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EDITORIAL

Navigating The Horizon of Artificial Intelligence (AI) in Medical Education and Clinical Research: Unveiling Foreseeable Issues

Rehan Ahmed Khan[1], Madiha Sajjad[2]

In the last two decades, technological advances have significantly affected the way we conduct research. Not too far back, the process of conducting research involved physically visiting libraries, performing literature searches, and locating the appropriate references. Writing a research article was a tedious job using a word processor, with days and months dedicated to the organization of references. Things changed with the advent of reference managers and easily available information on different databases available on the internet. With this came the risk of plagiarism, which was well detected by applications such as Turnitin. However, in the last year or so, Artificial Intelligence (AI) has revolutionized the way we approach the process of writing a research article. Chatbots can write complete articles. Applications based on AI can generate references, rephrase content, and refine research article writing.

However, this facility has to be used with caution. There are multiple issues that can affect the quality of research and hence its implication on medical education and clinical management. The various concerns stemming from the AI-driven revolution in research article writing are data bias and impact on quality control, lack of transparency, ethical considerations, issues related to reproducibility and rigor, resource constraints, security concerns, publication bias and limitations in creativity and innovation.

The algorithms used in AI for natural language processing have limitations. They use datasets that may have limited information on a particular subject. Also widely used chatbots, like ChatGPT's dataset extends only till 2021, hence producing literature search that will be outdated by 2 years. Shortly after ChatGPT was launched, multiple research papers were published with the chatbot as the first or co-author. However, the World Association of Medical Editors made it explicit that chatbots are not eligible to be granted authorship rights. There are many ethical concerns in research related to ChatGPT. This includes but is not limited to consent, data breach, taking credit for AI's work and lack of human creativity. It is also crucial to recognize that AI-driven research often lacks rigor and quality checks. This is especially the case for qualitative research, where quality assurance is achieved through ensuring the quality parameters such as credibility, dependability, confirmability, transferability, and reflexivity.

Another issue to consider is the impact on the neutrality of articles as the algorithms could potentially derive conclusions from datasets that are biased in a particular direction. Deep neural networks are considered as 'black boxes' of AI because of their complex nature leading to concerns about transparency as to how AI driven algorithms arrive at a conclusion. This should be of concern to the researchers who should understand the way deep neural networks work to draw conclusions.

We consistently witness the mushrooming of AI-powered applications that can generate academic text. Subsequently, other AI applications have the capability to rephrase this text, and some applications can even locate references for this content. It is very difficult to ascertain the authenticity and transparency of these applications. These applications have the ability to generate a complete research paper, based on the data set available to them. Such research which is not reliable can cause havoc in the management of patients.

While writing a research paper, one of the main concerns is the security of the data submitted to these applications. Data leak is a big potential issue in using these applications, as they are vulnerable to data breaches.

At present, when conducting and publishing research, a rigorous and robust methodology is employed. This process cultivates various skills in researchers including the ability to generate research ideas, identifying research gaps, defining problems, and generating engaging hooks. It also

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involves understanding different research methodologies conducting data analysis and effectively reporting the results of the study. This stimulates higher cognitive functions that foster creativity and innovation. Relying solely on AI applications is bound to impact these abilities.

Addressing these challenges and crucial issues is a current necessity. All relevant stakeholders including researchers, policy makers, educational and research institutions and publishers must address these concerns by formulating policies that maintain a balance between the utilization of AI and the processes of conducting and publishing research. To ensure this , researchers, policy makers and publishers should be trained in the ethics of AI, data management, and model interpretation, so they can make informed decisions.

In summary, while AI holds immense potential to aid and facilitate research writing, it is important that we acknowledge these anticipated challenges, as AI revolutionizes the research process. This will help us prevent the potential issues which may impact the quality of research. By adressing these issues proactively, we can harness the full potential of AI in research while upholding the principles of scientific integrity and ethics. This is the key to truly unlocking the potential of AI that significantly advances human knowledge and understanding.

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CONFLICT OF INTEREST

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DATA SHARING STATMENT

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ORIGINAL ARTICLE

Expression of SOX10 in Triple Negative Breast Cancer

Siyab Ahmad[1], Nadeem Zafar[2], Muhammad Owais Qurni[3], Muhammad Atif Khalil[4], Shabir Ahmad Orakzai[5], Wajahat Ahmad Khan[6]

ABSTRACT

Objective: To determine the frequency of SOX10 expression in patients with triple-negative breast cancer.

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Pathology, Combined Military Hospital, Rawalpindi, 01 Dec 2021 to 30 Sep 2022.

Materials and Methods: This study was conducted on 185 patients diagnosed with triple-negative breast cancer. Patients with any size, stage and grade of breast cancer that were negative for the presence of estrogen and progesterone receptors, as well as HER2, were included. Those who were chemo-experienced, had received radiation to the breasts or had relapsed were excluded. Immunohistochemistry was performed using staining with a SOX10 antibody on patients' tissue samples for SOX10 expression, which was quantified. Data was analyzed using SPSS 26.0, and comparison was made between patients who were SOX10 positive versus those who were SOX10 negative with regards to disease characteristics.

Results: The mean age of our sample population was 51.65 ± 9.81 years. SOX10 was positive in 138 (74.6%) cases, with patchy positivity seen in 55 (29.7%) samples, while focal and diffuse involvement was seen in 67 (36.2%) and 16 (8.7%) cases respectively. Higher SOX10 positivity was seen with advancing age, (p=0.014), larger tumour size, (p<0.001), and higher tumour grade, (p=0.003). Diffuse and focal involvement were associated with higher grade tumours, (p<0.001), while degree of SOX10 expression did not appear to have a statistically significant association with disease stage, (p=0.618).

Conclusion: SOX10 is a useful marker that can be frequently detected in triple-negative breast cancer and is associated with more aggressive disease characteristics at presentation.

Key Words: *SOX10, Triple-Negative Breast Cancer, Tumour Grade, Tumour Stage.*

Introduction

In 2022, it is estimated that more than a quarter of a million females were diagnosed with invasive breast cancer, while approximately 50,000 were diagnosed with in-situ lesions.[1] Close to 50,000 women died of breast cancer during this year.[1] In Pakistan, a staggering 1 in every 9 women is diagnosed with breast cancer in her lifetime.[2] Triple-negative breast cancer is an aggressive form which lacks the presence of estrogen, progesterone and human epidermal growth factor 2 (HER2) receptors, which are common targets for therapy.[3] Consequently, these tumours are usually high-grade at the time of presentation and, while initially responsive to chemotherapy, have high rates of recurrence, metastasis and are associated with significant morbidity and mortality.[4] This variant is fairly common and accounts for 12% of all cases of breast cancer in the United States.[5] SRY-Box Transcription Factor 10 (SOX10) is one of a series of transcription factors that performs integral functions in the embryonal development of the peripheral nervous system, neural crest, melanocytes and also plays a role in the development of the testes.[6] In addition, SOX10 is also found in salivary glands as well as in the mammary glands, and has been found to be expressed in malignancies of the liver, ovaries, prostate and the gastrointestinal tract.[7] The compound is also expressed in different carcinomas originating from the breast.[8] Measuring SOX10 expression is not only of value in diagnosing breast

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cancers that are triple-negative, but may also play a role in the prognostication of the disease as well as serve as a potential target for immunotherapy, however, this aspect requires eludication.[9,10] This study was conducted with the aim of determining what percentage of patients with triple-negative breast cancer in Pakistan have SOX10 positivity. If substantial, then this factor could be employed in the diagnosis of the disease in future. Moreover, determining the different characteristics of the disease with regards to tumour grade and disease stage, among other factors, and their association with SOX10 positivity will help to determine the effect of this factor on the prognosis expected. Lastly, SOX10 expression may serve as a future target for therapy, and it would be useful to establish a baseline presence in the Pakistani population. This research protocol was conducted to determine the frequency of SOX10 expression in patients with triple-negative breast cancer in this population.

Materials and Methods

We conducted this descriptive cross-sectional study between 01st Dec 2021 and 30th Sep 2022 in the Armed Forces Institute of Pathology, Combined Military Hospital, Rawalpindi on 185 patients with triple-negative breast cancer, after obtaining informed consent. Consecutive, non-probability sampling was used to select the patients. The study permission was obtained from institutional review board. The WHO sample size calculator was used to calculate the sample size keeping a confidence level of (1-α) of 95%, an absolute precision (d) of 0.07 and an anticipated population proportion (P) of 0.619, which was the percentage of patients with triple-negative breast cancer with positive staining for SOX10, from Ali et al.[11]

All patients diagnosed with any stage and grade of breast cancer that was negative for the presence of estrogen and progesterone receptors, as well as HER2, were included in the study. Patients who have received prior chemotherapy, radiation or have a recurrent breast carcinoma, were excluded.

All patients' demographic data, as well as tumour characteristics, including type and stage, were documented at the time of sample receipt. Only samples collected via excision, resection or core biopsy were examined. The diagnosis of breast cancer, its tumour grade, and its triple-negative status were re-examined via light microscopy. Immunohistochemistry was performed on the tissue samples, with xylene-based de-waxing and alcohol rehydration. A SOX10 antibody was applied to the tissue samples to determine whether the antigen was being expressed and, if present, its presence as a percentage and as a pattern were documented as displayed in Table-I.

Table I : SOX10 Degree of Histological Involvement Interpretation

Expression	Interpretation
<1% cells in tumor cells	Negative
1 – 10% cells in tumor cells	Patchy positive
11 – 70% cells in tumor cells	Focal positive
>70% cells in tumor cells	Diffuse positive

Data was analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows version 26, IBM Corp; Armonk, USA). Mean and standard deviation was calculated for quantitative variables specifically patient age at diagnosis, primary tumour size in largest diameter and percentage of SOX10 present. Qualitative variables like tumour stage, tumour grade and pattern of SOX10 presence were recorded in terms of frequency and percentage. Patients were divided into two groups: one with positive SOX10 staining, and the other with those who were negative, and the various patient and disease characteristics were compared across these groups. Quantitative variables were compared using the independent samples *t*-test while the chi square test was used for qualitative variables and a *p*-value of ≤ 0.05 was considered significant.

Results

This study was conducted on samples from 185 patients diagnosed with triple-negative breast cancer. The mean age of the population was 51.65 ± 9.81 years. The average size of the primary lesion as measured in its largest diameter for the entire sample was 3.28 ± 1.17 cm. A total of 12 (6.5%) patients had tumour grade I lesions, while 127 (68.6%) and 46 (24.9%) had grade II and III lesions, respectively. Stage I disease was seen in 25 (13.5%) cases, Stage II in 72 (38.9%) patients, while Stage III and IV disease was seen in 61 (33.0%) and 27 (14.6%) cases, respectively. The mean percentage of SOX10 positive cells per sample were 26.32 ± 29.04% for the whole sample. Samples were negative for SOX10 in

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47 (25.4%) cases, patchy positivity was seen in 55 (29.7%) samples, while focal and diffuse involvement was seen in 67 (36.2%) and 16 (8.7%) cases, respectively. Higher SOX10 positivity was seen with advancing age, (p=0.014), larger tumour size, (p<0.001), and higher tumour grade, (p=0.003), while disease stage did not appear to be statistically significantly associated with SOX10 positivity, (p=0.206). Table-I shows the difference characteristics of each patients distributed according to SOX10 status.

Table II: Patient Characteristics According to SOX10 Status

Variable	SOX10 Positive (n=138)	SOX10 Negative (n=47)	*p*-value
Age at Diagnosis (years)	52.71 ± 9.05	48.64 ± 11.34	0.014
Tumour Maximum Diameter (cm)	3.62 ± 0.99	2.28 ± 1.04	<0.001
Tumour Grade			
Grade I	4 (2.9%)	8 (17.0%)	0.003
Grade II	98 (71.0%)	29 (61.7%)	
Grade III	36 (26.1%)	10 (21.3%)	
Disease Stage			
Stage I	16 (11.6%)	9 (19.1%)	0.206
Stage II	58 (42.0%)	14 (29.8%)	
Stage III	42 (30.4%)	19 (40.4%)	
Stage IV	22 (16.0%)	5 (10.7%)	

Table-II displays the distribution of patients according to the pattern of SOX10 involvement. Diffuse and focal involvement were associated with higher grade tumours, (p<0.001). There did not appear to be a statistically significant association of SOX10 positivity with disease stage, (p=0.618).

