorial randomized controlled trial with an allocation ratio of 1:1 was conducted in the Department of Oral Diagnosis, Altamash Institute of Dental Medicine, Karachi during February–April 2022. With the ethical approval for the study from the Ethical review committee, Altamash Institute of Dental Medicine (ERB/AIDM_1, Dated: 12-01-2022) the trial was further registered with the clinical trial. gov. (NCT05245019). The sample size was calculated for a two-sample mean Satterthwaite's t-test using a reference article.[14] The estimated sample size evaluated was 22 with 11 patients in one group and was raised to 50 total with 25 patients per group. For control group X, an equal number of saliva samples were collected to evaluate the better comparison of the trial between the groups.

After voluntary informed consent, sampling was done in the dental clinic and individuals ≥ 18 years of any gender with complete dentate were included in the study. Subjects undergoing topical fluoride therapy, other chemotherapeutic procedures, antibiotics or drugs, also those suffering from any systemic diseases,[14] and individuals who were allergic or not willing to participate, were excluded from the study.

Following pilot testing on 5 samples, the main trial was carried out on 50 subjects who were selected based on eligibility criteria. All subjects were evaluated for diet patterns, chewing habits, and medical history. The study participants were randomly divided into two groups, chewing fennel seeds (group A) or cardamom seeds (group B). Each group comprised 25 subjects and the baseline salivary pH before chewing seeds was recorded by placing calibrated pH meter in the sterilized container of optimal size for saliva, which further was matched with the pH scale collared chart. The subjects in Group A were asked to chew a known standardized quantity (1.3 grams) of fennel seeds and in Group B, one pod of cardamom, both for 5 min. Patients were requested to sit comfortably on the dental chair and to spat into the sterilized test tube and almost 1 ml of saliva was collected as a sample. (CONSORT diagram. figure 1)

A calibrated pH meter Digital pH Meter (Mini Digital Pen Type ROHS pH-009) was used for the scrutiny of the salivary samples. Standard solutions of pH 7.0 and 4.0 were used for the calibration of the system, and standard tests of the system were conducted randomly in between the salivary pH readings. The electrode of the pH meter was cleaned with a stream of distilled water in between each reading and was placed in a standard solution of pH 7.0. This was done to ensure a stable reading on the pH meter to prevent drift and constant checks.

For comparison between the groups (control group X, group A after fennel seed chewing and group B after cardamom chewing) results were analyzed by ANOVA, (Group A before and after seed chewing, Group B before and after seed chewing) paired T test and Students T test was applied (Group A Vs Group B) for obtaining statistical significance between the groups.

Result

In the present clinical study, all the groups were statistically non-significant for age (p= 0.14) and gender (p= 0.85) **(Table 1)**.

For group A Vs group B at baseline, the mean salivary

pH was non significant (p=0.42). When we compared the results for groups, it was observed that for the baseline values were statistically non-significant, again making these two groups similar before intervention (p=0.42). Whereas after the use of fennel seed in groups A and cardamom seed in group B, the rise in pH was statistically significant (p< 0.001) with more ascent in group B **(Table:2)**

When we compared the results for the three groups (group X control, group A and group B) the results were statistically significant (p<0.01). Further, the means were estimated for statistical difference between the groups (group X vs Group A, p<0.01; group X vs group B,p<0.01; group A vs group B, p<0.001) **(Table:3A, figure 2)**

Table 1: *Socio-Demographic Characteristics, Group A VS B (N=50)*

S.no	Characteristics	Group X (n=25)	Group A (n=25)	Group B (n=25)	Sig
1	Age	44.0± 13.6	38.1 ± 12	37.4 ± 12.7	0.14
2	Gender				
	Male	12(48%)	11 (44%).	10 (40%).	0.85
	female	13(52%)	14(56%)	15(60%)	

*Statistically significant (ANOVA and chi square test applied)

Table 2: *Comparison of Before and After Intervention between Group A and Group B (Group A VS B) (N=50)*

S. no	Characteristics	Group A (n=25)	Group B (n=25)	Sig
1	pH before product chewing	6.87± 0.404	6.97 ± 0.45	0.42
2	pH after product chewing	7.56± 0.308	7.85± 0.29	<0.001*

Group X: Control group
Group A: Fennel group: pH after seed chewing
Group B: Cardamom group: pH after seed chewing
*Statistically significant (Students T test applied)

Table 3A: *Comparison of salivary pH between the Groups (Group X, A and B) (N=75)*

Group	n	mean	SD	Group X & A&B	Group X v A	Group X vsB	Group A vs B
Group X	25	6.94	0.09				
Group A	25	7.56	0.05				
Group B	25	7.85	0.06				
p-value				<0.01*	<0.01*	<0.01*	<0.001*

Group X: Control group
Group A: Fennel group: PH after seed chewing
Group B: Cardamom group: PH after seed chewing
*statistically significant (ANOVA and students T test applied)

After chewing fennel seeds, a rise in pH was observed with a statistically significant difference between before and after consumption of fennel in group A (p<0.01). Similarly, change in salivary pH scores before and after chewing cardamom seeds showed statistically significant results in group B (p<0.01). (Table:3B)

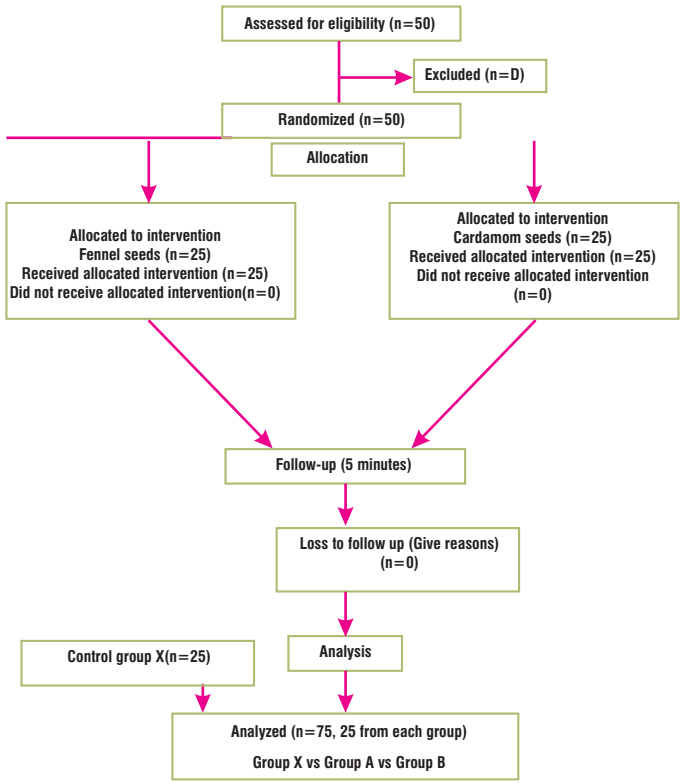

Fig-1: *Allocation of study participants according to CONSORT 2010*

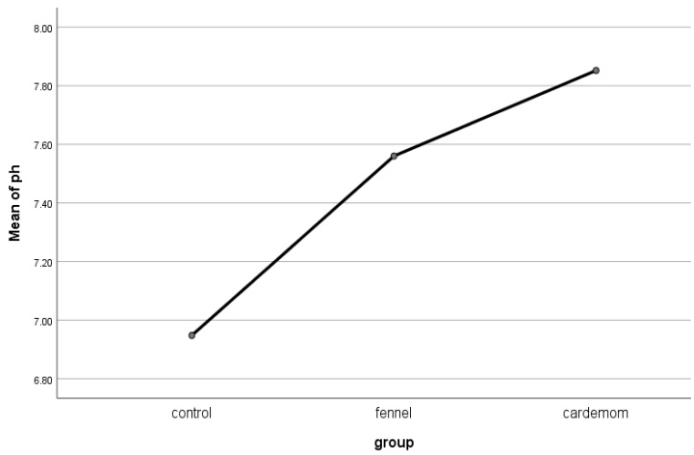

Fig-2: *Comparison of mean salivary pH between the Groups for control (Group X) and after seed chewing (Group A and B)*

Table 3B: *Comparison of salivary pH within the Groups before and after seed chewing (N=50)*

S. no	Characteristics	Group A (n=25)	Group B (n=25)	Sig
1	pH before fennel chewing	6.87±0.404		<0.01*
2	pH after fennel chewing	7.56±0.308		
3	pH before cardamom chewing		6.97±0.45	<0.01*
4	pH after cardamom chewing		7.85±.0.29	

Group A: Fennel group
Group B: Cardamom group
*statistically significant (paired T-test applied)

Discussion

In South Asia, fennel and Cardamom seeds are regularly chewed after suppers to help with assimilation while going about as a herbal mouth revitalization.[11] These are beneficial with therapeutic properties especially related to gut. Additionally possess hostile properties against microorganisms. Cardamom seeds are loaded with health benefits and rich in calcium, iron, phosphorous, volatile oils holds strong inhibitory effects, flavonoids, and ether extracts.[12,13,14]

Previous studies on spices and seeds have shown multiple effects of salivary pH immediately after chewing herbs.[15] A microbiological study on cardamom extract has shown antimicrobial activity against dental caries.[16] Studies have found that these traditional seeds not only inhibit the activity of oral flora but also alter salivary pH hence depicting the anti-cariogenic activity. According to Kang and Ajithkrishnan,

S. mutans, a very important oral floral microorganism, would not produce virulence factors with extracts of fennel seeds.[17,18] While Ravi documented that chewing fennel seeds caused a relatively brief drop in salivary pH.[19] Only a few researchers examined the alteration in salivary pH and antibacterial effects of fennel essential oil.[18,19,20] and further no clinical dental hospital-based study was reported from our population.

Even in our part of South Asia where these seeds are consumed very commonly, there hasn't been much research that specifically appraises the effects of chewing cardamom and fennel seeds on salivary pH. According to our findings, there was a statistically significant rise in salivary pH after consuming fennel and cardamom seeds even after 5 minutes of chewing. The results are similar to one study conducted by Ramesh Nagarajappa A, in which changes in salivary pH were noticed 30 min after chewing the fennel and cardamom seeds.[20] Thus our study predicts a significant early rise in the salivary pH just after 5 minutes in comparison to other studies. Even in that study the difference between the two groups was missing which was the main objective of our research. Results can further be clarified by the fact that chewing home-grown seeds animates salivation which builds the saliva bicarbonate fixation and subsequently increments salivary pH.

The results of mean salivary pH at baseline were comparable with investigations conducted by Ajithkrishnan[(18)] and Shirahatti.[21] The mean salivary pH significant rise after chewing fennel seeds was similar to the study conducted by Ajithkrishnan.[14] But, in another study conducted by Shirahatti only on fennel seed, documented the mean salivary pH decreased after chewing fennel seeds and is contradictory to our study results.[21] The reason could be other confounding factors as it was an Indian-based study where consumption of alcohol, betel nut and pan chewing are much more common and popular than in our country.

In our study, before chewing cardamom seeds the mean salivary pH at the baseline was contradictory to the results in an investigation conducted by Swathi.[13] However, our results were comparable further in the next half as the mean salivary pH augmented after chewing cardamom seeds in both studies. To the best of our knowledge, our study depicts significant results not only between the three groups (control, fennel and cardamom) but also revealed a statistical difference between cardamom and fennel groups, making cardamom better for salivary pH as showed significantly more values when compared to fennel.

Azrak conducted research with 12 boys and 13 girls with fennel tea, to see if there would be any differences in the pH of their saliva. Results were contradictory as the mean salivary pH dropped to 0.35 and 0.33 after 5 minutes and 10 minutes after the intake of enhanced fennel tea.[22]

Our study evaluated the a subsequent increase in pH for fennel and cardamom seeds and that further would prevent the fall of pH below the critical pH for enamel demineralization. This indicates that after consumption of a cariogenic diet the chances of salivary pH decline below critical pH reduces by chewing fennel and cardamom seeds, concluding the protective effect of these seeds against dental caries.

Further multi-centred studies can be conducted with a large sample size, to evaluate changes in salivary pH

at longer intervals, also to emphasise the impact of these seeds on antibacterial activity against many carcinogenic bacteria. Futher additional prospective researches should be carried out to evaluate their effects on salivary parameters such as salivary flow rate, viscosity, and buffering capacity.

Conclusion

According to the results, there was an elevation in salivary pH after chewing cardamom and fennel seeds at intervals of five minutes. Compared to fennel seeds, cardamom seeds are more effective at lowering salivary pH. Henceforth, can be used as an efficient way to buffer the pH of the saliva after consuming a diet high in sugars and cancer causing agents in the diet. Both fennel and cardamom seeds can be cost-effective if advocated as dentifrice when mixed with other components to improve their efficacy and as a herbal alternative for keeping caries-free oral cavities.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

TFB: Conceptualization of Project
MU, EA: Data Collection
RA: Literature Search
RA: Statistical Analysis
ZK: Drafting, Revision
ZK, TFB: Writing of Manuscript

Diagnostic Accuracy of Flamm and Geiger Scoring System as a Prediction Model for Outcome at the Time of Labour- A single-Centred Study

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Abstract

Objective: To develop a simple scoring system (model) based on the information available at the time of hospitalization to predict the probability of success/failure of vaginal birth after caesarean (VBAC).

Method: A prospective observational study carried out in a tertiary care hospital, from Punjab Province, Pakistan with recruitment of participants over a period of six months. Pregnant women underwent trial of labour after caesarean (TOLAC) with inclusion criteria as follow: Pregnant females with singleton fetus (on USG), of age ⩾ 18 years with prior history of one caesarean section, with vertex presentation of fetus (antenatal examination). Patients with any of the following excluded from study: have uterine surgery, fetal mal-presentation and Cephalo pelvic disproportion. One hundred and sixty (160) pregnant women were under trial for the development the prediction model using variables (maternal age, gestational age, body mass index (BMI),) at the time of admission. The outcomes, such as successful or failure of VBAC, were correlated with the VBAC score results.

Results: Out of 160 cases, 113 (70.6%) cases had successful VBAC while remained 47 (29.4%) had unsuccessful VBAC (p-value=0.0001). The scoring model indicated 33.3%, 68.6% and 80.5% successful VBAC for score 0-2, 3-7 and 8-10 respectively (p-value=0.045).

Conclusion: The present study demonstrates that the suggested VBAC prediction model is an effective tool for predicting the outcome of TOLAC and may be used to counsel females of reproductive age regarding the mode of childbirth in the current pregnancy and subsequent pregnancies.