Table III : Patient Characteristics According to Pattern of SOX10

Variable	Negative (n=47)	Patchy (n=55)	Focal (n=67)	Diffuse (n=16)	*p*-value
Tumour Grade					
Grade I	8 (17.0%)	4 (7.2%)	-	-	<0.001
Grade II	29 (61.7%)	44 (80.0%)	48 (71.6%)	6 (37.5%)	
Grade III	10 (21.3%)	7 (12.8%)	19 (28.4%)	10 (62.5%)	
Disease Stage					
Stage I	9 (19.2%)	6 (10.9%)	7 (10.4%)	3 (18.8%)	0.618
Stage II	14 (29.8%)	24 (43.6%)	28 (41.8%)	6 (37.4%)	
Stage III	19 (40.4%)	17 (30.9%)	22 (32.8%)	3 (18.8%)	
Stage IV	5 (10.6%)	8 (14.6%)	10 (14.9%)	4 (25.0%)	

Discussion

Triple-negative breast cancer represents a diagnostic and therapeutic dilemma, in that, it lacks the usual protein markers used for diagnosis, which is a particularly difficult hurdle to overcome if the focus of primary disease is unknown.[12,13] In addition, such proteins are used for targeted therapy and their absence results in the limitation of therapeutic options.[14,15] While a number of different modalities are used in conjunction with one another to establish the presence of triple-negative breast cancer, definitive diagnoses are established only on histology, even in such cases.[12] SOX10 may represent a biomarker that can be used to both diagnose these cases and potentially serve as a target for drug therapy in such patients.[15-16]

SOX10 was positive in 138 (74.6%) cases of triple-negative breast cancer, in the current study. Ali et al noted that 61.9% cases of triple-negative breast cancer were positive for the expression of SOX10 in their study.[11] Yoon et al reported a much higher positivity of 85.7% for SOX10 in this form of breast cancer in their study,[17] while Qazi et al reported a figure that was similar to ours: 74.0%.[18] However, the reported frequency of SOX10 positivity was not uniformly high across all studies: Jamidi et al noted that only 31.3% of triple-negative breast cancers had SOX10 positivity in their study sample.[19] We believe this variability in results may attributable to ethnic differences between the populations studied.

Samples were negative for SOX10 in 25.4% cases in our study, patchy positivity was seen in 29.7% samples, while focal and diffuse involvement was seen in 36.2% and 8.7% cases, respectively. Ali et al noted similar frequencies for the a fore mentioned patterns in their study: 33.0% samples were SOX10 negative, 15.0% had patchy positivity, 37.0% of the samples were focal positivity while 20.0% showed diffuse positivity.[11] Thus, the majority of samples show patchy or focal positivity in literature.

The mean age of women suffering from triple-negative breast cancer was 51.65 ± 9.81 years in our study sample. Higher SOX10 positivity was seen with advancing age, (p=0.014). Ali et al reported a slightly lower mean age of 44.31 ± 12.31 years in their patients,[11] and reported that advancing age was not associated with a higher frequency of SOX10 positivity, (p=0.290). Conversely, Jamidi et al

reported that SOX10 was seen at a significantly higher frequency in younger patients as opposed to older ones, (p=0.001), which was at odds with our study.[19] While these may also be attributable to differences in populations originating from a variety of geographical locations, the literature on the subject is conflicted and a more detailed review of the subject would be advisable before reaching concrete conclusions.

The average maximum diameter of the primary breast cancer lesions for our entire sample was 3.28 ± 1.17 cm. SOX10 positivity was associated with larger tumour sizes, (p<0.001). Jamidi et al noted that there was no association between SOX10 positivity and larger tumour size at diagnosis, (p=0.231),[19] a finding that was echoed by Ali et al, (p=0.33).[11] Conversely, Kriegsmann et al noted that SOX10 positivity was associated with smaller size lesions at the time of diagnosis, (p=0.039).[20] We believe that there are a number of confounding factors which had led to this variability in results, chief among which is the institution of screening programs for the early detection of breast cancer resulting patients being diagnosed at times when the primary tumour size was still small, as opposed to our populations where screening programs do not exist and patients present late.

In this study, 6.5% of patients had tumour grade I lesions, while 68.6% and 24.9% had grade II and III lesions, respectively. Patients with SOX10 positivity had a higher tumour grade at presentation, (p=0.003). SOX10 expression was associated with higher grade tumours at diagnosis, (p<0.001), in Qazi et al,[18] a finding that was reported by Klaric et al where 93.2% of cases with grade III lesions were positive as opposed to only 70.1% with grade II or I lesions, (p<0.001).[21] Saunus et al studied a number of biomarkers and their association with different disease characteristics in patients with triple-negative breast cancer and echoed our findings, reporting that tumour grade was higher in SOX10 positive patients at the time of diagnosis.[22]

In our study, Stage I disease was seen in 13.5% of cases, Stage II in 38.9% patients, while Stage III and IV disease was seen in 33.0% and 14.6% cases, respectively. The stage of the disease at presentation did not appear to have a significant relationship with SOX10 positivity, (p=0.206). Ali et al, Jamidi et al and Klaric et al all reported that SOX10 expression did not appear to be associated with a more advanced disease stage at the time of diagnosis, (p=0.619, p=0.295 and p=0.257, respectively),[11,19,21] however, studies such as Liu et al have noted that SOX10 expression was associated with a higher frequency of lymph node involvement at presentation in their study.[23] While SOX10 has been reported to be definitively associated with higher stage malignancy at presentation in other neoplasms originating from other organs,[24,25] its effect in breast cancer needs further elucidation before concrete conclusions can be drawn.

Study Limitations

We conducted this study in a single center, on a population derived military personnel and their families, the results of which may not be generalizable to the population at-large. Additionally, the study was focused on triple-negative breast cancer exclusively, whether SOX10 occurs at the same or different frequencies in non-triple negative breast cancer in the Pakistani population requires further study. Lastly, this study only established association: further study is required to determine the diagnostic validity of the marker before it can be used routinely in the diagnosis of these forms of breast cancer.

Conclusion

SOX10 can serve as a useful marker to establish a diagnosis of breast cancer in patients whose disease lacks receptors for estrogen, progesterone, and human epidermal growth factor. Moreover, it may also have a role in serving as a marker for more aggressive disease. Future research should focus on determining the diagnostic validity of SOX10 in predicting the presence of breast cancer and the presence of aggressive disease, as well as the development of effective drugs to target the compound in the hopes of providing an effective treatment modality in such cases.

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ORIGINAL ARTICLE

Comparison of Topical Acetic Acid and Gentamicin in Achieving Dry Ear in Chronic Suppurative Otitis Media

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ABSTRACT

Objective: To compare efficacy of topical acetic acid with topical gentamycin ear drops in achieving dry ear in patients with Chronic Suppurative Otitis Media (CSOM).

Study Design: Randomized control trial.

Place and Duration of Study: ENT Department, Fauji Foundation Hospital, Rawalpindi, from July 2021 to June 2022.

Materials and Methods: A total of 80 patients were included in this study through nonprobability consecutive sampling. Patients fulfilling the inclusion and exclusion criteria were divided into two groups of 40 each, by lottery method. Informed consent was obtained from all the patients and approval of the study was taken from the Hospital Ethical Committee. The patients in Group A received topical 1.5% Acetic acid and the other 40 in Group B received topical 0.3% Gentamicin sulphate. Patients were advised to cover their ear canals with ear plugs or cotton balls covered by Vaseline to prevent entry of water in the ear. Effectiveness was assessed by observing resolution of ear discharge, in term of achieving a dry ear on day 14.

Results: Average (±SD) age of cases in Group-A was 32.7 (±17.3) years and in Group-B was 26.2 (±15.4) years. In Group-A, ear discharge (Otorrhoea) resolution was achieved in 36 (90%) cases and in Group-B in 32 (80%). The efficacy was found better in the Group-A receiving topical Acetic Acid, but statistically the efficacy of both groups was similar.

Conclusion: The results of this study suggest that Acetic acid was equally effective to Gentamicin sulphate in achieving ear discharge control (dry ear) in CSOM.

Key Words: *Suppurative Otitis Media, Tympanic Cavity, Topical Anti-Infective Agents, Instillation.*

Introduction

Chronic Suppurative Otitis Media (CSOM) is an on-going intermittent or persisting ear discharge over 3–6 weeks through a perforated tympanic membrane secondary to chronic inflammation of the middle ear and mastoid cavity leading to a certain degree of hearing loss.[1] CSOM is categorized into two types, tubotympanic and atticoantral depending on whether the disease process affects the pars tensa or pars flaccida of tympanic membrane. CSOM is associated with persistent or recurrent ear discharge and conductive hearing loss.[2] Sometimes the hearing loss is disproportionately greater due to necrosis of the ossicles, and there is a definite risk of sensorineural hearing loss and complications too. The most common aerobic bacterial isolates in CSOM are Pseudomonas aeruginosa and Staphylococcus aureus. Other common organisms include Escherichia coli, Proteus mirabilis, Klebsiella spp., Streptococcus pyogenes, Candida spp. and Aspergillus spp.[3] However, this may vary according to topographical and other factors. Treatment for CSOM consists of topical antibiotics (administered into the ear) with or without steroids, systemic antibiotics (given either orally or parenterally), topical antiseptics and regular aural toilet, all of which can be used on their own or in several combinations. Patients respond better to topical therapy than to systemic therapy. Successful topical therapy is based upon proper use of an antimicrobial ear drops and meticulous ear toilet.[4] Broad-spectrum antibiotics such as second-generation quinolones and aminoglycosides, which are often active against the most frequently cultured micro-organisms (Pseudomonas aeruginosa and Staphylococcus aureus), are therefore frequently used.[5] These include gentamycin, tobramycin,

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neomycin, ciprofloxacin alone or combined with dexamethasone. All the aminoglycosides have a potential for ototoxicity. Popular prescriptions like Neomycin and Polymyxin B have lost their reliability against Gram negative bacteria due to drug resistance.[6] Topical antiseptics may be as effective as topical antibiotics in resolving otorrhoea (ear discharge) as found in several trials.[7] These inhibit the growth of bacteria by lowering the pH of the environment and interfere with the growth of bacteria. These alone with regular aural toilet is the cornerstone of a successful medical therapy. It has been observed that combination of topical and systemic therapy has no benefit over topical therapy alone.[8] Many antiseptics such as boric acid,[9] citric acid,[10] acetic acid, povidone iodine, alcohol and hydrogen peroxide have been used with mixed results. But these may cause irritation of the skin, and mucosa and sometimes as in case of alcohol, may be vestibulotoxic.[11] Due to irrational use of antibiotic ear drops that has resulted in antibiotic resistance and a certain amount of ototoxicity too, it was considered to switch over to a relatively safe alternative. Hence the use of acetic acid ear drops was considered for this study, as acetic acid has been proved to be an effective antiseptic. Furthermore, acetic acid is a household item and has shown to give good results in treating CSOM without causing any side effects or any drug resistance. Since much work has not been done in Pakistan on this topic, we carried out a study in ENT Department Fauji Foundation Hospital Rawalpindi from July 2021 to June 2022 to compare efficacy of topical acetic acid with topical gentamycin ear drops in achieving dry ear in patients with CSOM and hence using it as an alternative.

Materials and Methods

This randomized control study was carried out on a total number of 80 patients. The sample size was determined by WHO calculator.[12] Sampling was done by Nonprobability consecutive sampling technique. The inclusion criteria were: Any gender within the age bracket of 10 -70 years having CSOM tubotympanic type active disease, with mucopurulent ear discharge of more than 4 weeks duration. The patients having CSOM tubotympanic type with dry ear, CSOM atticoantral type, otomycosis, otitis externa, CSOM with complications, hypersensitivity to acetic acid and aminoglycosides, or immunocompromised individuals, pregnant and lactating females were excluded from the study.