Keywords: TOLAC, Vaginal birth after caesarean section, prediction model, caesarean section

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Introduction

Obstetricians' practices continue to serve with the best outcome provided to the delivering mother who has prior underwent one caesarean section. Generally, the prevalence of Vaginal birth after caesarean section (VBAC), ranging from 9.6% to 52.2% and is varied globally.[1,2] On the other hand, the prevalence of caesarean sections (CS) has been increased from last three decades.[3] According to Word health organization (WHO), the CS varies world widely but the highest rate had been observed in China.[4] In the past 20 years, caesarean section based deliveries has been increased enormously in many countries, including Pakistan. In most countries including Turkey, Egypt, and Brazil have reported the 50% child deliveries though CS. Similar trends have been observed in South Asian nations, like as Pakistan, where abrupt increased in the caesarean sections from 3.2% to 20% between 1990 to 2018.[5,6] The acceptable caesarean section rate was considered to be between

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10% and 15% by the international medical community from 1985 to 2015. Previous ecological studies' have revealed non-significant decrease in death rate subject to caesarean section frequency higher than 10% while other have shown increased in the risk of mother and fetus mortality when caesarean rate approaches 15%. [7-9]
The most prevalent medical justifications for caesarean deliveries include dystocia, previous caesarean delivery, cephalopelvic disproportion, protracted labour, the size of the infant, and multiple gestations[10] however, studies reported 2 to 4 times increased in mortality rate in women who give birth through caesarean section compared to women that deliver vaginal childbirth.[7,8] Despite the fact that modern surgical procedures' like CS are considered to be a significantly safe invasive procedure[11] but CS patients may have health risks including haemorrhage, blood transfusion, anesthesia-related difficulties, and surgical complications.[12]
Public health experts from all over the world have become concerned about the rapidly increasing rate of caesarean births in recent years. However, the WHO no longer advises countries to achieve a particular rate according on their population level due to the significant incidence in caesarean section frequency.[13] Furthermore, the mother's wishes for a caesarean section can also be considered as a non-medical aspect that has resulted in an increase in the caesarean rate.[14,15] Literature also demonstrates that females may request a caesarean delivery for a variety of cultural or particular reasons, such as past delivery experiences, protracted labour, anxiety about vaginal birth, and the cultural acceptance of caesarean sections.[14]
However, in Pakistan, a doctor's suggestion to perform a caesarean section viewed as the primary factor influencing the pregnant woman's decision. Given that the majority of Pakistani women give birth to their children at home, the increasing caesarean delivery rate in the country is on the rise. However, considering how often caesarean sections are performed inappropriately, it is possible to hypothesize that gynecologist's would do non-medically necessitated caesarean procedures in order to profit financially, save time, and gain surgical expertise.[16]
There are generally two alternatives available to a woman who has had one prior caesarean delivery: VBAC or an elective repeat caesarean procedure (ERCS). Both alternatives have different risks associated with maternal and perinatal morbidity, and rarely mortality. Uterine rupture, haemorrhage, endometritis, transfusion, increased chances of asphyxia or perinatal death of the infants are major risk related with VBAC.[1,17] These VBAC associated risk had found minimally in the patients with successful VBAC but unfortunately, no existing tool is reliable to identify women for successful VBAC. Maternal complication rates are lowest in successful vaginal deliveries, intermediate in planned caesarean deliveries, and greatest in unsuccessful vaginal deliveries. Institutions and the service providers also influence on the success rates of VBAC. Therefore, keeping in view the above facts, there is need of time to developed a reliable and observable algorithm or nomogram that correctly identifies or reliably predicts the success of VBAC. There is scanty data available in Asian ethnicities particularly from Pakistan that might evaluate the antepartum and intrapartum predictors for VBAC success/failure prediction, thus an accurate and reliable prediction model must be developed and validated to predict a successful outcome. The objective of the study was to develop and evaluate the novel approach (model) using preliminary information at the time of hospitalization to find out the probability of success of VBAC.

Material and Method

The current study being conducted in Department of Obstetrics & Gynecology, Lady Atchison Hospital, Lahore, and was taken fully approval by the Ethical review board of the institution and was conducted in accordance with the declaration of Helsinki. A sample size of 160 was calculated using 95% confidence interval (CI), 63.6% with sensitivity of Flamm and Geiger score system i.e. 72% with 7.5% margin of error and specificity i.e. 76% with 4% margin of error. Patients with one caesarean section history, Singleton pregnancy, vertex presentation of fetus (antenatal examination) with gestational age ≥ 37 weeks were included while patient with previous classical caesarean section; previous uterine surgery other than caesarean section, fetal mal-presentation (antenatal examination) and Cephalo pelvic disproportion (ultrasonography) being excluded from the investigation protocol.
The following system was used which was already purposed by the model of Flamm and Geiger.[18] In this proposed model, a total five (05) variables namely, maternal age, vaginal birth history, Reason for first cesarean section, cervical effacement on admission and cervical dilatation on admission were included, and named as Flamm and Geiger scoring system. The variable was assigned with score ranged from 0 to 4 based on the scoring system proposed by previous

models reported by Troyer and Parisi et al and Flamm and Geiger.[18,19]

Flamm and Geiger scoring system used in the proposed prediction model:

1. Maternal age (Years): a. <40= 2, b. >40= 0
2. Vaginal birth history:

a. Before and after first caesarean section= 4
b. After first caesarean section= 2
c. Before first caesarean section= 1
d. None= 0

3. Reason for first cesarean section: a. Failure to progress= 0, b. Other reason= 1
4. Cervical effacement on admission: a. >75%=2, b. 25-75%=1, c. <25%=0
5. Cervical dilatation on admission: a. >4cm=1. b. <4cm=0

All variables in the research were analyzed with the help of the statistical analysis tool using Statistical package for the social sciences (SPSS) version 21. (SPSS Inc. Chicago, IL). Descriptive statistics such as mean, standard deviation (SD) employed for maternal age, BMI, and gestational age while frequencies were used for variables in prediction model for success/failure of VBAC. The Chi-square and students-t test were performed for comparison amongst groups with 95%CI and p-value ≤0.05 was taken as statistically significant.

Results

In the current study, 160 pregnant women with mean age 27.62±4.23 were recruited. Majority n=71 (44.4%) of the females were in age group between 25 to 30 years with mean BMI 30.26±3.85 Kg/m^2. The mean gestational age was measured as 39.28± 1.16 weeks. Table 1. represented demographic and clinical information of the studied participants. Out of 160 patients, 113 (70.6%) cases had successful VBAC while remained 47 (29.4%) had unsuccessful VBAC. Table 2 demonstrated the association of the variables with success and failure of VBAC. The common indication of failure in VBAC was failure to progress, >75% Cervical effacement at admission and >4cm Cervical dilatation on admission. As shown in the (figure 1), the frequencies of all variables computed for successful and failed VBAC. The developed score was ranged from 0-10, patients with 0-2, 3-7 and 8-10 score have shown 33.3%, 68.6% and 80.5% successful VBAC respectively.

Table 1: *Demographic & Clinical information of studied subjects*

Demographic Characteristics	(n=160)	Successful VBAC n (%)	Failed VBAC n (%)	p-value
Maternal Age mean±SD(Years)	27.62±4.23			
<25	43 (26.9%)	32 (28.3%)	11(23.4%)	0.727
25-30	71 (44.4%)	48 (42.5)	23(48.9%)	
>30	46 (28.8%)	33 (29.2%)	13(27.7%)	
BMI (Kg/m^2)	30.26±3.85			
25-30	82 (51.3%)	60 (53.1%)	22(46.9%)	0.291
>30	78 (48.7%)	53 (46.9%)	25(53.1%)	
Gestational Age: mean±SD(Weeks)	39.28±1.16			
<39	38 (23.8%)	27 (23.9%)	11(23.4%)	0.519
39-40	86 (53.8%)	58 (51.3%)	28(59.6%)	
>40	36 (22.5%)	28 (24.8%)	8 (17%)	
Number of women underwent VBAC	n=160	113(70.6%)	47 (29.3)	**0.0001**

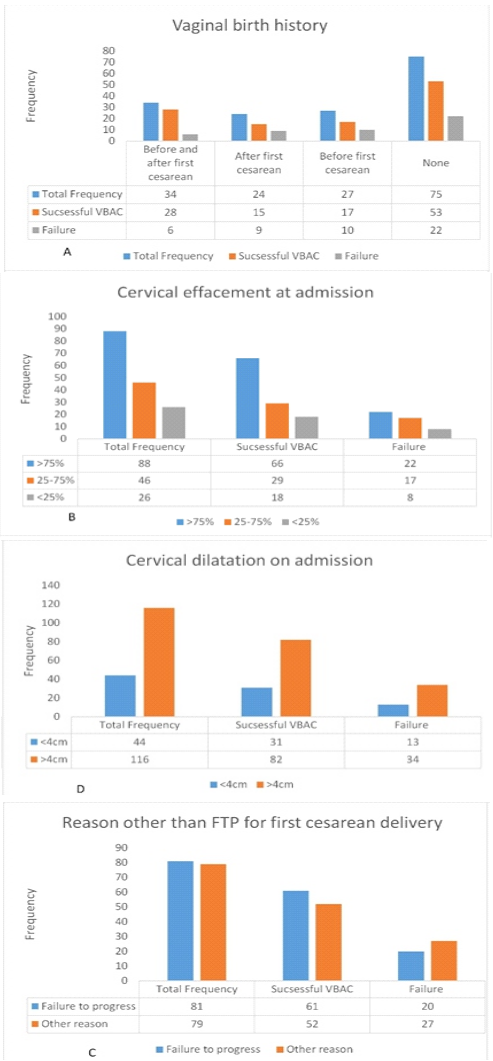

Fig-1. *Bar chart represented frequency of Successful and failure VBAC with; Vaginal Birth History (A),*

Table 2: . *Represented the frequencies of variables in (Predicted model) for Success/Failure of VBAC.*

Characteristic	Frequency	Successful VBAC n (%)	Failure VBAC n (%)	p-value
Age under 40	**n=160**	**113 (70.6%)**	**47 (29.4%)**	**0.001**
Vaginal birth history				0.286
Before and after first cesarean	34 (21.25%)	28 (24.78%)	06 (12.8%)	
After first cesarean	24 (15%)	15 (13.27%)	09 (19.14%)	
Before first cesarean	27 (16.9%)	17 (15.04%)	10 (21.27%)	
None	75 (46.8%)	53 (46.90%)	22 (46.8%)	
Reason other than FTP for first cesarean delivery	81 (50.62%)	61 (53.9%)	20 (42.6%)	0.188
Failure to progress	79 (49.38%)	52 (46.1%)	27 (57.4%)	
Other reason				
Cervical effacement at admission				0.348
>75%	88 (55%)	66 (58.4%)	22 (46.8%)	
25-75%	46 (28.75%)	29 (25.7%)	17 (36.1%)	
<25%	26 (16.25%)	18 (15.9%)	08 (17.1%)	
Cervical dilatation on admission				0.561
<4cm	44 (27.5%)	31 (27.4%)	13 (27.6%)	
>4cm	116 (72.5%)	82 (72.6%)	34 (72.4%)	
Score				**0.045**
0-2	03 (1.8%)	01 (33.3%)	02 (66.7%)	
3-7	121 (75.6%)	83 (68.6%)	38 (31.4%)	
8-10	36 (22.6%)	29 (80.5%)	07 (19.5%)	

Cervical effacement at admission (B), Reason other than FTP for first cesarean delivery (C), Cervical dilatation on admission (D)

Discussion

Models to predict VBAC success have been developed to determine which patients would be more likely to have successful VBAC. In our study, the success rate of VBAC was 70.6%, which is in similar direction (60-80%) reported by the American College of Obstetricians and Gynecologists (ACOG) 2010.[20] The mean age of the cases in our study was 27.62±4.23. The insignificant difference in age was found between successful and failure VBAC which is also observed in the study of Metz et al. in which insignificant difference in age was observed (27.9±4.3 and 27.5±4.6; p=0.20).[21] In the predicted model developed by Grobman et al. maternal information's including ethnicity, age, pre-pregnancy body mass index (kg/m^2), prior VBAC and indication of CS at the time of first antenatal visit were collected for developing the predicted model.[22] Development of such model, accurately predicts the successful VBAC. It had been evaluated whether using ultrasound to assess the thickness of a previous uterine scar area might help predict the probability of rupture and a failure VBAC. The meta-analysis performed by Uddin et al. (2013) in 21 studies revealed the significant role of uterine rupture risk in predicting successful VBAC.[23]

An important model in California in 1997 was developed by the Flamm and colleague. 5022 pregnant TOLAC were under trial using four variables that were noted at the time of hospitalization. These variables (maternal age, vaginal delivery before and after the cesarean section, a non-recurring indication of primary caesarean, cervical dilatation and cervical effacement) were used for scoring i.e. (0 to10). There were found significant difference in VBAC success rate amongst groups having score; 0-2 corresponded to 49.1%, 3-7 corresponded to 59.9%, 66.7%, 77%, 88.65%, and 92.65%, and the success of 8-10 was 94.9%.[18] In our study, the success of VBAC was observed for score 0-2 corresponded to 33.3%, 3-7 corresponded to 68.6% and 8-10 corresponded to 80.6% respectively. Our results were also strengthened by the results reported in Flamm model where high success of VBAC was observed in women having scoring range between 8-10. Another study from Gujrat (India) by Patel et al. in 2016 in 150 pregnant women having single caesarian section history were evaluated using Flamm model. The observed results indicated the successful VBAC (95%CI: 3.9 to 6.7) in women having mean score of 5.35 compared to the women having failure VBAC (95% CI: 27 to 4.57) with mean score 3.62 and they concluded that the chances of successful VBAC

increases with the increased in the score. 24 Two more significant variables, spontaneous onset of labour and parity, may be included in the current model for further strengthening of these findings. As there are limited models/studies in multiple variables are available that accurately predict the success of VBAC so other variables including gestational diabetes, preeclampsia, weight gain in pregnancy, race (reported in other models) may be evaluated to developed the VBAC prediction with greater accuracy. Therefore, predicting the success of TOLAC more accurately, keep in view of findings of our research and other similar models with numerous permutations for the development of standard prediction model.

The small sample size and single center is only the limitation of this study. Moreover, the current study was fully approved from ethical review board of the institute in accordance with the Helsinki declaration (1975), revised in 2000.

Conclusion

In conclusion, the present study revealed the significance of the scoring system for predicting the success of the VB AC and can be implemented in counseling the pregnant women regarding the mode of delivery in current and later on pregnancies. Patient age, vaginal delivery before and after the cesarean section, a non-recurring indication of primary caesarean, cervical dilatation and cervical effacement were significantly associated with success of VBAC. Further studies must been conducted with a relatively larger sample size with comparison of the existing model with other predicting models for strengthening of our findings in a given population.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

SI: Conceptualization of Project
AAU: Data Collection
AT: Literature Search
MS: Statistical Analysis
FI: Drafting, Revision
SI, AAQ: Writing of Manuscript

Prophylactic Anti-Ulcer Effect of Punica Granatum (Pomegranate) Peel and Seed Extract in Murine Peptic Ulcer Model

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Abstract

Objective: To assess the prophylactic antiulcer effect of methanolic extracts of Punica granatum (Pomegranate) peel and seed and its comparison to pantoprazole in diclofenac induced murine model of peptic ulcer.

Methods: Eighty-one male rats were segregated into 9 groups having 9 rats each. Control groups; G-1 (healthy control) and G-2 (disease control) were given only distilled water orally. Pantoprazole and Punica granatum peel (PGPE) and seed (PGSE) extracts were given orally once daily to the treatment groups (3-9) for 15 days as follow: G-3: pantoprazole 60mg/kg/d, G-4: PGPE 100mg/kg/d, G-5 PGSE 500mg/kg/d, G-6: PGPE 50mg/kg/d + PGSE 250mg/kg/d, G-7: Pantoprazole 30mg/kg/d + PGPE 50mg/kg/d, G-8: Pantoprazole 30mg/kg/d + PGSE 250mg/kg/d, G-9: Pantoprazole 30mg/kg/d + PGPE 50mg/kg/d + PGSE 250mg/kg/d. Groups 2-9 were then given 100mg/kg diclofenac orally on day 17 for induction of toxicity. Gastric parameters (gastric juice volume & pH, ulcer index) were assessed.

Results: All treatment groups demonstrated significant gastroprotective activity against diclofenac. However, group 9 (pantoprazole 30mg/kg/d + PGPE 50mg/kg/d + PGSE 250mg/kg/d) exhibited greater antiulcer activity than pantoprazole as well, shown by improvement in gastric parameters.

Conclusion: The study revealed that Punica granatum peel and seeds, generally considered worthless could be used for prevention of peptic ulcer.

Keywords: Peptic ulcer disease, Punica granatum, Proton pump inhibitor, Diclofenac

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Introduction

Peptic ulcer disease (PUD) is a common, chronic multifactorial disease with periods of activation and remission represented by discontinuity in the mucosal lining of upper gastrointestinal tract (GIT).[1] It affects 4% people globally between the ages of 30-60 years resulting in loss of productivity and increase in financial burden.[2] Its debilitating plethora of symptoms and complications range from anorexia, nausea, vomiting, dyspepsia, severe nocturnal epigastric pain to upper GI hemorrhage, perforation, and even gastric outlet obstruction.[3,4] PUD related morbidity and mortality resulted in 267,500 deaths in 2015.[2]

Peptic ulceration is characterized by decrease in gastric mucosal defensive factors and enhancement of offensive factors damaging the mucosa and is a result of various physical and psychological stressors with H.pylori infection and NSAIDs being the leading causes.[5] Diclofenac is frequently used as over the counter drug for pain, fever, inflammation and is one of the most commonly prescribed NSAID for a variety of musculoskeletal

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and rheumatological disorders, but has numerous adverse effects. NSAID-induced peptic ulcer is one of the most serious adverse effects due to any drug therapy and is mediated by inhibiting cyclooxygenase enzymes and subsequently prostaglandin synthesis and their protective effects.[6] According to international research approximately 16,500 arthritis patients receiving NSAIDs die from its gastrointestinal toxicity annually.[7]

Therapy of PUD is targeted at either counteracting aggressive factors or stimulating the mucosal defensive factors. Treatment options include; antacids; anti-secretory drugs like H2 antagonists and proton pump inhibitors (PPIs); mucosal protective agents; antibiotics for H. pylori eradication.[8] Proton pump inhibitors like Pantoprazole, irreversibly blocking the H+/K+ ATPase in the gastric parietal cells, provide superior acid suppression, symptom relief and healing rates and are thus recommended as initial therapy for most of the patients but have adverse effects and drug interactions.[9] Thus, novel, non-toxic, anti-ulcer preparation preferably of plant origin as an alternative for managing peptic ulcer is the demand of time. Several plants like cabbage leaves, ginger, bitter gourd, grapes, gooseberry, sweet potato, and pomegranate have been prescribed by healers to prevent and cure peptic ulcer because of their anti-secretory and gastroprotective properties but most of them have not been studied scientifically yet to confirm their pharmacological activity and safety profile.[10]

Punica granatum (PG) known as Pomegranate belonging to Punicaceae family, is an ancient, mystical fruit mentioned in various mythologies and religious writings as a sacred fruit and has been used for the treatment of a variety of diseases in traditional medicine. It is grown and utilized almost throughout the world. All parts of PG; roots, bark, leaves, flowers, peel, seeds have medicinal value and have been used since millennia across different cultures and civilizations.[11] Therefore, the current study was conducted to analyze the potential of PG peel and seeds in the prevention of peptic ulcer.

Materials and Methods

This experimental animal study was conducted in Post graduate medical institute (PGMI) Lahore, after approval from Institutional Review Board (IRB) of Federal post graduate medical institute (FPGMI) and was completed in 17 days. 81 healthy male albino rats weighing 130-170 grams were purchased from University of Veterinary and Animal Sciences (UVAS), Lahore, were kept in the animal house of PGMI in polypropylene cages under standard housing and lighting conditions and were given standard laboratory diet and water ad libitum. They were randomly assigned to 9 groups (G-1 to G-9) having 9 rats each by lottery method. Before starting the experiment, the rats were acclimatized to the new environment for one week. Pantoprazole tablets (40mg) and Diclofenac tablets (50mg) were bought from Servaid Pharmacy, Lahore, Fresh PG fruits were purchased from local fruit market of Lahore. The identification, verification and extract preparation were done in Applied Chemistry and Research Centre at Pakistan Council of Scientific and Industrial Research (PCSIR) Laboratories Complex, Lahore. Fruits were washed thrice with distilled water and peeled manually. 1 kilo peel and seeds were shade-dried and finely ground in the grinder. Separate extraction was carried out for the peel and seeds with 80% methanol in a Soxhlet apparatus for 4hrs, and further concentration was performed at 40°C under controlled reduced pressure using a rotary vacuum evaporator. The extracts were collected in capped bottles and stored at 4°C till further use.[12]

After acclimatization the animals in the healthy (G-1) and disease control groups (G-2) were given only 0.5ml distilled water orally daily for 15 days and were left untreated. The remaining seven groups were given prophylactic oral treatment once daily for 15 days as per group designation detailed below.

Group 3: (standard group) Pantoprazole 60mg/kg/d
Group 4: PG peel extract (PGPE) 100mg/kg/d
Group 5: PG seed extract (PGSE) 500mg/kg/d
Group 6: PGPE + PGSE (50+250mg/kg/d)
Group 7: Pantoprazole + PGPE (30+50mg/kg/d)
Group 8: Pantoprazole + PGSE (30+250mg/kg/d)
Group 9: Pantoprazole + PGPE + PGSE (30+50+250 mg/ kg/d)

Animals of groups 2-9 were then fasted for 24 hrs (day 16) and given Diclofenac 100mg/kg orally in a single dose on the 17th day.[13] The animals were surgically sacrificed 4hrs later to obtain stomach for evaluation of gastric parameters; gastric juice volume, pH and ulcer index. The upper and lower ends of stomach were tied by threads and stomach was isolated. A small cut was given at the lower end of the stomach and contents were collected in glass tubes. The collected gastric juice was centrifuged at 1000rpm for 10 min.[14] Total volume was directly read from marking of centrifuge tubes and pH was determined using digital pH meter. The stomach was then dissected along its greater curvature, fixed on a board with the help of thumb pins (Fig 1). Ulcer was noticeable as hemorrhagic streaks or linear / punctate discontinuity in the mucosal lining. Ulcers were scored

by examining the stomach macroscopically with hand lens based on grading on a 0–5 scale as presented in the following table.[15]

The ulcer index (U.I) was determined for each group

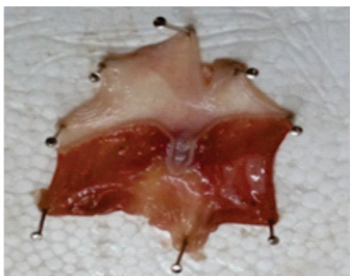
Score	Remarks
0	No lesion
1	Mucosal edema and petechiae
2	One to five small lesions (1-2mm)
3	More than five small lesions or one intermediate lesion(3-4mm)
4	Two or more intermediate lesions or one gross lesion (>4mm)
5	Perforated ulcers

using the following equation[15]:

Ulcer index (UI) = Total ulcer score / no. of animals ulcerated.

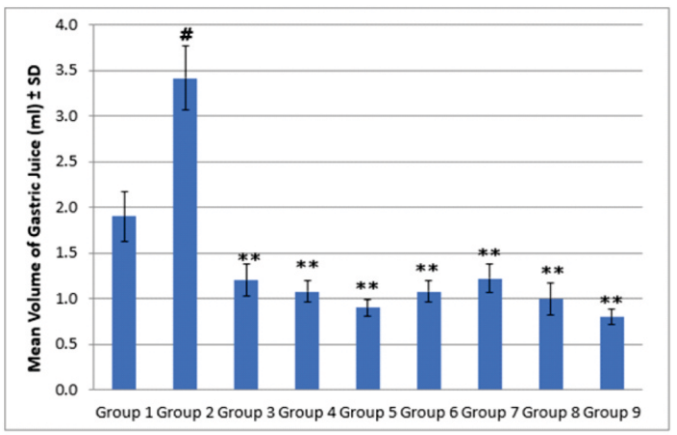
Data was analyzed using SPSS version 23.0 and was described by Mean + SD for each group. Comparison among groups was made by using one-way ANOVA test and pair wise comparison was done by Tukey's test. p-value < 0.05 was considered statistically significant and < 0.01 highly significant.

Fig 1: *Macroscopic examination of stomach*



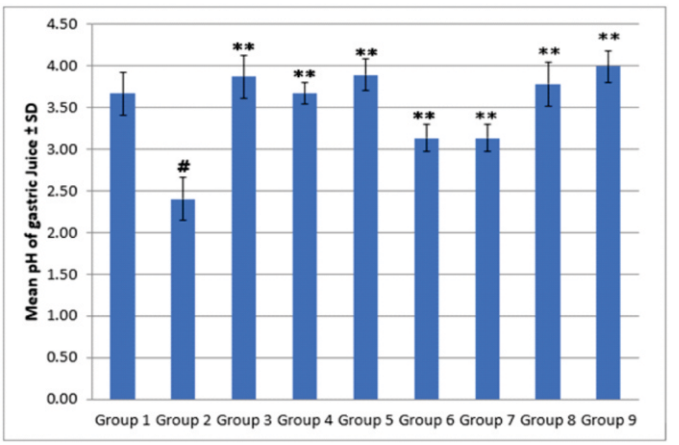
Results

*** (Highly significant values compared to group 2) # (significance of group 2 in comparison to group 1)*



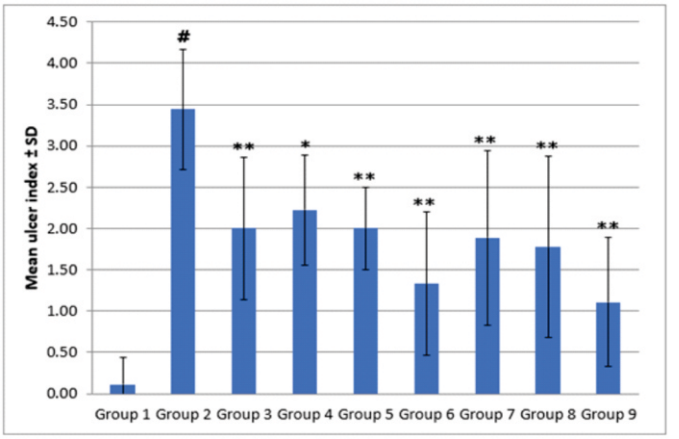
Graph 1: *Graphical representation of total volume of gastric juice (ml) of rats given Pantoprazole, PGPE and PGSE as per group designation (n=9)*

*** (Highly significant values compared to group 2) # (significance of group 2 in comparison to group 1)*



Graph 2: *Graphical representation of pH of Gastric Juice of rats given Pantoprazole, PGPE and PGSE as per group designation (n=9)*

** (Significant values) ** (Highly significant values) # (significance of group 2 in comparison to group 1)*



Graph 3: *Graphical representation of Ulcer Index of rats given Pantoprazole, PGPE and PGSE as per group designation (n=9)*

Discussion

PUD is a widespread gastrointestinal disorder characterized by breach in the mucosal lining of upper GIT, secondary to imbalance between the gastric mucosal defensive factors and offensive factors mostly caused by H. pylori infection and NSAIDs.[1] Several drugs have been available for the prevention and treatment of peptic ulcer but none is free of adverse effects.[10] Prevention and complete remission of PUD with minimal or no toxic effects is the main health concern nowadays.

Phytotherapy is one of the most promising alternative therapies for the treatment of peptic ulcer due to its minimal side effects, cost effectiveness, accessibility and wide range of antioxidant and cytoprotective properties.[16] Pomegranate fruit, peels and seeds have shown anti-ulcer effects in murine models due to their strong gastro-protective and antioxidant activity attributed to presence of phenolic compounds, flavonoids, tannins and anthocyanins.[17] Keeping this in mind, the current research project was designed to investigate the prophylactic antiulcer effect of PG peel and seed extracts (PGPE, PGSE) individually and in combination in comparison to Pantoprazole, a standard antiulcer drug (PPI) in the murine diclofenac induced gastric ulcer model. This specific model was chosen because diclofenac an NSAID, has a pronounced history of acute gastric ulceration secondary to cyclooxygenase pathway inhibition suppressing prostaglandin synthesis.[18] Moreover, no previous research existed to compare the amelioration of these parameters with PGPE and PGSE in comparison to the standard drug pantoprazole against diclofenac. Results of the research project are discussed as follows in detail: Group 1 (healthy control) showed a mean gastric juice volume, pH and ulcer index of 1.90 ± 0.27 ml, 3.67±0.26 and 0.11±0.33 respectively (Graph 1, 2 and 3). Group 2 (disease control) treated with diclofenac caused the highest increase in volume (44%) and maximum reduction in pH(34%) of 3.41±0.35 ml and 2.40± 0.26 respectively as compared to the healthy control group. It also had the highest ulcer index of 3.44±0.73 amongst all the groups which was 97% higher as compared to group 1, indicating its ulcerogenic potential which is due to inhibition of prostaglandins, increasing lipid peroxidation, production of reactive oxygen species and decreasing gastric mucosal blood flow.[7]

All the treatment groups (3-9) showed varying percentage of statistically significant (p-value=0.000) reduction in gastric juice volume (65%–77%), significant increment in pH of gastric juice (30% - 66%) and significant reduction in ulcer index (35% - 68%) as compared to the disease group. PG peel and seeds possess a variety of phytochemicals and their anti-ulcer and gastroprotective effects might be due to free radical scavenging (ellagic acid), inhibiting lipid peroxidation (tannins and ellagic acid), increasing mucus and bicarbonate secretion (flavonoids), promoting NO generation (proanthocyanidin) and increasing mucosal blood supply and strong antioxidant activity (punicalagin, flavonoids). Flavonoids are cytoprotective constituents that have been proven to stimulate prostaglandin, mucus and bicarbonate secretion and possess antioxidant activity as well.[19] Furthermore, tannins present abundantly in PG peel precipitate proteins at the site of ulcer, and form a protective covering that prevents further mucosal damage by toxins, a mechanism similar to sucralfate.[20]

Group 5 (PGSE 500mg/kg/d) showed 74% reduction in volume and 62% increase in pH of gastric juice as compared to disease group, and the results were even better than the standard group (Pantoprazole 60mg/kg/d). These results were in line with a previous study by Gautam et al in which PGSE showed maximum reduction in gastric volume as compared to PGPE and standard drug (Ranitidine 50mg/kg) in diabetic rats.[21] These effects prove strong antisecretory activity of PGSE. The best results were seen in Group 9 (Pantoprazole 30mg/kg/d+PGPE 50mg/kg/d+PGSE 250mg/kg/d) which showed 77% reduction in volume, 66% increase in pH of gastric juice and 68% reduction in ulcer index as compared to disease group. The results were even better than the standard and healthy control groups. This combination showed "synergistic activity" of pantoprazole with PG peel and seed extracts due to combination of the above-mentioned mechanisms of phytochemicals present in peel and seeds and additionally the anti-secretory and cytoprotective activity of pantoprazole by inhibiting H+/K+ ATPase and reducing mucosal oxidative damage respectively.[22] No previous study could be found to support or refute this synergistic effect.

Conclusion

The current study demonstrated that Punica granatum peel and seed extracts administered prophylactically, individually and in combination showed significant anti-ulcer potential in the acute diclofenac model comparable to the standard drug, pantoprazole; evidenced by significant reduction in gastric juice volume, ulcer index and increase in pH of gastric juice as compared to disease group. Therefore, it can be inferred that the peels and seeds of Punica granatum, a commonly used delicious fruit are an invaluable yet wasted resource which may provide new options for prevention of peptic ulcer disease.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

MIP: Conceptualization of Project
SSA: Data Collection
FAK: Literature Search
SMNZ: Statistical Analysis
SSA: Drafting, Revision
TZ: Writing of Manuscript

Molecular Identification of Forensically Important Blowflies By DNA Barcoding to Effectively Determine Postmortem Interval

Sundus Mona,[1] Muhammad Zahid Bashir,[2] Abdul Ahad,[3] Aimal Nasrullah,[4] Muhammad Mubashir,[5] Manal Mubarak,[6] Mudassar Rashid[7]

Abstract

Objective: To identify blowflies by molecular method of DNA barcoding and measure post mortem interval by studying their life cycles and calculating time since death retrospectively.