After approval from the Hospital Ethical Committee, written informed consent was taken from the patients included in the study. Patients fulfilling the inclusion and exclusion criteria were divided into two groups by lottery method. In Group-A, 40 patients received topical 1.5% Acetic acid and in Group-B, the other 40 received topical 0.3% Gentamicin sulphate. In both the groups, the patients were advised to instill two drops three times a day in the affected ear, and to hold these for 30 seconds by tilting their head to one side in a dependent position.

All the cases were followed up weekly for a total period of two weeks. Patients were advised to ensure prevention of water entry in ears while taking bath, either by blocking their ear canals with ear plugs or cotton balls covered by Vaseline. Effectiveness was assessed by observing otorrhoea resolution (dry ear) on day 14.

Data was analyzed through SPSS version 24. Descriptive statistics were calculated for qualitative and quantitative variables. Quantitative variables like age were measured as mean ±SD. Qualitative variables like gender were measured as frequency percentage. The Chi square test was applied for comparison of efficacy between the two groups. Stratification was done for age and gender to avoid effect modifier and post Stratification chi square test was done. All the results were presented in tables or charts.

Results

Gender distribution in both the groups is shown in Figure-1. The average (±SD) age of patients in Group-A was 32.7 (±17.3) years with an age range of 11 – 70 years, while in Group-B it was 26.2 (±15.4) years with an age range of 10 – 65 years. Age distribution in both the groups is shown in Table-I. It was statistically similar in both the groups (p-value=0.195).

The effectiveness of both groups was assessed by observing otorrhoea resolution (dry ear) on day 14. As shown in Table-II, the efficacy was better in Group-A (p-value=0.21), but statistically it was not significant.

Stratification was done according to gender and age. In both males and females, the efficacy (otorrhoea

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resolution) was statistically similar in Group-A & B (p-values=0.29 & 0.49 respectively) as shown in Table-III.

Similar results were found in all age groups, no significant difference was found between two groups in all age groups (p-values=0.49, 0.23 & 0.61 respectively) as shown in Table-IV.

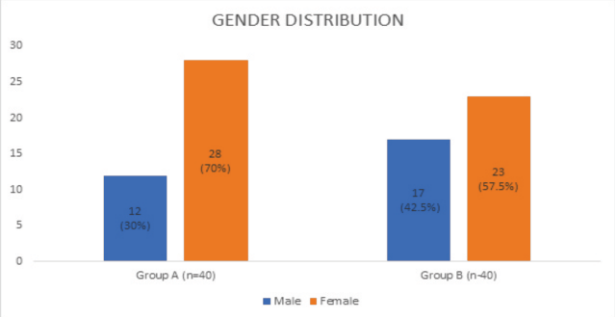

Figure 1: Gender Distribution (N = 80)

Table I: Age Distribution (N = 80)

Age (Years)	Group-A n = 40	Group-B n = 40	p-value
≤ 20	16 (40%)	24 (60%)	0.195
21 - 40	8 (20%)	6 (15%)	
> 40	16 (40%)	10 (25%)	

Table II: Otorrhoea Resolution (N = 80)

Dry Ear	Group-A n = 40	Group-B n = 40	p-value
Yes	36 (90%)	32 (80%)	0.21
No	4 (10%)	8 (20%)	

Table III: Otorrhoea Resolution According to Gender (N = 80)

Gender	Group	Dry Ear		p-values
		Yes	No	
Male	Group-A n = 12	11 (91.7%)	1 (8.3%)	0.29
	Group-B n = 17	13 (76.5%)	4 (23.5%)	
Female	Group-A n = 28	25 (89.3%)	3 (10.7%)	0.49
	Group-B n = 23	19 (82.6%)	4 (17.4%)	

Table-IV: Otorrhoea Resolution According to Age (N = 80)

Age (years)	Group	Dry Ear		p-values
		Yes	No	
≤ 20	Group-A n = 16	14 (87.5%)	2 (12.5%)	0.49
	Group-B n = 24	19 (79.2%)	5 (20.8%)	
21 - 40	Group-A n = 8	8 (100%)	0 (0%)	0.23
	Group-B n = 6	5 (83.3%)	1 (16.7%)	
> 40	Group-A n = 16	14 (87.5%)	2 (12.5%)	0.61
	Group-B n = 10	8 (80%)	2 (20%)	

Discussion

Chronic Suppurative Otitis Media (CSOM) worldwide, especially in developing countries, is a serious and avoidable healthcare concern. It not only causes a social embarrassment due to persistent or recurrent otorrhoea, but also causes a variable amount of hearing loss as well. It is one of the ENT diseases known for the increased incidence of resistance to antibiotics used in otitis media treatment. Among medical therapy, regular aural toilet, topical antiseptics, topical and/or systemic antibiotics form the whole spectrum of medical therapy. Topical quinolones are considered as the most effective medical therapy along with regular aural toilet in achieving dry ear.[13] Topical antiseptics may be as effective as topical antibiotics in resolving otorrhoea as found in several studies. For Acetic acid, various previous studies showed that it was widely used as an antimicrobial agent in different fields; for killing food-borne pathogenic bacteria, to inhibit Escherichia coli growth, and to treat ear infections.[14] The efficacy of acetic acid is based on their ability to reduce the pH in the ear and restrict the growth of microorganisms.[15]

In our study, the efficacy of Acetic acid group was found to be better, though statistically like genticyn sulphate group. Similar results were observed by Yogi et al (2020) in a study that showed otorrhoea resolution in 92% of the patients receiving acetic acid ear drops as compared to 88% in the group receiving topical antibiotic ear drops.[16] Akhtar et al (2019) in their study observed 2% acetic acid ear drops as significantly better than 0.3% ciprofloxacin ear drops in achieving dry ears.[17] Our observations were also supported by another study done by Vishwakarma et al (2015) where the efficacy of ototopical Acetic acid was found to be slightly better (92%) than its comparative Gentamicin sulfate group (88%).[18] In yet another study 1.5% topical acetic acid caused otorrhoea resolution in 88% of the patients as compared to 52% success in the patients who received topical antibiotic ear drops.[19]

The study done by Gupta et al (2015) showed that the resolution of otorrhoea by Acetic acid was 84% as compared to 58% otorrhoea resolution in the group receiving antibiotic ear drops.[20] In yet another study Joshi (2019) also observed acetic acid ear drops to be significantly better than gentamicin ear drops in

achieving dry ear.[21] In yet another study Goyal et al (2022) observed similar results with acetic acid ear drops (94%) as compared to 88% in topical antibiotic ear drops.[22]

However, there are studies that show better results with topical antibiotics as compared to topical antiseptics in terms of getting a dry ear in CSOM. In a study Macfadyen et al (2005) have shown better results with antibiotic ear drops as compared to topical antiseptics in achieving dry ears in cases of CSOM.[23]

As we see that most of these studies observe that topical acetic acid ear drops are better or equally effective in achieving otorrhoea resolution and hence can be used as an alternative to antibiotic ear drops. Since these are easily available, economical, and cost effective, it is recommended that topical acetic acid ear drops may be used as an alternate to antibiotic ear drops to achieve dry ear as first step towards management of tubotympanic type of CSOM. Besides these advantages, acetic acid ear drops do not cause any drug resistance and have no evidence of any ototoxicity. Although there is a study carried out on Guinea pigs that shows its ototoxicity at a higher concentration (4%).[24] But further studies need to be carried out to confirm its ototoxic potential. The limitation of our study was that it was performed on a small scale, so it is recommended that further studies may be carried out on larger scale to confirm better efficacy of topical acetic acid in comparison to other antimicrobial agents in achieving dry ears without causing any side effects or drug resistance.

Conclusion

The results of this study suggest that topical Acetic acid is equally effective to topical Gentamicin sulphate in achieving dry ear in CSOM (tubotympanic).

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Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Impact of Covid-19 on Mental Well-Being of Medical Students

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ABSTRACT

Objective: The purpose of this study was to identify the detrimental effects of Covid-19 on mental health of medical students' lives and their daily routine besides coping activities.

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: The research was carried out in a private medical college of Faisalabad. Its duration was from October 16,2021 to December 31, 2021.

Materials and Methods: The sample size was 377. Mental well-being status was assessed by using Kessler's psychological stress scale (K10). The influence of Covid-19 on everyday activities and management methods were also investigated. Consent was taken beforehand. SPSS 25 was used to analyse the data. The 95% confidence interval was chosen, with a margin of error of 5%.

Results: According to psychological stress score, more than half of the students (52.3%) were likely to have a severe condition, with 86 (22.8%) having a moderate issue, 59 (15.6%) having a light disorder, and only 35 (9.3%) being healthy. Most of the medical students i.e., 160 (42.4%) chose exercise and fitness as measures to improve their mental well-being. Significant relationship was found between age groups and concerns related to Covid-19, coping activities, and distress ($p = 0.00$); gender and concerns related to Covid-19 ($p = 0.00$), coping activities ($p = 0.00$) and distress ($p = 0.001$); class year and concerns related to Covid-19, coping activities, and distress ($p = 0.00$).

Conclusion: The COVID-19 pandemic has had a significant impact on the mental health of medical students, with a notable increase in reported psychological distress. It is recommended that actions are needed to alleviate student stress, which can have several harmful implications.

Key Words: *Covid-19, Medical Students, Mental, Well-Being.*

Introduction

Prior to the COVID-19 pandemic, there was already a high frequency of mental health problems among medical students, with a meta-analysis finding that depressed symptoms and thoughts of self-harm were reported by 27.2% and 11.1% of medical students from 167 countries, respectively.[1] The COVID-19 pandemic has had a significant impact on the mental well-being of individuals worldwide, including medical students. Medical students have been affected by the pandemic in various ways, including disruptions to their education, social isolation, and increased stress and anxiety related to their clinical duties and the risks associated with exposure to the virus. Also, the world economy suffered huge losses as a result of the outbreak, and the ambiguity and COVID-19-related fear was connected to an increase in mental illnesses and psychiatric problems.[2]

Medical students are particularly vulnerable to mental health problems, even under normal circumstances. However, the pandemic has exacerbated these issues. Medical students have reported increased levels of anxiety, depression, and burnout since the onset of the pandemic. Also, students who reported higher levels of anxiety and depression were more likely to report negative academic outcomes, including decreased motivation and difficulty concentrating. Due to the haste with which the communal shutdown and consequent changes occurred, many students struggled to acclimate to online learning and other curricula modifications.[3] The disruption of normal study was exacerbated by the cancellation of previously arranged face-to-face lectures, clinical training, and patient interaction. Other effects, such as the loss of

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peer interaction and social engagement, have the potential to negatively impact student well-being and generate additional psychological discomfort, as well as the interruption of everyday living.[4]

Because of the COVID-19 outbreak, several schools and institutions have delayed normal instructional activities. Health education is perceived as difficult and cancellable.[5] The removal of practical teaching sessions, which were generally substituted with video lectures, was one of the most significant changes.[6] Medical students' mental health suffers as a result of such settings. Students have significant distress, which has a negative impact on medical students' intellectual performance and cognition. Also, it was understood that students who reported higher levels of stress and anxiety were more likely to report negative coping strategies, such as increased alcohol consumption and decreased exercise.[7]

University students have been particularly hard hit by the COVID-19 pandemic. The COVID-19 pandemic forced medical colleges to examine and restructure their courses, as well as make substantial adjustments to hospital placements.[8] Given the data that medical students' mental health is already worse than the regular populace, such adjustments are certain to have a considerable impact on these students.[9] However, there is presently limited information on the steps taken by medical students to improve their psychological health and attitude during the COVID-19 era. There is an urgent need to comprehend the psychological impact among medical students to create practical mitigation techniques, as it has been suggested that the psychological effects of COVID-19 are likely to last long after the epidemic is finished.

It is important for medical schools to provide resources and support to help students manage their mental health during this challenging time. The current COVID-19 scenario in the world has had a negative impact on students' everyday lives, as well as on their psychological health. This may include access to mental health services, support groups, and resources for developing coping strategies and stress management techniques. Therefore, the study aimed to explore the specific impact of the ongoing pandemic on the mental health of undergraduate medical students and to examine the coping mechanisms they employed in response.