Method: 200 larvae were collected from different cadavers from mortuaries of Lahore that were brought for autopsies from different parts of the city. After DNA extraction, CO1 region of 658bp was amplified using suitable primers. Sanger sequencing was done and all sequences were submitted to BLAST for molecular identification. These sequences were then submitted into BOLD for sequence comparison.

Results: Two species of blow flies were identified Chrysomya megacephala in 142 samples and Chrysomya rufifacies in 34 samples, showing predominance of blow flies feeding on human dead remains.

Conclusion: Molecular identification is better, effective, time saving and more accurate than morphological identification of insects feeding on human dead remains. Forensic entomology is an effective method to measure post mortem interval when human dead bodies are found after many days unidentified and putrefied.

Keywords: Postmortem Interval (PMI), DNA (Deoxyribonucleic Acid), DNA barcoding, CO1 (Cytochrome oxidase subunit 1), BLAST (Basic Local Alignment Search Tool, BOLD (Barcode of Life Database), blowflies

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Introduction

Forensic entomology deals with use of insects to aid the legal investigations. The most important usage is the measurement of postmortem interval (PMI). Most common and important order of insects is Diptera and the most common Diptera are blow flies as they reach dead matter most initially. The eggs or larvae they hatch on dead bodies are picked by forensic entomologists to study their identification, life cycles and time of colonization to determine how long the body is dead.[1] When the postmortem interval gets prolonged and conventional methods become limited in its determination, then blowflies or Calliphoridae flies are evidence themselves, especially in criminal cases of unknown bodies.[2] Proper identification either morphological or molecular is extremely important whenever they are studied by forensic entomologists.[3] These flies lay eggs on moist parts of the dead bodies or directly deposit larvae which feed on the carrion and slowly mature into adult forms. Their growth cycle acts as natural biological clock that can be utilized to determine time since death as well as the habitat where bodies are found.[4]

Many a times flies infest bodies in domestic settings and investigators label such deaths as natural. Even in such cases, larvae, pupae, immature flies or adult ones should be preserved as their utilization afterwards can prove a crime even after cremation of such bodies.[5] As sometimes flies at larval stage look similar, their accurate

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and proper identification is vital for solving criminal cases. For proper identification taxonomic keys are used and sometimes they can be unavailable. This can be a huge drawback of morphological identification especially when mature forms of insects are not available. Morphological keys identify adult forms of insects generally which may require to hire a specialized taxonomist who can identify these insects accurately.[6] If insects are identified imprecisely, it can change understanding of habitat and its entomofauna entirely. Currently our knowledge of taxonomy and morphological format of identification lacks especially regarding immature forms of insects. So, in order to link both genders of same insects and their true identification, molecular methods of identification are getting attention.[7] Molecular methods overcome the difficulties of morphological key utilization in the sense that they can work with all forms of same insect, whether immature or adult. They take lesser time to process and identify forensic insects; moreover results are more authentic.[6]

The field of molecular identification is relatively new and evolving. That includes DNA analysis and matching molecular sequences of same species which has diversified with time. Entomologists need to follow updated guidelines of entomofauna as various factors affect the timeline of colonization and succession of insects on the dead bodies. Not only identification but differentiation of these insects from other similar ones can reduce chances of error while determining time since death mainly relying on time of colonization and life cycles of identified insects.[8] DNA barcoding has emerged as a revolutionary taxonomic method which can be reliable for saving an organized record of identified DNA sequences of insects studied until now for systematic identification of forensically relevant insects. The two main objectives of this newly developed technique are insect identification and locating its species group. The newly discovered insects add to data of already identified sequence pool.[9]

For DNA barcoding, mt DNA is commonly used as it has high mutation rate that enhances prospects of producing species-specific markers of relevant insects and possesses both variable and conserved bits. Also it is easier to extract as compared to nuclear DNA. The best gene for barcoding is cytochrome oxidase 1 (CO1) gene. CO1 gene is conserved as protein coding region in all aerobes and is frequently used to identify the species which makes it perfect for tracing the phylogeny of similar insects.[10] CO1 is therefore widely utilized region of mt DNA to study population genetics and biodiversity which makes it an effective tool to identify forensically relevant insects universally.[11] Regarding the essential prerequisite of proper identifi-cation of forensic insects, molecular identification of forensically important insects is direly needed. As it is new emerging technique in Pakistan, it needs more atten-tion by law enforcement agencies.

Material and Methods

Sampling was purposive and 200 larvae were collected from five cadavers in putrefaction phase of decomposition with larval colonization found on bodies, from mortuaries. After approval obtained from the Ethical Committee of UHS, we took 40 larvae from each of the five cadavers from mortuaries of Lahore. The appropriate animal care, experimental protocols, and the recommendations of the International Public Health Service Guide for the Care and Use of Laboratory animals were followed. The larvae were collected with soft forceps put in absolute alcohol with labels for each sample and stored at 4˚C in UHS. Pupae and adult flies were excluded from the study. DNA extraction was done by phenol-chloroform method and quantified by nanodrop. CO1 658bp region was amplified by using LCO1490 as forward and HCO2198 as reverse primer after optimization. PCR mix was placed in thermo cycler (Applied Biosystems by life technologies, ProFlex PCR System model) by adjusting the conditions. Each PCR product was gel purified. The CO1 region of mtDNA was amplified by PCR. Gel Electrophoresis was done with Agarose gel. Clearest bands were selected for annealing the primers with desired DNA products. Sanger sequences methodology was adopted to sequence the Amplified PCR products. The DNA sequence analysis was done by ChromasPro Version 2.6 to edit and confirm the sequence electropherograms. Each sequence was submitted to BLAST (Basic Local Alignment Search Tool) to verify sequence similarity to previously identified CO1 dipteral sequences. These sequences were then submitted into BOLD (Barcode of Life Data Systems) for sequence comparison. DNA Barcode analysis was carried out by Nucleotide sequence divergences for dipteral insects using software MEGA 7. Similar sequence was picked from NCBI and compared to the results.

Results

DNA was extracted by organic method of phenol-chloroform method. It was quantified by nano drop. Primers were optimized and bands were observed in gel dock through computer software.

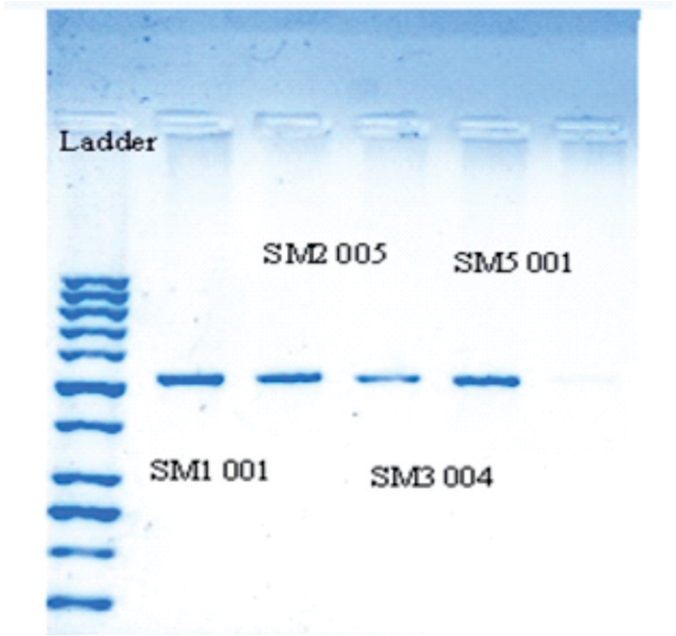

Fig-1: *PCR product in gel electrophoresis*

DNA Concentration of few extracted samples obtained from NanoDropTM

Sample 33 (Body 1) had 201.9ng/µl of nucleic acid
Sample 45 (Body 2) had 338.5ng/µl of nucleic acid
Sample 88 (Body 3) had 485.9ng/µl of nucleic acid
Sample 128 (Body 4) had 548.2ng/µl of nucleic acid
Sample 156 (Body 5) had 228.6ng/µl of nucleic acid

After submission of sequences to Blast, sequence similarity of each result sequence was verified and compared to previously identified CO1 dipteral sequences. These sequences were then submitted into BOLD (Barcode of Life Data Systems) where storage and preliminary data analysis was undertaken. Two (02) species were identified; Chrysomya megacephala in 142 samples and Chrysomya rufifacies in 34.

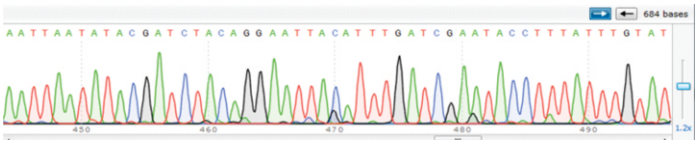

Fig-2: *Sequence clipping of Sample 1 (Chrysomya megacephala)*

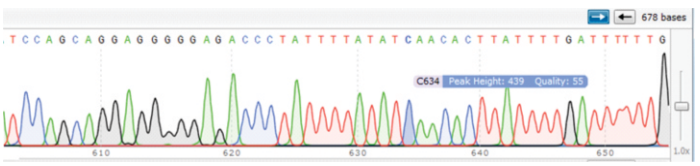

Fig-3: *Sequence clipping of Sample 187 (Chrysomya rufifacies)*

After sequences were received, their electropherograms were generated and the data quality checked. Fig. 2 & 3 indicates cutouts from sequences of the two collected species.

Table 1: *Similarity index for species identification using BLAST (Few samples)*

Query ID	Best ID	Search Database	Top% Similarity	Low% Similarity
Sample 1 Body 01	*Chrysomya megacephala*	COI species database	100	99.85
Sample 54 Body 02	*Chrysomya megacephala*	COI species database	100	99.81
Sample 98 Body 03	*Chrysomya megacephala*	COI species database	99.84	99.68
Sample 143 Body 04	*Chrysomya megacephala*	COI species database	99.85	99.65
Sample 187 Body 05	*Chrysomya rufifacies*	COI species database	99.87	99.16

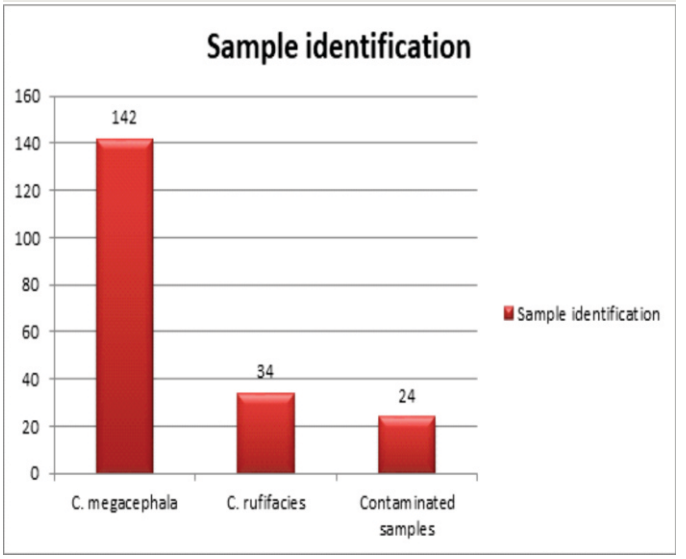

Table 2: *Abundance of flies in 200 samples*

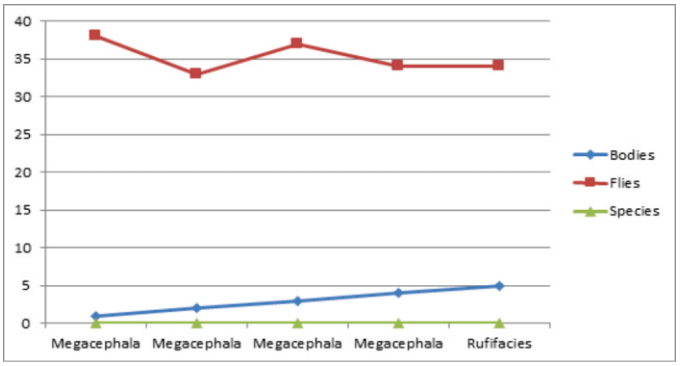

Table 3: *Species identified per body*

Discussion

Forensic entomology is a sporadically used science. After 72 hours of death, rate methods of determining port mortem interval hardly define an exact time since death, so as a concurrent method and circumstantial evidence; insects can tell time since death by their time of colonization, life cycles and genetic sequences fairly well. In our study we collected larval samples from human cadavers, all homicidal cases with identities unknown or amputated body parts and injuries pertaining to assault before death. These larval samples were preserved and analyzed by DNA extraction, PCR amplification of CO1 gene and after aligning sequences by MEGA software, the sequences were submitted in BLAST software to match with already stored sequences. These sequences were then submitted in BOLD (Barcode of Life Database). The sequences with 99 or 100% match were included in study, although 24 samples had to be discarded as they showed contamination by human DNA. Out of 176 samples that clearly identified insects, 142 samples belonged to Chrysomya megacephala while 34 samples showed Chrysomya rufifacies species. Chrysomya megacephala was discovered by larvae collected on four dead bodies, while Chrysomya rufifacies was found on only one.

The technique used for DNA barcoding was utilizing the 658-670bp of 5' end of mitochondrial CO1 gene. It is frequently used region for identification of forensic insects especially the blow flies shown in many studies.[12-17] Most frequent sequence was that of Chrysomya megacephala and its standard prototype sequences were available on National Center of Biotechnology Information (NCBI) and Barcode of Life databases (GenBank and BOLD), respectively.[13,14] In our study the most frequent blow fly was also C. megacephala which is consistent with study of Badenhorst et al., 2018 who found C. megacephala as globally distributed species, a most abundant one and most forensically relevant too. It is known as the earliest and dominant scavenger that colonizes dead bodies and the best entomological candidate to be utilized for determination of time since death.[18] Chrysomya megacephala is also abundant in Sub-continent and Middle East which makes its abundance in Pakistan usual, which is consistent with study of Akbarzadeh et al., in 2015.[19]

The second most abundant sequences we got were of Chrysomya rufifacies. It is a blowfly that is forensically relevant and fairly encountered on vertebrate dead carrions and commonly found in tropical climates with temperate weather like North and central Americas, the continent of Australia and Asia.[20] So, Chrysomya rufifacies (Macquart) which is a Calliphoridae is a common fly around the globe which is frequently found on human dead bodies.[21] It is also known as hairy maggot blowfly which causes human myasis and also found as an early colonizer on dead bodies.[22] It can be seen in all seasons as it adapts to all weather conditions and myasis cases among humans coincide with those of Chrysomya megacephala.[23] Its ability to cope in all seasons makes it abundant in both urban and mountainous zones.[24] The habits of C. Rufifacies are not well understood especially in their own habitats but it is still considered as an important forensic blowfly. Regarding their frequent discovery from under the dead bodies, sample collection from underneath dead bodies is very crucial and can be fruitful at the crime scene. [25]

After identification, the life cycles of insects are correlated with postmortem body changes and postmortem interval is calculated by adding life cycle duration of insects with time of colonization according to environmental differences. Postmortem interval is always measured retrospectively by calculating rate methods and then putrefaction timeline where insects' life cycles gives a clue of time spent after death. Though the study was limited and short, the results were promising. If the sample size was higher, more species may have been identified. Human contamination was another limitation of the study. We direly need trained forensic entomologists to assist in medicolegal framework regarding effective sampling at the crime scene and getting promising results to aid legal investigations.