Materials and Methods

During the months of October to December 2021, a descriptive cross-sectional study was conducted among medical students. Using the Raosoft sample size calculator, a sample size of 377 students was calculated. Written consent was taken from all the participants. Ethical approval was taken from institutional ethical committee. All those who are medical undergraduate students and gave consent were included. A structured and validated questionnaire was used in which the research participants' sociodemographic parameters and a self-rated evaluation of the influence of Covid-19 on their mental wellness state using the Kessler psychological stress scale 10 (K10) were both asked.[10] K10 consists of ten questions with a five-point response scale; each question is scored from one to five, with one being "none of the time" and five being "all of the time." The ten questions' scores were then added together, with a minimum of 10 and a maximum of 50 score. High scores indicate high levels of psychological stress, whereas low scores suggest low levels of psychological stress. Other queries focused on the influence of COVID-19 on many aspects of life, issues concerning COVID-19, and the participants' actions and solutions for dealing with the issue. This data was analysed with SPSS version 25. To see the association between multiple variables, the Chi square test of significance was used. A p-value of less than 0.05 was considered significant. (Significance starts if the value in probability table is more than 3.84)

Results

Total number of medical students participated in the study were 377. Majority of the participants age group was above 21-year age group i.e., 210 (55.7%) while below 21 years comprised of 167 (44.3%) participants. There were 207 (54.9%) females in the study while 170 (45.1%) males were included. Most of the participants were from 4th year i.e., 94 (24.9%) and 3rd year i.e., 80 (21.2%) while there were 70 (18.6%) 1st year students, 68 (18%) 2nd year and 65 (17.2%) students were from final year. Majority of the students were from urban areas i.e., 295 (78.2%) while only 82 (21.8%) were from rural areas. Most of the students were day scholars i.e., 249 (66%) while hostelite students 128 (34%). The information was coded and treated confidentially. The most

detrimental effect of Covid-19 on medical students were on their studies as 237 students (62.9%) said that Covid-19 had negative impact on their studies. More than 50% of students (52%) said it had negatively affected their physical fitness and exercise; social relationships (50.7%); stress level (49.9%); sleep quality (49%), diet and eating habits (48.5%) and financial status (48.3%) and friendships (39.5%). The only positive impact which Covid-19 had on most of the medical students were on their family relationships (35%) as shown in fig. I.

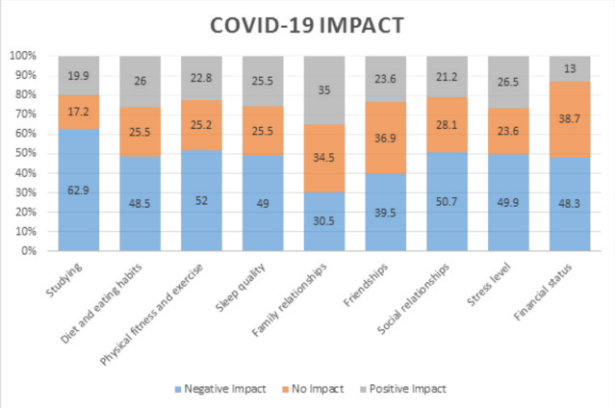

Figure 1: Covid-19's Influence on Medical Students' Life in Several Domains

When asked about concerns of negative impact of Covid-19, mostly i.e., 116 (30.8%) of participants were having concerns about being infected by Covid-19 while next most common concern was about problem in acquiring clinical skills i.e., in 84 (22.3%) participants while concerns about family members being infected with Covid-19 included 54 (14.3%) participants as shown in table I.

Table I: Concerns about Negative Impact of Covid-19

	Issues of concern	Frequency	Percent
1.	I'm anxious about the risk of one of my family members contracting Covid-19	54	14.3
2.	I'm apprehensive about being alone for an extended period of time	17	4.5
3.	I'm concerned about not being able to complete medical school	8	2.1
4.	I'm worried about not being able to travel overseas for examinations or optional courses	30	8.0
5.	I'm worried about getting illwith Covid-19	116	30.8
6.	I'm worried about dropping out of medical college	12	3.2
7.	I'm worried about not being able to learn additional clinical expertise and not being able to attend laboratories	84	22.3
8.	I'm concerned that after graduation, I won't be able to retrieve a good residency training position	26	6.9
9.	I'm concerned about not being able to participate in online classes and seminars using latest technology	30	8.0
	Total	377	100.0

When asked from medical students about activities and measures to enhance mental health, most of the medical students i.e. 160 (42.4%) chose exercise and fitness, followed by practicing hobbies like playing and listening to music, reading, watching movies, cooking and baking being done by 114 (30.2%) participants; while other measures were less commonly used i.e. meditation and praying (58, 15.4%); learning new language (20, 5.3%); Seeing a psychotherapy specialist (14, 3.7%); video chats and social media apps (11, 2.9%).

Table II: Responses of Participants to the (K10) Scale Questions

	None of the time		A little of the time		Some of the time		Most of the time		All of the time	
In the past 4 weeks,	N	%	N	%	N	%	N	%	N	%
1. How often did you get exhausted for no apparent reason?	8	2.1	54	14.3	110	29.2	152	40.3	53	14.1
2. How often did you feel nervous?	49	13.0	91	24.1	109	28.9	81	21.5	47	12.5
3. How frequently did you feel so anxious that nothing could make you feel better?	73	19.4	84	22.3	126	33.4	59	15.6	35	9.3
4. How often did you feel hopeless?	64	17.0	104	27.6	108	28.6	59	15.6	42	11.1
5. How often did you feel impatient or irritable?	33	8.8	87	23.1	137	36.3	82	21.8	38	10.1
6. How frequently did you get so agitated that you couldn't sit still?	84	22.3	93	24.7	119	31.6	52	13.8	29	7.7
7. How often did you feel depressed?	34	9.0	107	28.4	116	30.8	78	20.7	42	11.1
8. How often did you feel that everything was an effort?	31	8.2	91	24.1	126	33.4	87	23.1	42	11.1
9. How frequently did you feel so sad that nothing could make you feel better?	68	18.0	83	22.0	116	30.8	76	20.2	34	9.0
10. How often did you feel worthless?	75	19.9	81	21.5	123	32.6	68	18.0	30	8.0

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Medical students' responses to the K10 scale questions were shown in table II. Majority i.e., 9 out of the 10 answers of the questions chose option "some of the time" while the only question whose answer was "most of the time" was about how often did you get exhausted for no apparent reason?

The pupils' average psychological distress score was 29.11 ± 7.25. The scores categorized into likely to be well, or having a mild, moderate or severe disorder as shown in table III. According to psychological stress score, more than half of the students (52.3%) were likely to have a severe condition, with 86 (22.8%) having a moderate issue, 59 (15.6%) having a light disorder, and only 35 (9.3%) being healthy.

Table III. Levels of Distribution of Participants' Mental Disorders

		Mean	SD	N	%
Psychological distress score		29.11	7.25		
Likelihood of having a mental disorder	Likely to be well			35	9.3
	Likely to have a mild disorder			59	15.6
	Likely to have a moderate disorder			86	22.8
	Likely to have a severe disorder			197	52.3

Significant relationship was found between age groups and concerns related to Covid-19, coping activities, and distress (p = 0.00); gender and concerns related to Covid-19 (p = 0.00), coping activities (p = 0.00) and distress (p = 0.001); class year and concerns related to Covid-19, coping activities and distress (p = 0.00).

Discussion

The impact of the pandemic on students is significant, with long-term implications for medical students' future. This effect might be related to the direct psychological influence of the epidemic. Furthermore, new teaching techniques, such as online classrooms, may be difficult for some students to acclimate to; they may begin to feel behind their peers, which can contribute to their stressful situations. As a result of the pandemic's considerable mental health impairment, which has impacted even the general people around the world, health care providers are under increased strain. While the debilitating mental illnesses may have developed because of lifestyle changes and prohibitive decisions made by higher authorities, the disease's implications on medical students are found to be greater because they are more susceptible and at greater levels of exposure as compared to general public.

In our study, the most common negative impact which students felt were on their studies experienced by more than 60% of students. A research done by Meganne N Ferrel et al also stated that, Covid-19 has impacted every student in its own way and that the negative effect because of disruption of normal study schedules and structure will be felt for long time.[11] A study done by Servin-Rojas et al showed that the majority of students (82%) would consider redoing their last year of clinical training since four out of five thought their education was inferior to that of earlier generations.[12] A study done by Sumair Naseem Qureshi et al showed that, majority of students strongly agreed that they had no difficulty and were extremely comfortable using internet and computer during covid-19 pandemic for their studies. This is in contrast to results of our study.[13]

Similarly, a research done by Zaza Lyons et al showed that studies, social activities and stress were main negative effects experienced by participants.[14] A study done by Kazuki Tokumasu et al showed that A lower degree of perceived stress was linked to in-person interactions rather than online interactions.[15] These results are similar to our study where studies, physical fitness, social relationships and stress were among the top of categories negatively affected by Covid-19. A study done by Sophie Rainbow et al showed that the overload, a high casualty count, and the dread of having the infection during the outbreak have all contributed to an increase in psychological distress which is similar to our study where almost half of participants have stress because of Covid-19.[16] A study done by Naseem Ahmed et al showed that most of the participants were worried about getting the Covid-19 infection because of its high fatality rate and lack of facilities and also because they categorize coronavirus as the deadliest species.[17] This is similar to our results where most of the participants concern

was being infected by Covid-19. Another major concern of participants of our study was problem in acquiring clinical skills. As stated by Suzanne Rose et al that students were likely to progress their schooling and assist to the effort in other crisis situations, such as natural catastrophes, blackouts, fires, and the September 11 attacks but with this highly communicable pandemic, however, students may unintentionally spread the virus or get the disease, therefore, there were restrictions for the betterment of their own.[18] A study done by Nahal Salimi et al showed that students in higher education now confront more mental health difficulties as a result of the COVID-19 epidemic. College students now have to adjust to a virtual learning environment, make behavioral changes like social withdrawal, and deal with socioeconomic uncertainties. In particular, the 2019-2020 novel coronavirus has exacerbated the mental health challenges faced by college students.[19]

To improve mental well-being, some activities and measures are required as reported by our participants that most of them choose physical activities and exercise for this purpose. It is also reported by Conor Coyle et al that, most common measure taken by participants to improve mental well-being was physical activity.[20] Another study by Khaled Seetan et al found that baking, cooking, and leisure practice were by far the most preferred ways for people to enhance their mental health.[10] Another study conducted by Jasminka Talapko et al depicted contrasting results to our study which showed that because of Covid-19 and lockdowns, physical activity decreased in students which was also a contributing factor in their psychological distress.[21]

Another study conducted by Ružica Dragun et al showed that there was no change in physical activity before and after Covid-19 and it remained stable.[22] A study conducted by Hamza Mohammad Abdulghani et al showed that "indulging in religious activities" was the most common strategy adopted by students to improve their mental well-being.[23]

Research done by Azeema Noor et al showed that 1/3rd of participants had effects on psychological health due to Covid 19. These results vary from our study where more than 90% had effect on their psychological health.[24] A study done by Afia Matloob et al showed that perceived stress was severe in 25% among medical students. This is in contrast to our study where it is more than double.[25] A study done by Goolam Hussein Rassool et al showed that the majority of doctors reported a moderate level of stress (22%), while the majority of rescue workers reported extremely severe stress (10%). These results are in contrast to our study where (52%) of participants showed severe stress.[26] A study done by Asif Azeem et al showed that severe stress perceived by around 1/4th of participants which is very less as compared to our study.[27] A study done by Ala'a B. Al-Tammemi showed that most of the participants were likely to have a severe disorder and the mean of total K10 distress score was 34.2 $\pm$ 9.4.[28] This is similar to our study where most of the participants were likely to have severe disorder but the total K10 distress score mean was less, i.e. 29.11 as compared to 34.2. A study done by F. Rolland et al showed that according to the psychological distress scale, 21% of medical students experienced a high level of discomfort, while 39% of pupils had moderate distress.[29]

The research's limitations were the fact that it was a single-centre study, that sociodemographic factors varied, and that some class students were over-represented. Due to the study's non-probability sample design, it was unable to assess if the results were generally applicable to medical students. Additionally, the questionnaire was self-reported and online, which might cause recall and response bias. In addition to the variables we considered, there may be other factors that were related to the worsening of the prevalence of mental illness among medical college students.

Conclusion

The COVID-19 pandemic has had a significant impact on the mental health of medical students, with a notable increase in reported psychological distress. It is recommended that actions are needed to alleviate student stress, which can have a few harmful implications.

Future Recommendations

Future research on the effects of COVID-19 on mental well-being could focus on long-term impacts, vulnerable populations, effective coping strategies, and interventions to mitigate psychological distress. Exploring the relationship between mental health and pandemic-related factors like isolation,

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economic stress, and misinformation could provide valuable insights. Additionally, investigating the effectiveness of telehealth services, online support groups, and digital mental health tools in addressing mental health challenges during and after the pandemic could be beneficial.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Determination of Variation in Neonatal Serum 17 Hydroxyprogesterone Levels in Relation with Gestational Age & Low Birth Weight

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ABSTRACT

Objective: To determine the variation in neonatal Serum 17 – hydroxyprogesterone levels in newborns in accordance with the birth weight and gestational age.

Study Design: It was an analytical cross-sectional study.

Place and Duration of Study: The study was carried out at Armed Forces Institute of Pathology Rawalpindi. The duration of study was 6 months i.e., 17th Nov, 2021 – 17th May, 2022 after the approval from Institutional Review Board (FC-CHP21-12/Read-IRB/22/845).

Materials and Methods: A sum of 210 individuals were included by convenient non-probability sampling technique and divided into 3 groups. Group I included 70 neonates which were delivered at full term (38 – 40 weeks of gestation) with birth weight of 2500 – 4000 g as healthy controls. Group II included 70 neonates delivered at 32 - 37 weeks of gestation with birth weight of 1500 – 2500 g. Group III included 70 neonates delivered at 28 – 32 weeks of gestation with less than 1500 g weight at the time of birth.

Results: The gender-wise distribution of patients, was with males accounting for 65% and females for 35%. The mean value of Serum 17 hydroxyprogesterone (17 – OHP) exhibited a significant increase in Group III (118+8.05 nmol/l), followed by Group II (58+15.66 nmol/l), while Group I had normal levels (21+8.08 U/l) as shown in Figure II. After conducting a one-way ANOVA, post-hoc Tukey analysis was performed to compare three study groups. The Tukey HSD q statistics revealed significant differences between Group I and Group II (72.86), Group I and Group III (180.8), and Group II and Group III (107.95), all with a p-value of < 0.01. Significance in terms of statistics was determined by considering a Tukey HSD p-value below 0.05. Data was analyzed on SPSS version 23.

Conclusion: Neonatal Serum 17 – hydroxyprogesterone levels vary in accordance with the birth weight and gestational age. False-positive newborn-screening rates are disproportionately increased in prematurity and low birth weight. The optimal cut of levels adjusted to birth weight and gestational age of Serum 17 – hydroxyprogesterone should be established for screening of patients of congenital adrenal hyperplasia.

Key Words: *Birth Weight (BW), Congenital Adrenal Hyperplasia (CAH), 17 hydroxyprogesterone (17-OHP), Gestational Age (GA).*

Introduction

Congenital Adrenal Hyperplasia (CAH) is a very complex disease. In this disease there is impaired biosynthesis of cortisol and aldosterone resulting in increased production of 17-hydroxyprogesterone (17-OHP). CAH can be broadly divided into two major forms classical CAH and non-classical CAH. Classical CAH is a more severe form of disease and usually presented in neonates with markedly increased levels of (17-OHP) and ambiguous genitalia. While non-classical CAH is mostly presented later in life with moderate rise of (17-OHP). Screening of CAH is very complex due to variability in nature of serum (17-OHP) after birth. Adjusted Serum 17-hydroxyprogesterone levels according to gestational age and birth weight are used for screening of CAH and can be fatal if undiagnosed. (17-OHP) are erroneously elevated in prematurity and low birth weight.[1] Several countries are conducting the screening process of the neonates which have greater concentration of 17-hydroxyprogesterone for deficiency of classic (severe) 21-hydroxylase enzyme (the most routine kind CAH); However, co-

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syntropin stimulation testing in order to affirm the establishment or diagnosis non-classic (mild) subtypes.[1,6] The projected global incidence of classic CAH is around 1:14,000.[6] The scale of clinical presentations varies from forms with neonatal symptoms, i.e. Simple Virilizing (SV) and Salt Wasting (SW) forms, to non-classical forms which may not become obvious until adulthood. [3,14]

However, CAH screening is plagued by significant issues. Sensitivity of the diagnosis for Simple Virilizing SV-CAH is not optimal when screening is limited to one sample taken immediately after birth due to cost restraints. However, getting a 2nd sample can resolve this problem, it might increase the detection of non-classical CAH too, that isn't the optimal aim of CAH screening.[4] Rest of the problems come from the low specificity of the methods used for the screening of immunologically based 17-hydroxyprogesterone (17-OHP). Cross-reactivity, particularly with steroid sulphates, and illness-related stress causes an increase in the recall rate, more commonly in cases of infants that are born prematurely. The chances of little increased newborn 17-OHP levels because of heterozygosity for CYP21 mutations could potentially intensify this problem in newborns [5-7]. The main objective of the study was to determine the variation in neonatal Serum 17 – hydroxyprogesterone levels in newborns in accordance with the birth weight and gestational age. Increased false positive results of Serum 17-hydroxyprogesterone are associated with prematurity and low birth weight. No local study has been found after extensive literature review hence there is utmost need to establish adjusted gestational age and birthweight cut - off levels.

Materials and Methods

An analytical, cross-sectional research was carried out at Armed Forces Institute of Pathology Rawalpindi. The duration of the study was 6 months. An overall 210 neonates were included by using non-probability convenient sampling technique and divided into three groups on basis of birth weight and gestational age. The study started after the approval of Ethical Review Committee i.e., 17 Nov 2021 – 17 May 2022 (FC-CHP21-12/Read-IRB/22/845). Group I included 70 neonates delivered at full term 38 - 40 weeks with normal birth weight 2500 – 4000 g. Group II included 70 neonates delivered at 32 – 37 weeks of gestation period with less weight at the time of birth ranging from 1500 to 2500 grams. Group III included 70 neonates delivered at 28 – 32 weeks of gestation with very low birth weight that's less than 1500 g. The terminologies like little before term, long before term, lower weight at the time of birth and seriously less birth weight is as per classification of World Health Association (WHO).[25]

We have excluded neonates delivered with maternal steroidal history and other endocrine disorders. As they could interfere with our results misleading the diagnosis.

All eligible participants were informed of the objectives of this study. For participation in research groups and venipuncture, all parents of study participants were provided with written consent. The voluntary nature of participation in this study was highlighted. During a standard interview, sociodemographic variables and the background characteristics of CAH were also emphasized. In addition, each participant received a standard, comprehensive medical examination, which included collecting blood. Each participant's venous blood was taken in quantity of 5 ml while making use of a disposable vacutainer equipment (Plain tube). Within half an hour, serum or plasma was separated and then analyzed accordingly. Serum 17 – OHP was analyzed on Snibe Maglumi immunoassay analyzer using chemiluminescence technique.

Data was parametric therefore One-way ANOVA and post-hoc Tukey analysis was used to compare the intergroup mean. Variance and Tukey HSD q statistics were also calculated among groups. p value of < 0.01 was believed to be statistically substantial.

Results

The gender-wise distribution of patients as depicted in Figure 1, was with males accounting for 65% and females for 35%. The mean value of Serum 17 hydroxyprogesterone (17 – OHP) exhibited a significant increase in Group III (118+8.05 nmol/l), followed by Group II (58+15.66 nmol/l), while Group I displayed normal levels (21+8.08 U/l) as shown in Figure 2. After conducting a One-way ANOVA, post-hoc Tukey analysis was performed to compare the different groups. The Tukey HSD q statistics revealed significant differences between Group I and Group II (72.86), Group I and Group III (180.8), and Group II and Group III (107.95), all with a p-value of < 0.01.

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Significance in terms of statistics was determined by considering a Tukey HSD p-value below 0.05. Data was analyzed on SPSS version 23.

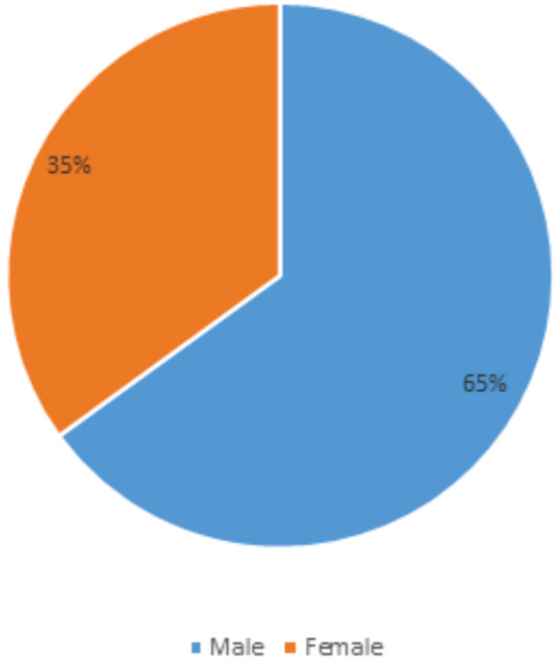

Figure 1: Gender Wise Distribution of Patients

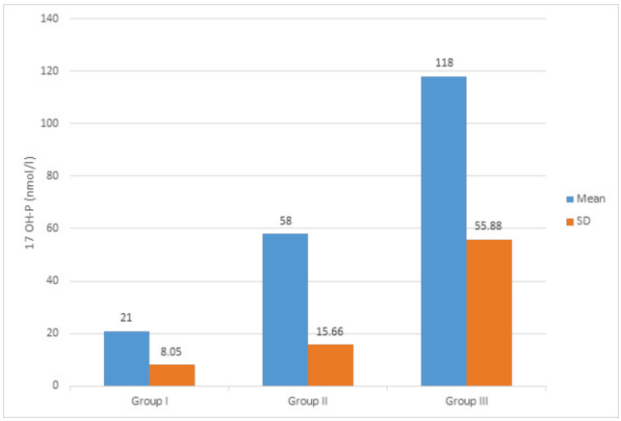

Figure 2: Comparison of Mean & SD of 17-OHP among Groups (N = 210)

Table : I Results of Post hoc Analysis among Groups (N = 210)

Groups	Comparison	Tukey HSD q Statistics	Tukey HSD p-Value
Group I	Group II	72.86	< 0.001*
Group I	Group III	180.8	< 0.001 *
Group II	Group III	107.95	< 0.001 *

**p* value < 0.05 considered as Statistically Significant

Discussion

CAH is a collection of multiple genetic disorders of autosomal recessive pattern resulted by transformations in specific genes encoding for enzymes in cortisol biosynthesis pathways: 21-hydroxylase (21OH), 11-hydroxylase (11OH), 17-hydroxylase (17OH; also named as 17,20-lyase), 3-hydroxysteroid dehydrogenase type 2 (3HSD2), steroidogenic acute regulatory protein (StAR), P450 (POR). CAH manifests with a spectrum of biochemical and clinical phenotypes, with or without changes in glucocorticoid, production of sex steroid and mineralocorticoid. Due to these disorder, there are some direct and indirect effects on steroidogenic pathways and the rarity of these conditions, congenital adrenal hyperplasia remains among the most difficult endocrine disorders to diagnose, treat, and manage. Continued advances in the field of genetics, metabolomics, and treatment strategies result in improvement of patient outcomes by enhancing our understanding of these complex diseases.[9,15,18]

High financial and psychological expenses are related to false-positive CAH screening results. The laboratory charges associated with a false result of positive screening, including copies of internal repeats and following samples, and the separate sample processing, are approximately ten times the price of a standard sample of screening. When we include the charges associated with optional clinical follow-ups, the total becomes considerably high. Therefore, schemes that are meant for the considerable physiological variation in the values of newborn 17-OHP have been implemented, such as the adjustment of the cut-off values of 17-OHP in relation to Gestational Age (GA) and Birth Weight (BW).[10]

In this study, it is evident that there are significant differences in serum 17-OHP levels between infants who are premature and those with low birth weight. This variation results in suspiciously elevated levels of serum 17-OHP, which ultimately leads to false positive results for coronary artery disease. The mean serum 17-OHP concentration ranges from 21 nmol/l in the control group to 118 nmol/l in Group III, which consists of neonates born between 28 and 32 weeks of gestation and weighing less than 1500 g. The following studies support our findings as well.