Conclusion

Molecular identification is better, effective, time saving and more accurate method than morphological identification of insects feeding on human dead remains. Forensic entomology is an effective technique to measure post mortem interval when human dead bodies are found after many days unidentified and putrefied. Insect's species, habitat and life cycle determines place of death, time since death, time since colonization and levels of insect succession to aid in legal investigations.

Conflicts of interest *None*

Funding Source *None*

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Authors Contribution

SM: Conceptualization of Project
SM, MM: Data Collection
SM, MZB, AA, AN: Literature Search
MR: Statistical Analysis
SM, MZB, MM: Drafting, Revision
SM: Writing of Manuscript

Perceived Academic Stress Among Undergraduate Medical Students and Their Coping Strategies

Syeda Shaista Waheed

Abstract

Objective: To identify the factors causing academic stress among undergraduate medical students of government and private sector medical colleges. To identify the methods adopted by these students to overcome academic stress.

Method: It is a quantitative study done on medical students of one public and one private sector medical college. Nawaz Sharif Medical College, Gujrat and Islam Medical and Dental College, Sialkot was included. It was done over 6 months i.e. 1.1.2021 to 30.6.2021. Ethical approval was taken from both colleges. 50 students each from fourth and final year were taken from both medical colleges. Total sample size was of 200 students. Simple random sampling was done. The data was collected using PASS scale. The questionnaire was distributed among 50 students of each class of 4th and final year and asked to fill on voluntary basis. Data is analyzed using SPSS version 20.

Results: Academic stress level in public sector medical college was low in 25%, moderate in 40% and severe in 35%. As compared to this, the private sector students were having low stress level in 10%, moderate in 30% and severe in 60%. The major coping strategies adopted by the students to relieve stress were Venting off emotions, use of social support, and religious coping.

Conclusion: This study guides the authorities to modify the curriculum and teaching environment of medical colleges of Pakistan to decrease the academic stress and ultimately improve the academic performance of our students. This also indicates the student`s personal awareness of stress and need for psychological support.

Keywords: academic stress, PASS Scale, examination, assignments.

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Introduction

Stress is a natural response to day to day activities which may be due to elating or depressing events. Every human being has a different response to stressful circumstances. Some take it as a challenging task while others perceive it as a threat to their identity.[1]

When the students are entering in professional studies, they are new in that environment. It leads to development of academic and non-academic stress. If not managed effectively, this can lead to certain minor or major problems.[2,3]

Presence of academic stress in undergraduate medical students is a known entity. Various factors can influence the development of academic stress which may include non-academic factors like social conditions, emotional state, family support and health status of the students. All these influence the ultimate final performance of the student in examination and can affect their performance badly. Also it can result in acquiring psychological illnesses like depression and anxiety. The high dropout rate of medical students is also due to high stress levels.[4,5] High pressure of parents and society to perform best

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at each and every step of medical college is an important contributing factor for development of stress in students. There is intense pressure by peers and siblings as well. All this stress can lead to development of psychiatric illnesses in medical students.[6,7] Insecurities about the future are also contributing to high stress levels. Unrealistic goals set under all the above stated pressures lead to high failure rates and poor self-esteem. Self-regulation and mindfulness are two very important tools in efficient functioning of day to day tasks. It is also seen that self-regulation has an important role in decreasing academic stress and improving overall performance.[8-10]

Material and Methods

It is a quantitative study done on undergraduate medical students of one government and one private sector medical college. Nawaz Sharif Medical College, Gujrat. Islam Medical and Dental College, Sialkot. Ethical approval was taken from Institutional review boards of both colleges before start of the study. This study was done in 6 months i.e. from 1 Jan 2021 to 30 June 2021. Ethical approval was taken from IRB of each college. 50 students each from fourth and final year were included from each medical college. Total sample size was of 200 students. Simple random sampling was done. All students of fourth year and final year was included. Participation of students was totally on voluntary basis. Both male and female students are included. Students of first, second and third years are excluded. The students not willing to participate voluntarily are excluded. The data is collected using PASS (Perception of Academic Stress Scale). This calculated the level of academic stress. The commonly adopted coping strategies for stress by students were identified. The questionnaire was distributed among students of each class of 4th and final year and asked to fill these on voluntary basis. Anonymity is observed during the whole process. Individual scores on the PASS can range from 0 to 40 with higher scores indicating higher perceived stress. Scores ranging from 0-13 would be considered low stress. Scores ranging from 14-26 would be considered moderate stress. Scores ranging from 27-40 would be considered high perceived stress. Data is analyzed using SPSS version 20. Means and standard deviation is calculated of each causing factor for academic stress.

Results

Females were in majority as compared to male students. Most of the students in our study were living in their homes **(Table-1)**. Public sector medical college students were having less academic stress as compared to private medical college students in this study **(Fig-1).** But students of both categories of medical colleges were able to identify academic stress effecting their mental health and learning capabilities. Fourth year medical students were having less score for stress at PASS as compared to

Table 1: *Demographic factors*

Demographic variable	No of Students (%)
Gender	
-Male	55(27.5%)
-Female	145(72.5%)
Age	
-20-21 yrs.	85(42.5%)
-22-23 yrs.	90(45%)
-24-25 yrs.	25(12.5%)
Residence	
-Home	89(44.5%)
-Hostel	111(55.5%)

Table 2: *Mean score of stress according to PASS among fourth and final year students*

	Fourth year Mean Score	Final year Mean Score	Total Mean Score
Public Sector Medical College	25	36	30.5
Private Sector Medical College	26	40	33

Table 3: *Coping strategies adopted by students*

Sr No.	Coping Strategies	No. of Students Adopting the strategy	Percentage
1	Focus on and venting of emotions	114	57
2	Use of instrumental social support	150	75
3	Denial	89	44.5
4	Religious coping	167	83.5
5	Planning	102	51
6	Mental disengagement	54	27
7	Positive reinterpretation	98	49
8	Humor	147	73.5
9	Acceptance	134	67

final year students **(Table-2)**. Different type of coping strategies were used by students to overcome stress. In our study religious coping was seen most common followed by social support and humor to alleviate stress **(Table -3)**.

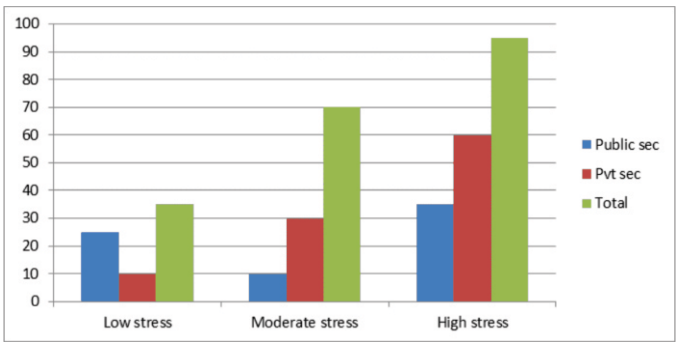

Fig 1: *Distribution of students according to perceived stress levels*

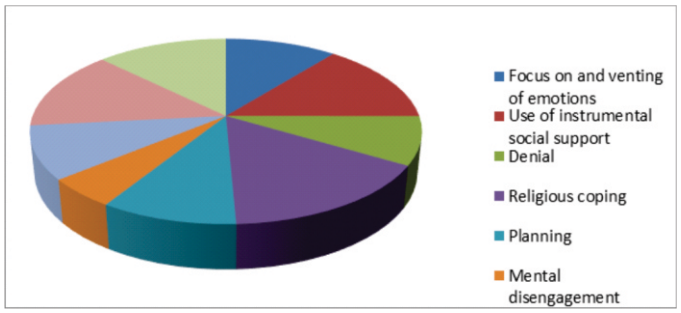

Fig 2: *Coping strategies adopted by students*

Discussion

The study revealed that the presence of academic stress among undergraduate medical students is an important factor affecting their performance. It can be modified by varying strategies at college campus. In this study, the high level of stress is seen more in private sector medical college students as compared to public sector medical college. The public sector medical students have low to moderate stress commonly.

Students used different coping methods to overcome the stress. Religious beliefs, social contacts and humor were most important coping factors to decrease stress level.

These are comparable to the study conducted by Manjiri C.Datar et al in 2017[11] and Leonardsen A-CL, Jelsness-Jørgensen in 2019[12] which concluded that the students develop stress during academic activities which can be decreased affectively by focused management strategies.

The results are also similar to the study conducted by George Essel et al in 2017[13] and Paudel U, Parajuli A et al in 2020.[14] It also showed that stress affects academic performance of the students. Affective strategies and regular sessions for stress management could help in improving performance of the students. A study done by Nieve O Brien in 2014 and Onieva-Zafra MD et al in 2020 addressed the important point that output of a student can be improved by addressing different aspects of student's life including health, finances, teaching sessions, focused and constructive feedback, time management and study methods etc. All these strategies help in developing a strong bond between student and teacher. These results are in accordance with our study.[15,16] The same results are seen in study conducted by Nur Hamizah Hj Ramli et al in 2017. It showed that academic stress is a very commonly present condition that effects the student`s performance. Multiple factors like lengthy syllabus, peer pressure, exam fear and future plans etc. effect the mental health of the student. All these can be managed effectively by using coping strategies like self-regulation and mindfulness.[9] Joseph N, Nallapati Aet al in 2022 showed same results.[17] Also comparable results are seen in a study conducted by Sherlyn S Jimenez et al in 2018 which suggested that mindfulness help in targeting negative emotions, low mood and negative self-image.[18] Another study done by Priya Gangadharan in 2014 also stated that academic stress exists in under-graduate medical students and certain methods can effectively reduce it.[19] In a study done by Purna Prabhakar Nandamum et al in 2011 concluded that stress is high in professional degree program students. Different aspects of stress are curriculum and staying updated in their subject, pressure of colleagues, communication difficulties, future goals etc. Identification of these factors could help in adopting strategies to lower the academic stress.[20] Wang Y, Xiao H et al in 2020 also showed similar results.[21] In the studies, conducted by R. Anuradha et al in 2017, Kötter T, Wagner J et al in 2018 and Thomas C, Zolkoski S. et al in 2020, it was found that the stress level increase with promotion in next class and with increase in age which is also seen in our study.[22-24]

Conclusion

This study identifies the severity of the stress in under-graduate medical students of government and private sector medical colleges of Punjab, Pakistan. Various

coping strategies were adopted by students to cope the stress. This study guides the authorities to modify the curriculum and the teaching environment of medical colleges of Pakistan to decrease the academic stress and ultimately improve the academic performance of our medical students. This also indicates the student`s personal awareness of stress and need for psychological support to them.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

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

Comparison between Efficacy of Flipped and Traditional Methods in Teaching-Learning Human Physiology

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Abstract

Objective: To compare the efficacy of flipped classroom and traditional teaching techniques in topics from Physiology.

Method: It was a comparative descriptive study conducted at Physiology Department, Sharif Medical and Dental College , Lahore from July to September 2022. It included 100 second year M.B.B.S. students. Students were categorized into two groups (Group 1 & Group 2) comprising of 50 students each, by lottery method. Flipped technique was introduced for teaching two topics in Thyroid physiology to second year MBBS students. In the first part, Group 1 attended traditional lecture and Group 2 attended flipped technique. The same pretest and posttest was given before and immediately after each session. In the second part, the two groups were interchanged, where Group 2 attended traditional lecture and Group 1 attended flipped classroom technique. The data was entered in SPSS version 22 and analyzed.

Results: The significant p-value of posttest by both techniques showed that both teaching techniques do not equally enhance students' perception, and the mean value of traditional lecture technique is superior to the flipped technique to enhance the students' perception in Physiology.

Conclusion: In the present study the mean value of traditional lecture technique was superior to the flipped technique to enhance the students' perception regarding any study topic in Physiology.

Keywords: Traditional Lecture, Flipped Classroom, Physiology

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Introduction

Transfer of knowledge to students occurring through a traditionally based setting such as in-class lectures within the institute, somehow has lost its charm to the upcoming generation students. This has been observed in their poor attendance, lack of attentiveness and average result outcomes.[1,2] Physiology is an essential branch of health sciences, and many advancements are continually occurring in key physiological mechanisms, making it very important as well as complicated for medical students to understand.[3] They are deficient in critical thinking and problem solving.[4] Consequently, students have started showing more interest in interactive learning.[1,5] This new competency based medical education demands for the progress in critical thinking and problem solving abilities. It also lifts up the use of novel interactive teaching, demanding methods, and technology in teaching. Some teaching methods like small group discussions are helpful in this regard but do not always suffice. To fulfil these demands we decided to test the efficacy of an alternative learning also known as "flipped classroom technique". It is a type of hybrid and mixed-mode learning where study material and full guidance about what, how, and from where to study is provided to students beforehand. Therefore, students come well prepared for an interactive session. In this

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way they can apply their learned knowledge in critical thinking. In recent times, many studies have also been conducted in different areas of the world to get feedback from both teachers and students about flipped classroom technique.[6,7,8]

This study was designed to determine and compare the efficacy of both the flipped and traditional teaching techniques in teaching and learning physiology. Results were built on the basis of outcomes from the Thyroid Physiology MCQ test. This study will help us to obtain students perspective about flipped technique verses traditional lecture technique in learning physiology. This study will also help to reinforce the thought process of learning, critical thinking, and problem-solving skills in Second Year Medical students of Physiology.

Materials and Methods

This comparative descriptive study included 100 second year M.B.B.S. students enrolled in Physiology course for 2021-2022, after taking informed consent and with permission from the institutional ethical committee. The study was conducted at Physiology Department, Sharif Medical and Dental College, Lahore from July-September 2022. Students were categorized into two groups (Group 1 & Group 2) comprising of 50 students each, by lottery method. Students of both gender who were fresh entrants in the Second Year MBBS between the age group 20-23 years, and were present in class were included in the present study. Any student who was absent or a repeater in any of the classes during the activity was excluded from the research.[9] Students who did not agree to participate in the study were also excluded. Flipped technique was introduced for teaching two topics in Thyroid physiology to second year MBBS students. In the first part, Group 1 attended traditional lecture and Group 2 attended flipped technique class on the topic of Synthesis and Regulation of Thyroid Hormone. Specific topics were taught by specific teachers using traditional lecture and flipped classroom methods. Reference material was provided a day in advance to those attending flipped class, in the form of standard book references with specific page numbers (Reference from Guyton & Hall Medical Physiology & Sherwood), whereas no reference material was given to students attending traditional lectures. A 10-minute question-answer session was held after the traditional lecture and at the end of flipped classroom a discussion related to the topic was held, facilitated by the specific teacher. The same pretest and posttest (consisting of 10 MCQS with 1 mark each) was given before and immediately after each session to judge students' critical thinking and problem solving skills. In the second part, the two groups were interchanged, where Group 2 attended traditional lecture and Group 1 attended flipped technique class on Hypothyroidism and Hyperthyroidism. The efficacy was measured by the level of effectiveness of flipped classroom method and traditional lectures in teaching-learning Thyroid physiology as concluded by paired t-tests performed on each type of study. The data was entered in SPSS version 22 and analyzed. Mean and standard deviation was calculated for quantitative characteristics. Paired t-test was applied to compare the pretest and posttest results of both techniques. Independent sample t-test was applied to conduct the comparison between flipped and traditional lecture techniques' pretest/posttest results. Pearson's correlation was applied to observe the association between flipped and traditional lecture techniques on the basis of posttest results. Box plot was plotted to assess the normality of results obtained through pretest and posttest by using flipped classroom or traditional lecture techniques.