Danny Joma et al screened newborns for CAH, both with and without a reported Gestational Age. Screening based on GA was performed on infants with a reported Gestational Age; elsewise, screening

based on Birth Weight was performed. Using this method, 2,588 infants (0.37%) positively tested, including newborns with congenital heart disease. The re-screening of the population was done, but infants having unreported Gestational Age were screened again using GA-adjusted cutoff levels after a thorough history was taken. A sum of 2,562 infants (0.36%) tested positive, where all the true positive cases had corrected identification. 26 cases were identified as false positive, and these cases were eliminated. It increased the positive predictive value (PPV) of the test from 1.31 percent to 1.33 percent. This variation was caused by a 24% elevation in the Positive Predictive Value of newborn screening for unreported Gestational Age.[1]

Miranda et al. subdivided the neonates based on their birth weight and determined that after applying stringent cut-off levels, body weight was adjusted accordingly. This results in a reduction of false positive results to 0.73 percent and a growth in the positive predictive value (PPV) for neonates born with an extremely low birth weight, i.e., below 2000 grams.[10]

Atsumi et al study's focuses on the primary cause of cross reactivity in immunoassay, which leads to an increase in false positives in screening preterm neonates for CAH. In preterm infants, 17-hydroxypregnenolone sulphate and 15-hydroxylated compounds are elevated. Immunoassay screening for CAH identified 653 individuals with positive results; 38 cases were confirmed, resulting in a PPV of 5.8% (38/653). Alternatively, the PPV for LC-MS/MS screening was 40% (6/15). In response, the Ministry of Health added LC-MS/MS as a second-layer CAH screening test with BW and GA adjusted levels having 99.95 % specificity with minimal risk of missing CAH. [11]

Conclusion

Neonatal Serum 17 – hydroxyprogesterone levels vary in accordance with the birth weight and gestational age. False-positive newborn-screening rates are disproportionately increased in prematurity and low birth weight. The optimal cut of levels adjusted to birth weight and gestational age of Serum 17 – hydroxyprogesterone should be established for screening of patients of congenital adrenal hyperplasia.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

CT Findings in Adult Patients Presenting with Non- Traumatic Acute Abdomen

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ABSTRACT

Objective: To determine the frequency of different radiological findings on CT scan in patients presenting with acute abdomen pain for accurate interventions.

Study Design: A Descriptive Cross-Sectional study.

Place and Duration of Study: The study was conducted in the department of Radiology Northwest General Hospital Peshawar, from 24th November 2018, to 24th April, 2019.

Materials and Methods: The study encompassed 197 patients referred from the outpatient department, regardless of gender, aged 15 years or older, and experiencing severe abdominal pain within a 48-hour period. Complete information, including patient age, gender, and symptom duration, was meticulously documented, along with CT findings essential for precise interventions. These details were recorded on a pre-designed proforma. The CT scans were conducted using either a 16-slice Toshiba machine or a 16-slice GE machine.

Results: As per frequencies and percentages for CT Findings between ages 15 years to 60 years, 142 (72.08%) patients were recorded with cholecystitis, 37 (18.78%) patients were recorded with diverticulitis and 18 (9.13%) patients were diagnosed with acute appendicitis.

Conclusion: In this study we concluded that cholecystitis is the leading cause of acute non-traumatic abdominal pain followed by diverticulitis and acute appendicitis. The preferred method for diagnosing acute abdominal pain is CT, which will have a significant impact on how individuals with acute abdominal pain are treated in a substantial manner & urgent management of patients in our local population.

Key Words: *Appendicitis, Diverticulitis, Cholecystitis, Tomography Spiral Computed, Diagnostic Imaging.*

Introduction

Acute abdomen is a medical emergency in which the correct diagnosis can be delayed or prevented by various factors, with subsequent adverse patient outcomes. It is crucial to take abdominal pain seriously since it frequently indicates a severe underlying condition and the potential for misdiagnosis.[1,2,3.]

The use of imaging techniques such as plain radiography, ultrasonography, CT scans, and magnetic resonance imaging (MRI) has become progressively more crucial in evaluating patients with acute abdomen. Plain abdominal X-rays and erect chest X-rays serve as valuable initial screening methods, but their results often lack specificity.[8] Ultrasonography, on the other hand, offers a cost-effective and radiation-free approach without the need for contrast agents. However, its accuracy may be compromised in obese individuals or those with limited mobility, and it can cause discomfort in patients with highly sensitive abdominal areas.[1]

Computed tomography plays a major role in reaching the diagnosis regardless of the nonspecific clinical presentations[5], which may be vague, ranging from self-limiting to serious life-threatening conditions. Evaluating a patient's pain involves considering various factors, including positional, palliating, and provoking elements, as well as the quality of pain, its location, radiation, referral patterns, severity, and temporal aspects such as the time and mode of onset, progression, and any previous episodes.[2] CT scan is the preferred imaging modality for diagnosing acute abdominal pain[8,9], as it significantly impacts the treatment approach for patients experiencing

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this condition.

Studies have been conducted on other modalities in our local population; however, there is a scarcity of research focusing on CT scans for individuals experiencing non-traumatic acute abdominal pain. Given the precision of CT scan in diagnosing the pathology, there arose a need for a study to comprehensively record these findings. This documentation would contribute to efficient management and reduced hospitalization duration.

This study aims to ascertain the prevalence of CT findings in individuals with acute abdominal pain, with the goal of enabling precise interventions, thereby facilitating timely diagnoses. Understanding the frequency of various radiological findings in cases of non-traumatic acute abdominal pain would significantly impact the treatment and management of patients within our local population.

Materials and Methods

This cross-sectional descriptive study was conducted from 24th November, 2018 to 24th April, 2019, at Radiology Department of Northwest General Hospital Peshawar as per the ethical approval received from the Institutional Review Board and Ethical Committee of the hospital vide their letter reference number IRB&EC/2018-GH/0111 dated 01 Nov 2018. The study was conducted with total sample size of 197 keeping proportion. Confidence interval being 95% absolute precision was required 4% using WHO calculator. The sampling technique used was non-probability consecutive sampling technique. The inclusion criteria were that patient of any gender, greater than or equal to 15 years of age, presenting with severe abdominal pain (> 4 VAS Pain Score) within 48 hours was included in the study. Exclusion criteria was previously operated cases and patients with known disease process. All the patients referred from the outpatient department of Northwest General Hospital Peshawar or any referral from outside fulfilling the inclusion and exclusion criteria was taken.

An informed consent was taken from all the patients included in the study, the nature of procedure, any risks, time consumed, data review and publication were explained completely to the patients. CT scan was performed using either 16 slice Toshiba or 16 slice GE machine. All the above information including age, duration of symptoms, and CT findings for accurate interventions was recorded.

Computation and analysis of the data was performed by using SPSS version 23. Frequencies and percentages were calculated for categorical variables like CT findings and gender. Mean and Standard deviation was calculated for numerical variables like age, weight, BMI and duration of symptoms. CT findings were stratified among age, gender, diabetes mellitus, hypertension, weight, BMI, and duration of symptoms. The technique of post stratification was implemented using the chi-square test to assess statistical significance, with a threshold set at a P value equal to or less than 0.05.

Results

The study encompassed a cohort of 197 participants, who were enrolled from the Diagnostic Radiology department. Descriptive statistical analysis revealed that the average age was recorded as 45 years with a standard deviation of 11.94. Additionally, the mean duration of symptoms was found to be 35 hours, accompanied by a standard deviation of 8.13.

Regarding the distribution of age groups, the study observed that 29 patients (14.72%) fell within the 15-30 years age category, 73 patients (37.05%) were categorized in the 31-45 years age group, and 95 patients (48.22%) were classified within the 46-60 years age range. (Table No II).

As per frequencies and percentages for CT Findings, 142 (72.08%) patients were recorded with cholecystitis, 37 (18.78%) patients were recorded with diverticulitis and 18 (9.13%) patients were diagnosed with acute appendicitis. (Table No. I). Stratification of CT findings with respect to age, duration of symptoms, are shown in Table No. II to III.

Table I :Frequency and Percentages for CT Findings (n=197)

CT Findings	Frequencies	Percentages
Acute Appendicitis	18	09.13%
Diverticulitis	37	18.78%
Cholecystitis	142	72.08%
Total	**197**	**100%**

Discussion

In our study, cholecystitis was identified in 142 patients (72.08%), while diverticulitis was documented in 37 patients (18.78%). Additionally, 18 patients (9.13%) received a diagnosis of acute

Table II: Stratification of CT Findings with Age (n=197)

Age	Age Group Frequencies	CT Findings Positive	Frequencies	Percentages	P Value
15-30 Years	29 (14.72%)	Acute Appendicitis	4	2.03%	0.000035
		Diverticulitis	6	3.00%	
		Cholecystitis	19	9.64%	
31-45 Years	73 (37.05%)	Acute Appendicitis	7	3.55%	0.00001
		Diverticulitis	13	6.59%	
		Cholecystitis	53	26.90%	
46-60 Years	95 (48.22%)	Acute Appendicitis	7	3.55%	0.00001
		Diverticulitis	18	9.10%	
		Cholecystitis	70	35.53%	

Table III: Stratification of CT Findings with duration of Symptoms (n=197)

Duration of Symptoms	CT Findings Positive	Frequencies	Percentages	P Value
≤ 30 Hours	Acute Appendicitis	08	4.06%	0.00001
	Diverticulitis	16	11.67%	
	Cholecystitis	55	27.91%	
> 30 Hours	Acute Appendicitis	10	5.07%	0.00001
	Diverticulitis	21	10.65%	
	Cholecystitis	63	31.97%	

appendicitis. When scrutinizing age distribution, our study showcased a predominant inclusion of patients within the age bracket of 15-60 years, constituting the highest count at 95 individuals (48.22%).

In a study carried out by Shamim in Pakistan, the leading reason for hospital admissions requiring surgical intervention was found to be diseases related to the digestive system, with a prevalence rate of 29.1%. This was followed by urinary tract diseases, accounting for 21.4% of cases. Among the specific causes of acute abdominal admission in this series, acute urinary tract infection (UTI) was the most common at 9.4%, followed by nonspecific abdominal pain at 7.2%. Acute appendicitis accounted for 4.8% of cases, acute retention for 2.4%, acute intestinal obstruction for 2%, ileal perforation for 0.6%, and duodenal perforation for 0.4%.[7]

The CT findings in elderly patients presenting to ER in a study conducted by Gardner CS showed that the occurrence rates of different conditions were as follows: S0mall Bowel Obstruction (SBO) accounted for 18%, Diverticulitis for 9%, Non-ischemic vascular-related emergencies for 6%, bowel ischemia for 4%, appendicitis for 3%, and colonic obstruction for 2%. CT scan findings had an impact on treatment strategies, with 65% of cases leading to treatment adjustments, 48% involving surgical interventions, and 52% involving medical interventions.[4]

Unlike the findings observed in the studies, which highlighted urinary tract infections (UTIs) and small bowel obstructions as the prevalent issues, our investigation demonstrates a distinct trend. Cholecystitis emerges as the dominant concern within our local population, reflecting its prominent prevalence attributed to specific causative factors. This significantly will aid in the effective treatment and immediate management of patients within our local community.