Results

Randomly allocated student's pretest mean with lecture technique was higher than the pretest means with flipped classroom technique. Similarly, the students 'posttest results put on lecture technique was higher than the posttest mean of students put on flipped technique. In the present study, ratio of flipped classroom to traditional lecture techniques, lecture technique provided better results as compared to the flipped technique (Table-1). The significant p-values in Table-2 showed that both techniques significantly enhance the knowledge of students either they are put on flipped technique or traditional lecture technique, but the mean value in our study showed that the traditional lecture technique is better than the flipped technique. The insignificant p-value of pretest by both techniques showed that the students either put on flipped technique or traditional lecture technique had almost same knowledge/concept but the significant p-value of posttest by both techniques showed that both teaching techniques do not equally enhance students' perception, and the mean value of traditional lecture technique is superior than the flipped technique to enhance the students' perception regarding any study topic (Table-3). The insignificant p-value showed the positive relationship between flipped and

traditional lecture techniques (Table 4). It means that both techniques are enhancing the student's learning/ perception/knowledge level but the mean value declare that the lecture technique is better than the flipped technique to enhance the student's learning, perception, and knowledge.

Table 1: *Descriptive Statistics*

	N	Minimum	Maximum	Mean	Std. Deviation
Pretest results with flipped classroom technique	49	1	7	3.53	1.324
Pretest results with traditional lecture technique	49	2	7	4.10	1.544
Overall pretest results with flipped classroom/traditional lecture techniques	98	1	7	3.82	1.460
Posttest results with flipped classroom technique	49	4	9	6.06	1.329
Post test results with traditional lecture technique	49	5	10	7.73	1.186

Table 2: *Pretest vs. Posttest by both Techniques-Paired t-test*

Technique	Pretest vs. Posttest	Mean	Std. Deviation	P-Value
Flipped classroom technique	Pretest	3.53	1.324	0.000
	Posttest	6.06	1.329	
Traditional Lecture technique	Pretest	4.10	1.544	0.000
	Posttest	7.73	1.186	

Table 3: *Flipped classroom technique vs. Traditional Lecture Technique-Independent Sample t-test*

Technique type	Test	Mean	Std. Deviation	P-Value
Flipped classroom	Pretest	3.53	1.324	0.052
Traditional lecture		4.10	1.544	
Flipped classroom	Posttest	6.06	1.329	0.000
Traditional lecture		7.73	1.186	

Table 4: *: Association between Flipped classroom and Traditional lecture Techniques-Pearson's correlation*

Technique	Mean	Std. Deviation	P-Value
Flipped technique	6.06	1.329	0.639
Traditional Lecture technique	7.73	1.186	

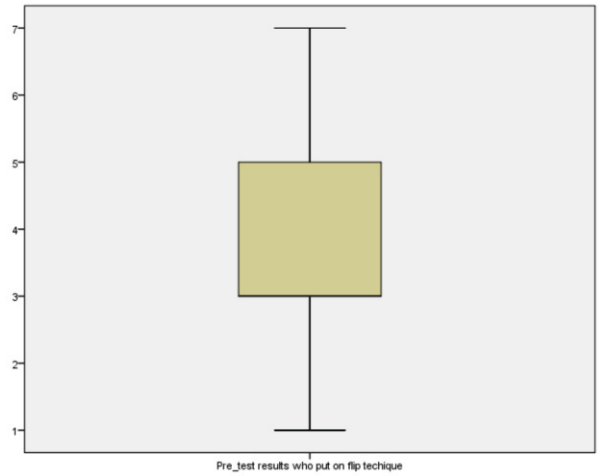

Figure-1: *The pretest result of students who attended Flipped classroom technique followed the non-normal distribution.*

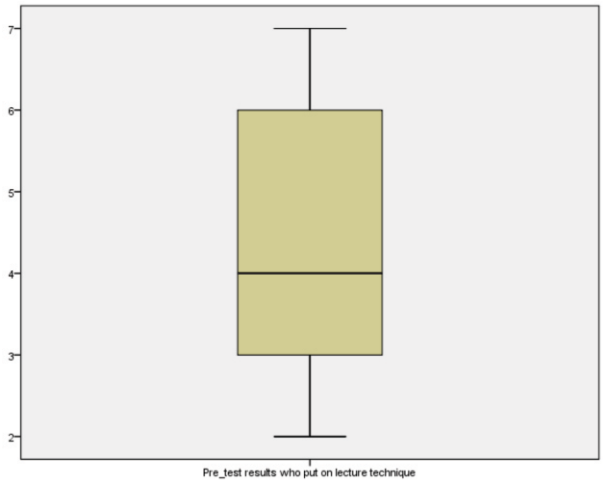

Figure-2: *The pretest result of students who attended Traditional lecture technique followed the normal distribution approximately.*

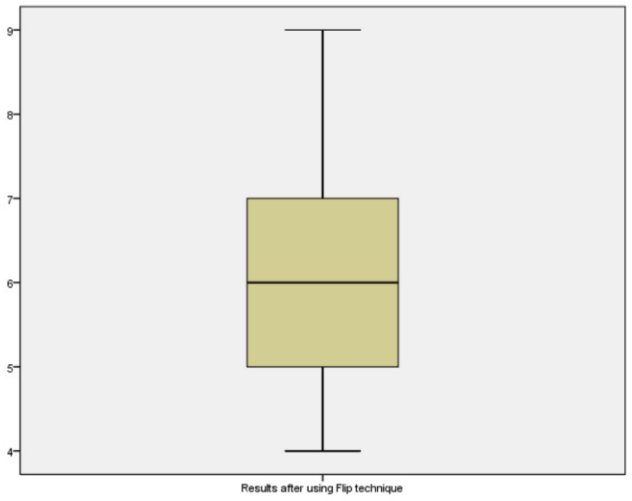

Figure-3: *The posttest result of students who attended*

Flipped classroom technique followed the normal distribution approximately.

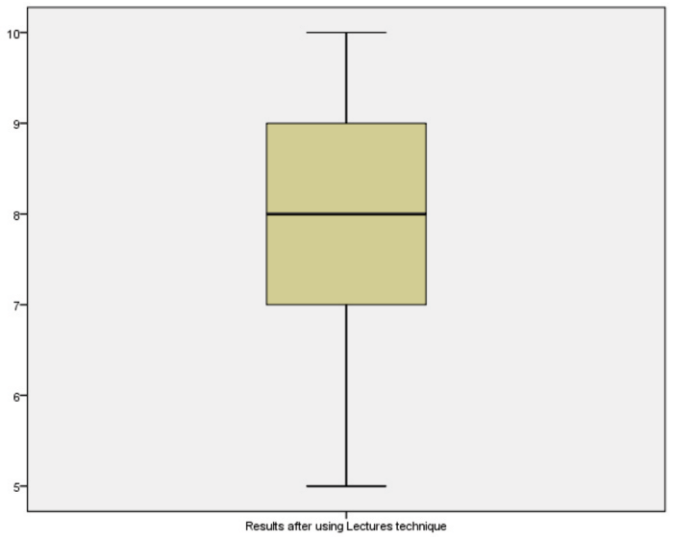

Figure-4: *The posttest result of students who attended Traditional lecture technique followed the normal distribution approximately.*

Discussion

The concept of flipped classroom is new and trending in medical teaching. In this teaching technique the students are provided with reading material prior to the class to familiarize them with the basic concept of the topic which is to be taught in the class.[10]

The present study was conducted to study and compare the efficacy of both the flipped classroom and traditional teaching techniques of teaching and learning Physiology. Our study showed that both techniques significantly enhance the knowledge of students either they are put on flipped technique or traditional lecture technique, but the mean value in our study showed that the traditional lecture technique is better than the flipped technique. In a study by Aggarwal K et al., concluded that a hybrid of both traditional and flipped teaching methods can be used as the mean assessment scores in the flipped and traditional classrooms were not statistically significant.[10] A study by Alaagib et al., in 2019 pointed out a significant improvement in the understanding of Physiology concepts in lectures based on problems.[1] Another study by Aristotle et al., in 2021 showed that posttest results improved significantly as compared to pretest scores in both the traditional and flipped teaching techniques, however, student showed more satisfaction towards the flipped classroom technique.[11] These studies' results are comparable with our study.

In a study by Ming Ji et al., in 2022 showed that although flipped teaching technique is a promising technique to increase learning effectiveness, however, the time investment in the subject of Physiology increased by applying flipped technique.[12] Another study in 2013 concluded that flipped classroom teaching technique by providing pre-recorded lectures before class was a highly efficient way of improving important concepts in Physiology.[13] Dharmendra et al., concluded that flipped class room improves teaching-learning outcomes as well as significantly enhances academic performances of Medical students in the subject of Physiology as compared to the traditional lecture based teaching.[9] A study by Zhang et al., experimented a small online course flipped classroom teaching method in teaching Physiology to medical students of a Kumming Medical College in China. They found that as compared to lecture based learning, students' scores in both preclass and postclass tests improved a lot upon application of flipped class room method in a small online course.[14] A recent study by Patkar et al., in 2021 concluded that flipped classroom technique was an efficient way of improving self-learning, critical thinking, and problem solving skills in Physiology when compared with traditional didactic lecture technique.[8] Jain et al. also highlighted that flipped classroom method is more effective in teaching physiology as compared to the traditional lectures in a diversified group of students.[15] All these studies favor the application and effectiveness of flipped classroom teaching technique both in online as well face to face teaching.

Conclusion

Our study is unique as it is a nascent attempt that shows that both the techniques are equally efficient in enhancing the understanding of taught concepts in Physiology. In fact, in the present study the mean value of traditional lecture technique is superior to the flipped technique to enhance the students' perception regarding any study topic in Physiology.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

ZR, RA, M: Conceptualization of Project
SJ, Q: Data Collection
SQA, GM: Literature Search
SQA, M: Statistical Analysis
GM, RA: Drafting, Revision
SQA, ZR: Writing of Manuscript

How Accurate are the Clinical and Biochemical Markers in Predicting Histological Chorioamnionitis After Preterm Prelabor Rupture of Membranes?

Ameelia Sadaqat,[1] Saira Rathore,[2] Nayyer Sultana,[3] Rashida Mushtaq,[4] Sanam Mahmood[5]

Abstract

Objective: To investigate the effects histological chorioamnionitis(HCA) can produce on clinical features and biochemical inflammatory markers in mothers and infants after PPROM which may help with detection of HCA.

Method: This cross-sectional study included 70 mother-infant pairs presenting to GTTH and CPTH Lahore. Gestational age at presentation, duration of ROM, maternal pulse, abdominal tenderness, colour of liquor, maternal and cord blood TLC and CRP, results of HVS, neonatal blood culture and mode of delivery were recorded on a pre-designed proforma.

Results: Mean age of females was 27.5±4.05 years, mean gestational age at ROM was 32 weeks 6 days, median 34 and mode 35 weeks. Mean duration of ROM was 46.4± 51.4 hours. HCA was confirmed in 14/70 patients. Maternal TLC in HCA+ve group was 14784.29±5958.44 / ml3 and in non-HCA group was 12834.29 ± 3772.56 /ml^3. Maternal CRP in HCA and non-HCA group was 23.2±20.58 and 14.82±19.19 mg/L respectively. According to our study the sensitivity and specificity of maternal TLC for detecting HCA was 21.4% and 87.5% respectively. Sensitivity of CRP was 14.2% and specificity 57.1%. Mean cord blood TLC and CRP in HCA +ve was 15182.86±6114.96/ml^3 and 5.958±.27mg/L. In HCA-ve group cbTLC was 13097.04±8437.26 ml^3 and CRP was 5.84±11.88mg/L.

Conclusion: None of the specific clinical features or the biochemical investigations were statistically significant in detecting histological chorioamnionitis in patients presenting with PPROM.

Keywords: Chorioamnionitis, preterm pre-labor rupture of membranes

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Introduction

Preterm pre-labor rupture of membranes (PPROM) is the rupture of fetal membranes with resultant loss of amniotic fluid between the gestational age of 24 weeks and 37 weeks before onset of uterine contractions. PPROM complicates up to 3% of pregnancies and is associated with 30–40% of preterm births.[1]

PPROM can result in significant neonatal morbidity and mortality, mainly from prematurity, sepsis, cord prolapse and pulmonary hypoplasia. Furthermore, there are risks associated with chorioamnionitis and placental abruption. Intrauterine infection and inflammation is an important determinant of spontaneous preterm birth following PPROM. The term 'clinical chorioamnionitis' refers to the presence of fever (>37.8°C) and at least two of the following criteria: maternal tachycardia (>100 beats per minute), maternal leukocytosis [white blood cell count (WBC) > 15,000 cells/mm^3], uterine tenderness,

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fetal tachycardia (>160 beats per minute), and foul-smelling amniotic fluid.[2,3]

Tissue inhibitors of Matrix Metalloproteinases bind to MMPs and inhibit MMP-associated proteolysis, thereby helping to maintain fetal membrane integrity.[4,5] A host of events like subclinical/overt infection, inflammation, mechanical stress and bleeding can disrupt this and initiate a cascade of biochemical changes that culminate in PROM.[6] Chorioamnionitis is definitively diagnosed by histological examination of the placenta. Histological chorioamnionitis (HCA) is often asymptomatic and clinical signs, such as fever, uterine tenderness, maternal or fetal tachycardia and malodorous amniotic fluid, lack both sensitivity and specificity.[7] Amniotic fluid culture has also been used to identify fetal infection but was seen to be negative for microorganism in 50% of cases of HCA.[8] The poor predictive value of clinical signs and amniotic fluid culture for identifying HCA has increased interest in biochemical inflammatory markers. These include Total leukocyte count (TLC) specially and C-reactive protein. The vital decision is whether to induce labor (or perform cesarean delivery) or to manage the pregnancy expectantly. These biochemical markers can help in making that decision. The median latency after PPROM is 7 days and tends to shorten as the gestational age at PPROM advances.[9,10] CRP is an acute phase reactant produced by the liver in response to pro-inflammatory cytokines like interleukin (IL-6). Plasma levels increase 12–24 hours after the onset of inflammation and remains elevated until after the stimulus resolves.[11] We also want to correlate the intrauterine infection and inflammation to neonatal sepsis. Neonatal sepsis is defined as a single isolate cultured from a sterile site with suggestive clinical features and a treatment course of antibiotics.[12]

Materials and Methods

This was a cross-sectional study conducted in Ghurki Trust Teaching Hospital and Central Park Tea-ching Hospital. The sample size was calculated using the following sample size formula[13] which came out to be 79.

$$n_o = Z_{1-\frac{\alpha}{2}}^{2} \frac{p(1-P)}{d^2}$$

Where n_o is the sample size. P is the prevalence rate. Level of significance is 5% and d is the margin of error. Using prevalence rate as 5.4%.[14]

Mothers with fetus having major congenital anomalies and those who refused to give consent were excluded. Gestational age was estimated by LMP. If a woman was unsure of LMP then a dating scan was used to ascertain gestational age.

Diagnosis of PPROM was by direct observation of amniotic fluid leaking from the cervical os or pooling while doing a sterile bivalve cuscos speculum examination. HVS was sent in a sterile tube. Patients' pulse, BP and temperature was recorded 4 hourly and the one recorded in data was closest to decision of delivery. Blood sample from the mother was taken for WBC and CRP.