Limitation of Study

Ultrasound is generally used as the diagnostic tool of choice[8,17,18]. The sample in this study excluded those patients who were diagnosed using ultrasound and pregnant patients, as CT is contraindicated in pregnant patients.[13,19] Due to its high cost, extended scan periods, and restricted availability, Magnetic Resonance Imaging (MRI) has traditionally had a relatively limited role in the assessment of appendicitis. However, the absence of ionizing radiation makes it a desirable modality for patients who are pregnant.[20] In fact, Gatta et al. shows that when evaluating pregnant women, MRI is far better to transabdominal ultrasonography.[15] Additionally, it appears that MRI for appendicitis has similar sensitivity and specificity to computed tomography (CT) scanning.[14] However, using MRI were out of scope of this study.

In comparison to other modalities, CT findings in acute abdominal pain are more accurate with more sensitivity and specificity to diagnose the pathology.[21,22] It is suggested to extend the study to diagnose the pathology according to the precise location of pain in relation to the quadrants. This would help to specify the pathology and make accurate differentials in our local population.

Conclusion

In this study we concluded that cholecystitis is the leading cause of acute non-traumatic abdominal pain followed by diverticulitis and acute appendicitis. This help in a substantial manner in treatment & urgent management of patients in our

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local population. We have also concluded that patients presenting with acute nontraumatic abdominal pain can be evaluated with abdominal CT. The preferred method for diagnosing acute abdominal pain is CT, which will have a significant impact on how individuals with acute abdominal pain are treated and managed in our population.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

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ORIGINAL ARTICLE

Laparoscopic Appendectomy in Children-Study of 331 Cases and Analysis of Outcome

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ABSTRACT

Objective: The aim of this study was to present the experience of 331 cases treated by laparoscopic appendectomy in children operated by single pediatric surgeon and to analyze the outcome.

Study Design: A descriptive retrospective study design

Place and Duration of Study: All the children treated by laparoscopic appendectomy between period of June 15, 2011, to October 15, 2021 at Northern Area Armed Forces Hospital, Hafr al Batin, Saudi Arabia.

Materials and Methods: This was a retrospective study of 331 cases of acute appendicitis in children treated by laparoscopic appendectomy between the period of June 15, 2011, to Oct 15, 2021. Acute appendicitis was diagnosed on clinical basis supported by lab tests including leukocytosis and increased neutrophils count and occasionally by radiological studies including AXR showing fecalith, ultrasound abdomen showing free pelvic fluid and CT scan abdomen with thick walled or perforated appendix. All cases were operated by the same pediatric surgeon. Patient's gender, age, weight, clinical symptoms and signs, laboratory and radiological data, results of surgical treatment, operative and post-operative complications and outcome were studied. The electronic data of the operation room was collected and analyzed by the operating pediatric surgeon with permission from the hospital ethical committee. The outcome of laparoscopic appendectomy was analyzed.

Results: Three hundred and thirty-three children with acute appendicitis were treated by laparoscopic appendectomy. There were 199 males and 132 female patients. The mean age was 10 years (1 to 14 years). The mean surgery time was 45 minutes. The peritoneal suction -wash was performed in 300 cases and drainage of peritoneal cavity was done in 3 cases of perforated appendicitis. No conversion to open appendectomy was done in this series. The rate of operative and post-operative complications was zero percent. The overall incidence of postoperative wound infection was low (<1%). All the children resumed normal daily activities after 7 days of average time. The families and the children were found satisfied with the outcome.

Conclusion: Laparoscopic appendectomy in children is a feasible, effective, safe and appropriate procedure in the treatment of acute appendicitis in children with excellent cosmetic outcome.

Key Words: *Acute Abdomen, Acute Appendicitis, Laparoscopic Appendectomy, Complications, Follow Up.*

Introduction

Acute appendicitis (AA) is one of the most common surgical emergencies that requires surgical intervention in children. It represents 15% to 20% of surgical emergencies in pediatric age. AA is seen in all ages, but it peaks between the ages of 8 to 14 years.[1] AA is a childhood disease being more common in boys (63%). The mean age of AA is 10 years. AA is classified as simple when there's no perforation and is defined as advanced when the appendix is gangrenous with peri appendicular abscess formation or it is perforated with peritonitis[2].

In children perforation may occur after 12 to 15 hours of start of abdominal pain. Twenty-five percent patients have perforation after 24 hours, 50% after 36 hours and 80% have perforation by 48 hours.

Gangrenous or perforated appendix is seen in one third to one half of the admitted patients.[3] Although morbidity of ruptured appendicitis is high, the mortality has been reduced to less than 1%. Most deaths are noted in very young when the diagnosis is not considered.

Appendicitis is for sure cured by appendectomy performed by conventional open appendectomy

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(OA) or by laparoscopic appendectomy (LA).[4] Minimal invasive surgery in the pediatric age is being practiced all over the world like in other surgical specialties.

Kurt Semm treated the first patient in 1983 with LA. Since that time, this method has gained attention in management of AA. With advances in minimal invasive surgery, LA is a suitable procedure for treatment of AA in children.[5]

Many authors have disregarded the perceptions of increased rate of intra-abdominal abscess formation in post-operative cases of LA in advanced appendicitis. In fact, the complication rate is low and hospital stay is shorter in patients with advanced appendicitis treated by LA leading to financial advantage for the family and the health care providing facility.[6]

Increasing LA experience, improvement in surgical techniques and advancement in technology have led to superior outcome of LA as compared to OA. LA is the most common procedure being performed in children followed by laparoscopic orchiopexy for abdominal testis and laparoscopic cholecystectomy.[7]

LA has intrinsic appeal shared by all minimal invasive surgeries. This is due to reduced postoperative pain, short hospital stays, early return to normal activities and superior cosmetic outcome. Delay in diagnosis leads to advanced appendicitis with gangrene and perforation depending on nature of disease. The incidence of wound infection is less in LA as compared to OA. LA provides a good opportunity to follow surgical principle" to see to properly operate."[8]

LA is no longer considered a luxury but an important surgical break through as it can resolve many problems which are encountered in OA.[9] The Meckel's diverticulitis with normal appendix is especially diagnosed at laparoscopy and Meckel's diverticulectomy is performed to treat it.[10]

The aim of this retrospective study of acute appendicitis treated by three trocars LA by single pediatric surgeon is to present the experience and review of literature to compare the outcome with published literature in a series of 331 cases in children for analysis of outcome.

Materials and Methods

This was a retrospective study of all the consecutive patients of AA admitted in our hospital at Northern Area Armed Forces Hospital, Hafer Al Batin, Saudi Arabia, who underwent LA between June 15, 2011, and Oct 15, 2021, by single Pediatric surgeon. All the patients presented in emergency department directly or were referred from primary health care centers. The total number of patients treated was 331. There were 199 boys and 132 girls. AA was diagnosed on clinical bases supported by laboratory and occasionally by radiological studies. The lab tests showed leukocytosis and raised neutrophils in most of the patients. AXR showed appendicolith in 9 patients. Ultrasound abdomen showed free pelvic fluids especially in advanced acute appendicitis. CT scan abdomen showed thick-walled appendix with perforation in advanced cases. All patients were operated by same pediatric surgeon.

All patients presented in emergency department with complain of sudden severe abdominal pain associated with vomiting and fever. The diagnosis of AA was supported by leukocytosis and abdominopelvic ultrasound which was done in all female patients to exclude genitourinary pathologies and occasionally in male patients in case of any doubt. The classification of advanced appendicitis was made based on clinical findings of generalized abdominal pain and tenderness and operative findings of gangrenous perforated appendix with peri appendicular abscess and signs of peritonitis. In the absence of these findings AA was classified as simple appendicitis. All the patients who were diagnosed as a case of mesenteric appendicitis improved with conservative management and were excluded from the study.

The parameters including gender, age, weight, clinical features (abdominal pain, vomiting, fever, tenderness and rebound tenderness RIF), leukocytosis and abdominal ultrasound data, duration of surgery, operative and post-operative complications, length of hospital stay, time till resumption of normal activities, outcome of LA and degree of satisfaction of parents and child himself were studied. The electronic data of operation room was collected and analyzed by the operating pediatric surgeon with permission from hospital ethical committee. The outcome of LA was analyzed.

An average follow-up of 12 months showed no long-term problem. There were 199 boys and 132 girls. All patients received 2nd generation cephalosporin and

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metronidazole at admission. In our series all children underwent LA under general anesthesia. The stomach was emptied by nasogastric tube and urinary bladder was also catheterized. The patients were kept in supine position on operating table with head side down and right side raised, keeping left arm secured by the side of the body. The surgeon and the assistants were operating on the left side of the patient with the position of laparoscopy monitor towards the surgeons.

The umbilicus was held with two arteries, everted and incised. The Linea Alba and peritoneum were opened with a pair of scissors. The 10 mm umbilical trocar was introduced, and pneumoperitoneum was established with CO2 insufflation with a flow of 6 l/min and a pressure of 8 mm of Hg to 12 mm of Hg depending upon the age of the patient. Two 5 mm working trocars were inserted in the right upper abdominal quadrant in midclavicular line and left iliac fossa.

The abdominal cavity was explored with a 30- degree camera and appendix were identified and the diagnosis of AA was confirmed.

Findings of suppuration, gangrene, or perforated appendicitis with or without peri appendicular pus or free fluid were noted to define simple and advanced AA. Hemostasis was secured by coagulation of mesoappendix along the surface of appendix with bipolar hook. Appendix was ligated at its base with three vicarly endo loops. Appendectomy was done between the 2nd and 3rd ligature. The appendix was removed through umbilical trocar to avoid port site infection. Suction washing of peritoneal cavity was optionally performed with drainage if required in perforated appendicitis. The trocars were removed under direct vision and complete exsufflation was done.

Umbilical wounds for camera ports were closed with absorbable sutures. The two working ports wounds of 5 mm each were closed by a subcuticular stitch. (Figures 1-5).

Intravenous paracetamol was given to all patients for perioperative analgesia. Two doses of post-operative antibiotic therapy were administered in simple cases of AA and after 48 hours of being afebrile with an average of 5 days in advanced appendicitis.