At delivery cord blood was sent for WBC and CRP. After delivery a section of umbilical cord, membranes and at least one section including the chorionic plate was sent for histopathology in a plastic container containing formalin and saved at 4° C until transported to lab. Histopathological analysis was done by histopathology department (Chughtai institute of Pathology) at Central Park Medical College. It was diagnosed by acute granulocyte infiltration of choriodecidual space. All data was recorded in a predesigned proforma (attached) and analyzed by SPSS 22.0. Continuous data was summarized using non-parametric statistics: medians, and ranges (R). Categorical data was summarized using frequency distributions. Pearson's chi-square tests or Fisher's exact test was used to compare frequency distributions between HCA and non-HCA groups. Sensitivity and specificity, positive predictive value and negative predictive value of metarnal TLC and CRP were calculated.

Results

A total of 79 pregnant women participated in the study, out of which blood samples of two mothers were lost, 3 samples of cord blood were hemolysed and 4 placental specimens were autolysed. We did analysis of 70 patients. Mean age of pregnant participants of the study was 27.5± 4.05 years. Average gestational age at which PPROM occurred was 32 weeks and 6 days (range 25-36 weeks), median 34 weeks and mode 35 weeks. The mean duration of ROM was 46.4± 51.4 hours at the time of delivery either spontaneous or planned due to clinical chorioamnionitis. The median duration of ROM was 28 hours and mode was 48 hours. Mean maternal pulse was 91.9±9.98 per minute (range 82-120/min). Biochemical markers showed mean maternal TLC was 13224.29±4265 cubic ml (range 5000-26000)

and mean maternal CRP was 16.50±19.46 mg/L (range 0.12-62). Mean cord blood TLC and CRP were 13526.47 ±7976.09(range 3800-46900) cubic ml and 5.87± 11.11 (0.01-45.20) mg/L respectively. Labor started spontaneously in 25.7%, induced in 14.3% and 60% opted for cesarean on diagnosis of clinical chorioamnionitis. Out of the spontaneous and induced labors 28.6% had vaginal delivery and 71.4% ended in cesarean delivery. Antenatal steroid was given in 74.3% and in 25.7% it could not be given.

Out of the 70 patients who presented with PPROM

Table 1: *Comparison of parameters in cases with and without HCA.*

Parameters	Chorio-amnionitis	No chorio-amnionitis	p-value
Age(years)	28.9	27.39	0.61
Gest age(weeks)	31	33	0.315
Duration of ROM(hours)	52.43	44.93	0.736
Maternal pulse (per min)	98.5	90.25	0.47
Abdominal tenderness	nil	2	0.612
Discolouration of liquor	2	6	0.93
Maternal TLC (cubic milliiliter)	14784.29± 5958.44	12834.29± 3772.56	0.286
Maternal CRP(mg/L)	23.2±20.58	14.82±19.19	0.312
Spontaneous labor(n)	8	10	0.02
Induced labor(n)	4	6	
Vaginal delivery(n)	8	6	0.61
Cesarean(n)	6	44	
CB TLC	15182.86± 6114.96	13097.04± 8437.26	0.546
CB CRP	5.95±8.27	5.84±11.88	0.312
Neonatal sepsis(n)	4	8	0.37
Birth weight (kg)	1.81	2.09	

20% (14) showed histological chorioamnionitis in the placental specimen submitted after delivery while 80% (56) revealed no evidence of chorioamnionitis.

In cases with histological chorioamnionitis average duration of rupture of membranes was 52.4±32.4 hours, mean maternal pulse was 98.5±13.2 per min, abdominal tenderness was not positive, discolored liquor in 14.2%. No patient was febrile. Maternal TLC in this group was 14784.29±5958.44cubic ml and mean maternal CRP was 23.2±20.58mg/L. Spontaneous labor started in 57.1% and induced in 28.5%(ended up having emergency cesarean) Two women (14.2%) opted for cesarean delivery. Vaginal delivery took place in 57.1% and 42.8% had cesarean delivery. Average level of cord blood TLC was 15182.86±6114.96per cubic milliliter and average cord blood CRP was 5.95±8.27 mg/L. Neonatal sepsis was seen in 28.5%. Mean birth weight was 1.81±0.9 kg. According to our study the sensitivity and specificity of maternal TLC for detecting HCA was 21.4% and 87.5% respectively. Sensitivity of maternal CRP was 14.2% and specificity 57.1%.

Placental specimen with no histological chorioamnionitis revealed following clinical and biochemical parameters. Average duration of rupture of membranes was 44.93 ± 55.63 hours. In this group mean maternal pulse was 90.25±8.48 per min. Abdominal tenderness was positive in just 2 patients out of 56 and yellowish discoloration of amniotic fluid was seen in 6 patients. Maternal TLC and CRP mean values were 12834.29±3772.56 cubic ml and 14.82±19.19 mg/L. respectively. Labor started spontaneously in 17.8% and was induced in 10.7%. It was decided to deliver the baby by cesarean section in 78.5% and vaginal delivery took place in 21.4%. Average cord blood TLC in this group was 13097.04±8437.26 cubic milliliter and mean cord blood CRP 5.84±11.88 mg/L. Neonatal sepsis was seen in 14.2 % cases and mean birth weight was 2.09±0.71 kg.

Discussion

Preterm prelabor rupture of membranes complicates about 0.1 to 0.7% of pregnancies at the verge of viability.[14-16] Upto 14 % of pregnant females stop leaking amniotic fluid and about 25% reaccumulate amniotic fluid who present with PPROM at the verge of viable gestational age. For this reason, there is always a period of latency where obstetricians give this margin of doubt in management, where they weigh and balance the risk of infection with the benefit resealing of membranes can bring. During this wait and see period maternal and fetal surveillance is done to detect chorioamnionitis, give antenatal corticosteroids for fetal lung maturity and antibiotic cover is given for prevention of ascending infection.

In our study the mean age of pregnant females who participated was 27.5± 4.05 years and the mean gestational age at which they presented with PPROM was 32 weeks and 6 days (range 25-36 weeks). Median gestational age at which rupture of membranes occurred and mode in our study was 34 weeks and 35 respectively. Median gestational age at PPROM was 24 weeks in a study conducted by Lorethe E et.al in 2018.[17] The mean duration of ruptured membranes was 46.4±51.4 hours at the time of delivery in our study, median was 28 hours

and mode was 48 hours. It is quoted to be 35.5 ± 20.7 days in a study conducted by Lille University Hospital, France from 2009 to 2018.[18]

Clinical chorioamnionitis was 75% in our study as a result their labor was either induced or cesarean section was done. In 43% of HCA+ve cases clinical suspicion was correct. In HCA –ve cases clinical chorioamnionitis was suspected in 82.2%. In a similar study performed in Obstetrics Department of Rennes University Hospital (level III maternity unit) clinical suspicion of chorioamnionitis was 80% in histology proven chorioamnionitis and 46% in HCA –ve.[19] Quite contrary to what was revealed in our study. Maternal TLC in the group with HCA was 14784.29±5958.44 per cubic milliliter and in non-HCA group was 12834.29±3772.56 per cubic ml. No significant difference was found between them similar to the study conducted by Ivana Musilova in 2017 at Department of Obstetrics and Gynecology, University Hospital in Hradec Kralove, Czech Republic which showed that maternal white blood cell count can not identify the presence of microbial invasion of the amniotic cavity or intra-amniotic inflammation in women with PPROM.[21] Maternal CRP in HCA and non-HCA group was 23.2±20.58 and 14.82±19.19 mg/L respectively. According to our study the sensitivity and specificity of maternal TLC for detecting HCA was 21.4% and 87.5% respectively. Sensitivity of CRP was 14.2% and specificity 57.1%. Abha Suryavanshi conducted a research concluding sensitivity of CRP for diagnosing maternal chorioamnionitis was 48% (95% confidence interval [CI] −35.99–61.12), specificity was 81% (95% CI 71.55%–88.98%) at People's College of Medical Science and Research Centre, Bhopal.[22] PPV of maternal TLC 22.2% and NPV was 87.5%. PPV of maternal CRP was 25% and NPV was 87.5%.

In the HCA+ve group the values of cord blood TLC as well as CRP were similar to the non-histological chorioamnionitis group and not markedly raised. In contrast a study conducted at a tertiary perinatal center in Western Australia by Rebecca A and colleagues showed that both Cord blood TLC and CRP were raised in the HCA group.[20] PPV of cord blood CRP in detecting neonatal sepsis was 22.2% and NPV was 84.6%.

Conclusion

None of the specific clinical features or the the biochemical investigations are statistically significant in detecting histological chorioamnionitis in patients presenting with preterm prelabor rupture of membranes. No association of duration of rupture of membranes or gestational age with HCA. These lab markers only have a high negative predictive value. Newer markers like IL-6, MMP and TNF should be investigated in future researches to find its role in prediction of HCA.

Conflict of Interest *None*

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Authors Contribution

AS, RM: Conceptualization of Project
RM, NS: Data Collection
AS: Literature Search
SM, AS: Statistical Analysis
SR, AS: Drafting, Revision
AS: Writing of Manuscript

Outcomes After Close Reduction and Percutaneous Pinning of Gartland Type III & IV Supracondylar Distal Humerus Fracture in Children

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Abstract

Objective: To assess the outcome and complications after close reduction and fixation with k wires of Gartland type III & IV supracondylar fracture of Humerus in children.

Method: This prospective study was done using a non-probability purposive sampling technique between November 2009 to October 2020. 200 children, age between 01 -10 year Gartland III & IV supracondylar fracture of distal humerus presented within 48-hour of the injury were included, and children with neurovascular injury, refracture, skeletal dysplasia, open fractures, and trauma presenting after 2 days were excluded. Maximum three Close attempts were made to reduce the fracture and K-wires were used to fix the supracondylar fracture. Flynn criteria, ROM, Ulno-humeral angle, carrying angle, and Bouman angle were assessed at each follow-up visit. Bone union by hammer et al and complication were evaluated.

Results: There were 133 (66.5%) were boys, and 67 (33.5%) were girls. The mean age of the children was 5.2 ± 3.1years having right side dominance 122 (61%). Gartland type-III fracture was 115 (57.5%), and type IV was 85 (42.5%). Only 03 (1.5%) had transient ulnar nerve palsy while there was no vascular injury. Superficial infection at the pin site was observed in 10 (5%) children and one (0.5%) case of pin migration. Cubitus varus deformity was observed in 03 (1.5%). Although, the operative site has decreased ROM by Baumann angle, and carrying angle, results were excellent (61%) to good (39%) according to Flynn's Criteria.

Conclusion: Closed reduction and pin fixation in Gartland type III & IV supracondylar fractures in children is the preferred option with early pin removal and physiotherapy.

Keywords: Gartland type III & IV, Supracondylar Fracture, Humerus Fracture, Percutaneous Pinning.

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Introduction

Supracondylar distal humerus fractures represent the most common upper limb skeletal injuries in children. The current treatment of choice is closed reduction and percutaneous pin fixation.[1] Displaced supracondylar fractures of the humerus are common pediatric injuries treated by orthopedic surgeons that have a high rate of complications if not reduced and fixed in the optimal position, e.g., neurovascular injuries and residual deformities. Amongst various methods for treating these fractures, closed reduction and percutaneous Pinning have shown satisfactory results.[2] Supracondylar humerus fractures are first classified as either flexion or extension injuries. A flexion supracondylar humerus fracture is called when the distal fracture is either flexed or displaced anteriorly to the proximal shaft of the humerus. More common fractures are the extension-type supracondylar

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humerus fractures in which the distal segment is extended or displaced posteriorly to the proximal shaft of humerus, and these extension type fractures are further classified as follows.[3] Type I fractures are nondisplaced or minimally displaced, Type II fracture is a displaced fragment with an intact posterior cortex, Type III injury is a completely displaced fragment, and Type IV injury in which distal fragment is unstable in both flexion and extension due to the loss of the periosteal attachment with instability in flexion and extension. Previously, open reduction is preferred for type III & IV fractures. complications including neurovascular injury and cubitus varus are mostly associated with type III &IV.[4] After Treating displaced fracture, complications are compartment syndrome leading to Volkmann's ischemic contracture, nerve injury, arterial injury, myositis ossificans, and cubitus varus deformity. Cubitus varus deformity develops after an inadequate reduction of the internally rotated and medial displaced distal segment. Fracture is irreducible after multiple attempts, maybe because of entrapment of soft tissue inside the fracture, e.g., brachialis muscle, joint capsule, and neurovascular bundle. Intraoperative stability criteria depend upon assessing the following: anterior humeral line, Baumann's angle ulnohumeral angle, radiocapitate line, and rotatory movements under image intensifier while keeping an eye on avoiding posterior fat pad sign and fishtail sign.

A scant data is published regarding closed management of Gartland type IV supracondylar fractures. In this study, we will focus on the effectiveness of close reduction and pin fixation in displaced SCH fracture of type III & IV and complications associated with close reduction and pinning e.g pain, restricted ROM, pin site infections, nerve palsy, vascular compromise, and any rotational mal-alignment.[5]

Material and Method

This prospective study was done using a non-probability purposive sampling technique at the Orthopedic Surgery department, King Edward medical university, Mayo hospital, Lahore between November 2009 to October 2020. 200 children, age between 01 -10-year supracondylar Gartland III & IV fracture presented within 48-hour of the injury were included, and children with neurovascular injury, refracture, skeletal dysplasia, open fractures, and trauma presenting after 48 hours were excluded. Ethical approval was obtained from the university, institutional review board. Informed written consent was taken from the parents of the children. All children were treated using close reduction (preferably percutaneous fixation (CRIF) with cross-K-wires with a back-slab above elbow for three weeks. We documented fracture type, compartment syndrome, neurovascular injury, superficial & deep infection, pin migration, Cubitus varus deformity, malalignment, union, and functional outcome were noted. Postoperative children were assessed at immediate, three weeks, six weeks, three months, six months, nine months, and one year. The back slab was removed at three weeks, and physiotherapy was started. Complications including Compartment syndrome, nerve injury, superficial & deep infection, pin migration, Cubitus varus deformity, malalignment was assessed clinically. Bauman angle and Ulno-humeral angle were drawn on a postoperative radiograph at the final visit. Functional outcome and union were assessed using Flynn criteria and Hammer et al. criteria, respectively. K-wires were removed after six weeks. Patients who had postoperative nerve palsy sensory/motor were followed, and an NCS study was done at three months. Data was entered and analyzed using SPSS version 21.0. Quantitative variables like ages, carrying angle was presented as mean ± standard deviation. Qualitative variables like gender, compartment syndrome, nerve injury, pin migration, superficial and deep infection as frequencies and percentages. Chi-square test was applied for the gender and type of the fracture with the union, and a p-value less than <0.05 was taken significantly. All procedures were done in general anesthesia in the supine position. Initially, traction was applied, and then fracture is reduced under the fluoroscopic image. Close reduction internal fixation with 2-3 K-wires has been performed either cross based fixation. 1cm incision was given on the medial epicondyle of the humerus to save the ulnar nerve. A maximum of three reduction attempts were made to reduce the fracture closely. Anterior humeral line, the ulno-humeral angle, was used as a criterion for fracture reduction. Postoperatively, backslap was applied in 70-90 degrees depending upon swelling and vascular status. Postoperative radiographs are used to confirm fracture reduction.

Results

Out of the total 200 children, there were 133 (66.5%) were boys, and 67 (33.5%) were girls. The mean age of the child was 5.2 ± 3.1year. The fractured elbow was the right in 122 (61%) and left in 78 (39%). Gartland type-III fracture was 115 (57.5%), and type IV was 85

(42.5%). The was no case of postoperative compartment syndrome. Only 03(1.5%) had ulnar nerve injury while there was no vascular injury. Three children presented with paresthesia along with the little finger and decrease the power of the little finger. He was observed and closely monitored at 4 months; all of the patients exhibited marked improvements. Superficial infection was observed in 10 (5%) children. There one (0.5%) case of pin migration. Cubitus varus deformity was observed in 03 (1.5%) children of 9.1 degrees while there was no case of mal-rotation.

According to Flynn's criteria, all patients were in excellent and good scores except four non-compliant patients with poor follow-up and physiotherapy. They had an upper limb in flexed attitude due to decrease arc of motion (Table 2). The mean difference between the Baumann angle and the ulno-humeral angle was 8±2 degrees between the operated and healthy sides. The operative site had a decreased range of motion, and a decreased carrying angle was observed (Table 3). As compared to the normal site operated site has a decreased range of motion of 19.5 degrees (p-value 0.02).

Table 1: *Demographic data of supracondylar fracture type III &IV*

Variables	Frequency (200)	Percentage	P-Value
Age in years (Mean)	5.2 ± 3.1		0.04
Gender			0.05
Male	133	66.5	
Female	67	33.5	
Affected side			0.03
Right	122	61	
Left	78	39	
The duration between injury & surgery in days	0.5 ±1.3	-	0.03
Follow-up duration (Mean)	6months	-	0.04
Gartland type			
III	115	57.5	0.03
IV	85	42.5	

Table 2: *Flynn's Criteria for supracondylar fracture of pediatric patients*

Results	Rating	Cosmetic Factor (Loss of Carrying angle in degrees)	Functional Factor (Loss of Motion in degrees)
Satisfactory	Excellent	0-5 (61%)	0-5 (65%)
	Good	6-10 (39%)	6-10 (33%)
	Fair	11-15 (0%)	11-15 (0%)
Unsatisfactory	Poor	>15 (0%)	>15 (02%)

Table 3: *Radiographic criteria and ROM of operated as compared to normal*

Variables	Operated	Normal	P-Value
Boumann Angle	62± 4	70±6	0.04
Ulnohumeral angle	168±6	160±5	0.03
Carrying Angle	15.6± 5.1	10.8±3	0.03
ROM Arc	149±6.5	130± 8	0.02

Discussion

This study evaluated percutaneous Pinning's outcomes in a supracondylar fracture in terms of infection, deformity, and functional ROM. Closed reduction and internal fixation is the preferred choice of surgery in Gartland extension type III and IV. The old school of thought to openly reduce the displaced type IV fractures is on a decreasing trend. This study showed a few complications of pin site infection 5%, decreased range of motion 1.5%, and 1.5% nerve palsy.

Although Open reduction and internal fixation with Pinning is an acceptable treatment options in irreducible, gravely communicated, and old neglected supracondylar fracture of the humerus. The open fixation techniques have higher chances of complications, e.g., surgical site infection and ROM limitation as compared to closed procedures.[6,7,8] This study showed that we could manage all types of fractures initially closely with auspicious outcomes. The risk of the scar and delayed activity can be avoided with a meticulous approach. Apart from the minimally invasive approach, We believe that our results support the fact that first-line use of the CRIF e K-wires is cosmetically and functionally superior in terms of patient satisfaction and functional activity.

2% of the patients showed unsatisfactory results due to decreased range of motion. Non-compliance with physiotherapy and medical therapy is the main reason for poor scores. They were subjected to aggressive physiotherapy protocols, which markedly improved their functional status. In this study, Pins were removed at six weeks as compared to some studies advocating their removal at three weeks. Pin site infection was 5% in this study, while other studies showed a 3% pin site infection.[9] Yuji Tomori compared close reduction with the mini-open technique. It showed ROM 143.8±6.9 with close Pinning, while our study narrated a 149.5 Arc of range of motion. Karamitopoulos stated that migration of pin does not affect the management and treatment of the patient.[10]

Ultimately, all bony fractures heal. In our study, not a

single case of non-union was reported.

Vallila et al. reported complications around 1% of distal humerus fractures in Finland; the risk is too little as compared to the highest number of patients being treated. Ponce et al. explained that simply follow-up radiographs could not reduce complication rates. One to two cases of permanent iatrogenic nerve injuries happened to patients in Noora Tuomilehto study because of the same surgeon's intervention. The number of nerve related complications can be reduced by concentrating on the surgeries at a specialized center or surgeries performed by properly trained surgeons with aequate experience and skill to closely reduce and fix these fractures.[11]

Adequate reduction assessed by intraoperative normalization of radiological parameters along with stable fixation can reduce the incidence of cubitus varus deformity.

This study's limitations include small sample size, retrospective study, unicentred study, no control group was made. A much larger multicentered study is required to delineate close pinning outcomes in Gartland types III and IV. Longer follow-up period studies are required to evaluate the late deformity of the injured elbow.

Conclusion

We prefer Close reduction internal fixation with K-wires in Gartland types III and IV to reduce the complications associated with the open technique. Pin site infection and reduced range of motion are the known complications. Early removal of pins and timely physiotherapy can markedly reduce the adverse effects. In this study, all nerve palsies heal without consequences at 5months of follow-up visits.

Conflict of Interest *None*

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Authors Contribution

MA: Conceptualization of Project
MTJ: Data Collection
FM: Literature Search
AA, MT, OIC: Statistical Analysis
AA: Drafting, Revision
SAQ: Writing of Manuscript

Protective effect of Aqueous Garlic Extract on Monosodium Glutamate Induced Toxicity on Johnson's Scoring of Infertility in Adult Wistar Rats

Hafiza Sadia Ahmed,[1] Fatima Inam,[2] Asma Siddique,[3] Faeza Rauf,[4] Shagufta Nasreen,[5] Sibgha Fatima[6]

Abstract

Objective: To observe the effect of aqueous garlic extract (AGE) on the MSG-induced toxicity on the Johnson score of infertility in adult Wistar rats.

Method: This study was conducted at the University of Health Sciences, Lahore. A total of 24 adult male Wistar rats weighing 150-175 g and aged 6-8 weeks were collected and divided into 4 groups (6 rats each). Group A acted as a control, with 6 ml / kg of distilled water given orally by gavage and intraperitoneally for 14 days. Group B received 4 g / kg MSG dissolved in 6 ml of distilled water intraperitoneally for 14 days. Group C orally administered 200 mg / kg AGE dissolved in 0.4 ml of distilled water for 14 days by forced oral administration, and Group D first intraperitoneally administered 4 g / kg of MSG dissolved in 6 ml of distilled water. Subsequently, AGE 200 mg /kg dissolved in 0.4 ml of distilled water was given for 14 days by forced oral administration. All doses were administered once daily.

Results: At the end of study, one way ANOVA and Post hoc Tukey test were found to be significant (0.000) proving toxicity induced by MSG and protection rendered by AGE in B and D groups respectively.

Conclusion: Aqueous garlic extract improves and protects against the deleterious effects of MSG on Johnson's Scoring of infertility of adult Wistar rats.

Keywords: Monosodium glutamate (MSG), Johnson's Score, testes, Aqueous garlic extract (AGE), Wistar rats.

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Introduction

Monosodium glutamate (MSG), a salt of glutamic acid (an amino acid), is a well-known flavor enhancer and a typical ingredient in foods such as canned vegetables, soups, processed meats, and traditional flavorings. It is also found in many Chinese dishes. Glutamate is a nonessential amino acid synthesized by the human body and processed in almost all natural edible substances, especially protein-rich foods such as dairy products, meat and many vegetables.[1]

MSG disrupts the typical histology of testes. This fact becomes important as infertility is estimated to affect 15% of couples, a total of 48.5 million couples worldwide.[2] Continued use of MSG induces oxidative stress in liver and heart tissues as well as testes of experimental animals due to metabolic disturbances. Oxidative stress increases the formation of free radicals and reactive oxygen species (ROS), leading to oxidative damage to biomolecules that cannot be neutralized by antioxidant resistance frameworks.[3] High oxidative stress causes lipid and protein changes in cell membranes, leading to the initia-

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tion of dysfunctional metabolic pathways.[4] Allium sativum, commonly known as garlic, is an invigorating and exceptional scent that adds aroma, flavor and nutrition to daily dinner.[5] It contains a variety of potent sulfur compounds contributing to its medicinal efficacy. Ajoene is the best of the compounds explored. Allicin (diallylthiosulfinate) and S-modified cysteines are the basic thiosulfinates, approximately 60-80% of which is allicin.[6,7] Alliin is converted to its metabolites. Allicin, pyruvate and alkali by the activity of the garlic button enzyme allinase.[8] AGE can lower cholesterol levels by up to 75%. It has the effect of reducing calcium transfer in the coronary arteries. The addition of garlic plays a crucial role in supporting the structure and validity of endothelial cells along with their endothelial capacity. AGEs are thought to lower homocysteine levels, increase micro-circulation, and protect endothelial cells from oxidative stress. Garlic reduces the risk of prostate tumors and various malignancies.[9] Rationale of current study is to observe the protective effect of AGE on MSG induced toxicity leading to male infertility.

Materials & Method

The present research was conducted at the Department of Anatomy, University of Health Sciences Lahore after ethical approval was obtained. A total of 24 Wistar rats weighing 150-175 g, aged 6-8 weeks were purchased from the animal facility of the University of Health Sciences, Lahore. These 24 rats were split into 4 groups. A, B, C, D, each having 6 rats. Experimental animals were maintained at a controlled temperature of 23±2 °C, 55 ± 5% humidity and a 12 h light-dark cycle each. Rats received standard rat chow and water ad libitum and were acclimated two weeks before beginning of the experiment. The rat's body weight was measured at its first and final day (day 15) of the experiment. Group A served as a control and was administered with distilled water daily by gavage and intraperitoneally at a dose of 6 ml/kg for 14 days. Group B received 4g/kg MSG dissolved in 6 ml distilled water intraperitoneally daily for 14 days. Group C was gavaged daily with 200 mg/kg of AGE dissolved in 0.4 ml of distilled water for 14 days. Oral gavage daily for 14 days. MSG with a concentration of ninety nine percent was purchased from the local market. The 4 gm/kg of MSG was dissolved in 06ml of distilled water.Local garlic was obtained from a new crop to produce AGE. Garlic cloves were separated, peeled, washed with distilled water and left to dry at room temperature for 1 hour. 50 grams of these cloves were taken, cut into small pieces, and finally she was ground with a pestle and pestle containing 100 ml of distilled water and filtered using a cotton cloth. The final concentration of garlic in this filtrate was 500 mg/ml. AGE weighing 200 mg / kg body weight was prepared daily to treat the rats and orally administered by nasogastric tube feeding. The scoring was performed with the help of an X40 objective. In the event of uncertainty regarding the spermatozoa some tissues were checked at greater magnification also. Tubules in one field at the corner were chosen, their score recorded and the slide was shifted in figure of 'S' to take in the neighboring zone within the field while the scoring continued. Impaired tubules at the borders of the area were rejected. At least ten seminiferous tubules from every slide were examined and scored. Three slides from every animal were analyzed and an aggregate of 720 measurements were made. Following is the scale of scoring (Johnson et al., 1970):

10. Normal tubules with complete spermatogenesis and many spermatozoa present
9. Many spermatozoa (>5) present but disorganized seminiferous epithelium with sloughing or obliterated lumen
8. A few spermatozoa (less than 5 per tubule)
7. No spermatozoa in lumen but many (>5) spermatids
6. No spermatozoa but a few spermatids (less than 5 per tubule)
5. No spermatozoa or spermatids but many spermatocytes
4. A few spermatocytes (less than 5 per tubules), no spermatozoa or spermatids
3. Only spermatogonia and Sertoli cells present
2. Sertoli cells present, no spermatogenic cells

Table 1: *Effect of MSG (4g/kg body weight) given intraperitoneally for 14 days on the mean Johnson's score of rats. Values given are mean ± standard deviation of 6 animals. Statistics according to one way ANOVA for comparing mean Johnson score among all groups A, B, C & D (n=6).*

Parameter	Group A (n=6)	Group B (n=6)	Group C (n=6)	Group D (n=6)	*p – value
Mean Johnson's score	9.56±0.21	5.7±0.33	9.0±0.322	8.9±0.25	0.000

*p ⩽ 0.05 is considered as statistically significant.

1. No cell in the section of tubule

Results

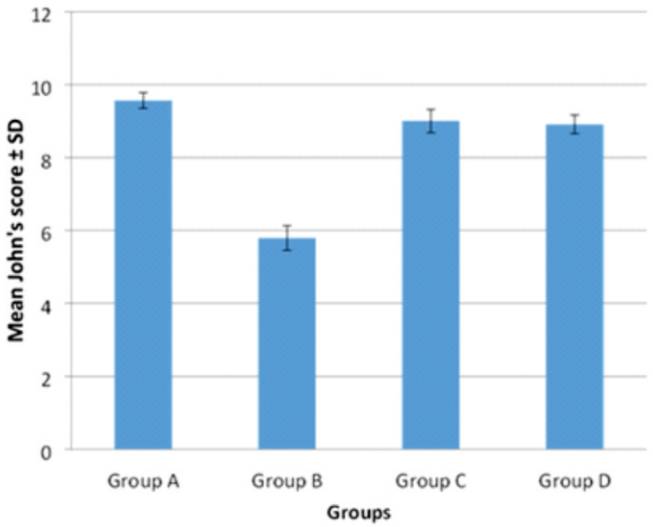

Fig-1: *Bar chart depicting the mean Johnson's score among groups (n=6).*

Table 2: *Effect of MSG (4g/kg body weight) given intraperitoneally for 14 days on the mean Johnson's score of rats. Each value is the mean of 6 animals. Statistics according to Post hoc Tukey for multiple comparison of mean Johnson's score among all groups A, B, C & D.*

Group I	Group J	Mean Difference (I-J)	Standard Error of Mean	*p-value
A	B	3.77	0.172	0.000
	C	0.565	0.164	0.013
	D	0.648	0.164	0.004
B	A	-3.77	0.172	0.000
	C	-3.2	0.172	0.000
	D	-3.12	0.172	0.000
C	A	-0.565	0.164	0.013
	B	3.20	0.172	0.000
	D	0.0833	0.164	0.956
D	A	-0.64	0.164	0.004
	B	3.12	0.172	0.000
	C	-.0833	.164	.956

Discussion

MSG consumption is associated with a variety of health hazards, including reproductive toxicity. It is worth looking for a phytochemical strategy with effective protection and a wide range of safety profiles. Previous studies have shown the presence of functional glutamate transporters and receptors in the testes of rats and mice.[11] Compared with control rats, rats treated with monosodium glutamate had a significantly reduced caudal epididymal sperm reserve.In the present study, Group B which was administered with MSG showed statistically significant results with low scoring in Johnson's score of infertility. Group C exhibited near normal results and Group D showed the protective effects of AGE against toxic effects of MSG. The deteriorating changes in germ and somatic cells of seminiferous tubules may have emerged from the interactivity of MSG with proteins and enzymes disrupting the antioxidant defense mechanism prompting collection of free radicals leading to inflammatory reaction and mitochondrial damage.[12]

Conclusion

Aqueous Garlic extract protected against the MSG induced low levels in Johnson's scoring of infertility in adult Wistar rats.

Funding Source *None*

Conflict of Interest *None*

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Authors Contribution

HSA, FR: Conceptualization of Project
SF, FR: Data Collection
SN, FR: Literature Search
FR, HSA: Statistical Analysis
AS, HSA: Drafting, Revision
FI, HSA: Writing of Manuscript

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