Results

In this series 331 children with AA were treated by

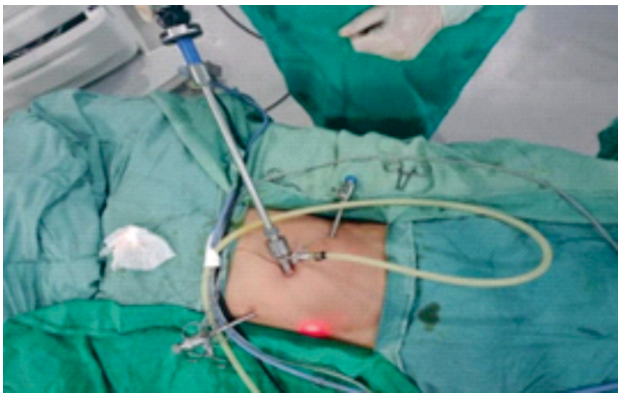

Figure 1; All Three Ports in Place

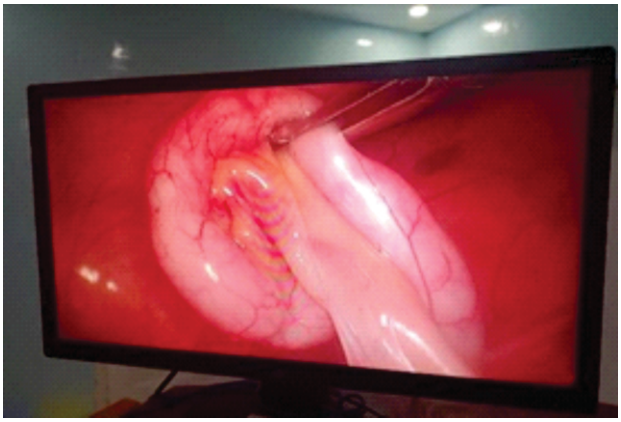

Figure 2: Acute Appendicitis with Free Peri-Appendicular Fluid

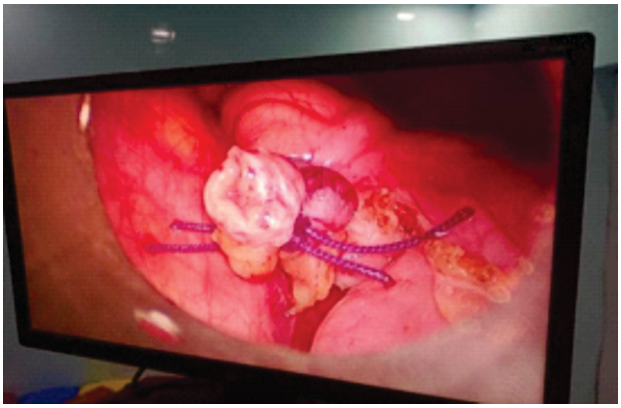

Figure 3: Ligated Appendicular Stump

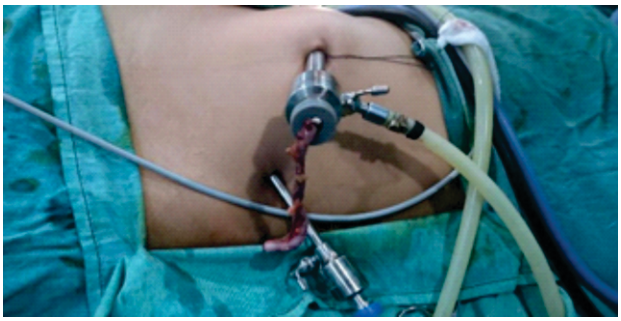

Figure 4: Removal of Appendix Through Umbilical Port

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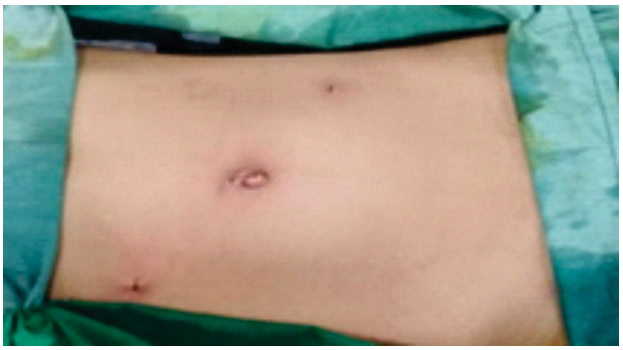

Figure 5: Closed Wounds of All 3 Ports

LA. There were 199 boys (62%) and 132 girls (38%). There were 194 patients in the 10 to 14 years of age group, 122 patients in range of 5 to 9 years and 15 patients in 2 to 4 years of age group. The mean age in our series was 10 years (2 years to 14 years). The average weight of patients between the ages of 2 to 4 years was 16 kg (ranging between 11-17 kg), average weight of patients between the ages of 5 to 9 years was 28 kg (ranging between 18-34 kg) and average weight of patients between the ages of 10 to 14 years was 39 kg (ranging between 22-58 kg). The overall mean weight of our patients in this series was 27 kg. LA was performed as emergency surgery. The patients presented in the emergency department after an average delay of 48 hours (ranging between 48 to 250 hours or 1 to 7 days) with predominant symptoms of pain abdomen, vomiting and fever. Examination findings showed sick look, tachycardia, tenderness and rebound tenderness in right iliac fossa with an average of unremarkable systemic examination. The AXR done in emergency department showed appendicolith in 9 cases. Ultrasound abdomen and pelvis were performed in 150 cases which reported free pelvic fluid. Laboratory tests showed an increase in total and differential leukocytes counts in 300 patients (Table 1).

LA was associated with cleansing of peritoneal cavity by suction-washing in 300 cases. Peritoneal drain was not kept in any patient. The mean operating time was 45 minutes (35 min-120 min). There was no conversion to OA in this series. Oral feeding was on an average allowed after 24 hours in simple AA and after 72 hours in advanced appendicitis. Most patients were discharged home after 72 hours of surgery. There were no operative complications in this series. One patient had umbilical wound infection which was treated by intravenous antibiotics according to culture sensitivity. In our series, the mean hospital stay of patients was 3 days (1-10 days). There is no complication of intrabdominal access formation in our series. There is no mortality. There was no problem found after a mean follow-up of 12 months (Table 2). Our patients and the parents were found happy with the results of LA.

Table I: Preoperative and Per-Operative Demographic Data

Demographic Data	Number of Patients	Percentage
Gender		
Boys	199	62 %
Girls	81	38%
Age (Mean)		
2-4 years	15	4.5 %
5-9 years	122	36.8 %
10-14 years	194	58.6 %
Weight (Mean)		
2-4 years	16 (11-17)	4.8 %
5-9 years	276 (18-34)	83.3 %
10-14 years	39 (22-58)	11.7 %
Fever >38 C	305	92.1 %
Leukocytosis	308	93 %
Ultrasound	150	45.3 %
Free Fluid	130	39.2 %
Grade of Inflammation		
Suppuration	200	60.4 %
Gangrenous	81	24.4 %
Perforated	50	15.1 %

Table II :Per-Operative and Post-Operative Complications

Complications	Number of patients	Percentages
Visceral injury	Nill	0%
Vascular injury	Nill	0%
Bleeding	Nill	0%
Conversion to open	Nill	0%
Wound infection	1	0.3 %
Post-operative intraabdominal collection	Nill	0%

Discussion

Acute appendicitis (AA) is a childhood disease being more common in boys (63%).[11] In our series, there are 62% boys and 38% girls.

The mean age of AA is 10 years [12,13]. Diagnostic delay in AA leads to advanced appendicitis with gangrene and perforation [14,15]. In our series, there is an average

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delay of consultation for AA within 2 days. In another study a duration of 6 days prior to consultation showed 74% cases of advanced appendicitis. In cases where there is doubt in diagnosis, clinical evaluation should be complemented with abdominal and pelvic ultrasound and CT scan abdomen for confirmation.[16,17]

Preoperative antibiotics including 2nd generation cephalosporin and metronidazole were given in all patients prior to surgery in our series.

Minimal invasive surgery in pediatric age group is being practiced all over the world as in other surgical disciplines. Increasing experience in minimal invasive surgery, improvement in surgical techniques and advancement in technology all have made superior outcome possible with LA possible as compared to open appendectomy (OA).[18,19]

LA is the most common procedure in children followed by laparoscopic cholecystectomy. LA has a natural attraction as in all minimal invasive procedures.[20, 21] This is due to decrease in postoperative pain, early return to routine activities and excellent cosmetic outcome.[22]

The mean operating time in our series was 45 minutes which is comparable to that of the literature.[23, 24] Several authors have already demonstrated that, with increased experience, the operative time with LA for advanced appendicitis is same as with OA.[25]The conversion of LA to OA varies from 0% to 11%. The average conversion rate is reported as 2.8%.[26,27] The conversion reasons may include unusual appendicular position, perforated appendicitis, and a gangrenous appendix involving it's base or Meckel's diverticulitis.[28] Another reason for conversion reported is technical difficulties.[29] In our series we did not need conversion to OA in any patient.

The gross pathology noticed in our series of AA is either suppurative, gangrenous or perforated appendix. Two doses of post-operative antibiotic therapy were administered in simple cases of AA and after 48 hours of being afebrile with an average of 5 days in advanced appendicitis. The mean hospital stay in our series is 3 days in simple appendicitis which is comparable with other studies [30, 31.] The rate of wound infection is reported less in LA as compared to OA [32, 33]. In our series only one patient had an umbilical wound infection which was treated by intravenous antibiotics according to report of culture sensitivity. There is controversy in determination of risk factors leading to intraabdominal collections in advanced appendicitis. Some authors have reported higher incidence of this complication after LA with perforated appendicitis. However, most of the series have reported deceased rate of intraabdominal abscess formation in advanced appendicitis treated by LA [34]. In our series, there is no case of postoperative intraabdominal collection.

The overall incidence of adhesive small bowel obstruction due to adhesions following appendectomy in children is reported relatively low (0.7-3%) [35,36]. However appendectomy is the most common abdominal surgical procedure in childhood with a lifelong risk of developing small bowel obstruction of 7-8% [37, 38]. LA may have the advantage of decreased formation of adhesions compared to OA as it causes less trauma to abdominal wall and operative site[39,40]. Available studies on adhesive small bowel obstruction in children comparing LA and OA are relatively few compared to studies in adults and the results are conflicting.

Laparoscopy provides a good opportunity to follow surgical principle “to see in order to properly operate” [41]. LA is no longer considered as a luxury but an important surgical treatment as it can resolve many problems under direct vision [42]. Marker et al [24,] have reported that decreased duration of hospital admission and early resumption of routine life activities minimizes the psychological effects on children. In our series, all patients returned to routine life activities within 8 days and the families and children were found happy as regards the cosmetic outcome of LA. This is an important point to keep into consideration while treating children.

Conclusion

LA in children is feasible, effective, safe and appropriate procedure in treatment of AA in children with excellent cosmetic outcome.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Anti Hbs Antibody Sero-Prevalence among Extended Program of Immunization Vaccinated Children Born between Year 2009-2016 in Urban Community of City Peshawar Pakistan

Aftab Khan[1], Sawan[2], Erum Bahadur[3], Israr Ahmad[4], Ulfat Sultana[5], Ambreen Arif[6]

ABSTRACT

Objective: To determine the sero-prevalance of antibody against Hepatitis B virus surface antigen among EPI vaccinated children born between year 2009-2016.

Study Design: Descriptive cross sectional study.

Place and Duration of Study: Study was carried out among urban area children born in Peshawar city between 2009-2016 from 2 August, 2020 to 30, April 2021.

Materials and Methods: This was descriptive cross-sectional study carried out among children born in city Peshawar "between" 2009-2016, using non-probability convenient sampling technique. After taking the written consent from the parents a predesigned questionnaire was filled. About 3 to 5 ml of blood was collected for anti HBs Ag test through using ELISA technique. Results were collected and analysed using SPSS version 21.

Results: This study included 184 EPI HBV vaccinated children vaccinated "between" 2012 to 2016. Out of 184 children 118 (64.1%) were female belonging to the middle socio-economic class 170 (92.4%). The mean age of the study participants was 7.834 years ±2.045. Anti Hbs antibody titre revealed that out of 184 study participants 75.5% were vaccinated within last 10 years. It was observed that only 33 (17.9%) children out of 184 were immune against HBV (Antibody level > 100 mIU/ml). The study showed that there was no significant difference ($p>0.05$) in the immune status of the children with respect to the demography like age of child $p=0.529$, gender $p= 0.461$, place of vaccination $p=0.918$, economic status $p=0.190$.

Conclusion: The EPI HBV vaccinated children lost protective anti Hbs antibody level after five years of vaccination.

Key Words: *Vaccination, Anti HBs Antibody, Sero-prevalence, HBV Vaccine, Immune Response, Immunization, Children, EPI.*

Introduction

Hepatitis B infection is a grave devastating global public health issue .The causative agent of this infection is hepatitis B virus(HBV).[1] This virus can causes progression of serious liver diseases such as liver cirrhosis, hepatic decompensation and hepatocellular carcinoma[2] , this leads to higher rate of mortality and morbidity.[1] The significant reservoir for HBV is human. The route of transmission of HBV is most common among people who come in contact with blood or body fluids of HBV infected person, unsterilized injections, use of contaminated needles among drug users, and unsafe sexual practices. [1,3] Dr. Baruch was the first to discover hepatitis B virus in 1965. In the beginning, the virus was named as" Australia Antigen". Vaccine therapies are available for Hepatitis B virus infection. HBV vaccine consists of three or four doses, given to the infants over a 6 month period.[4]

Almost 2 billion people are worldwide infected with HBV infection that is one third of the total world population. Among them, are 360 million chronic carriers of HBV which makes 6% of the world population.[5] Chronic HBV infection prevalence differs among regions. The infection rates in USA and Western Europe are low (0.1-2.0%), intermediate (2.0-8.0%) in Japan and Mediterranean countries, and with a high rate of infection (8.0-20.0%) in sub-Saharan and southeast Asia regions.[6] Countries endemic with HBV infections includes Asia, Southern

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Europe, Africa and Latin America.[7] Africa is considered as a whole to have high endemicity levels of HBV infection and the children of Africa aged between 0-14 are at a high risk of HBV infection.[2] A retrospective study conducted in South Korea included the children vaccination data of 2012 to 2015 showed that the titter of Anti Hbs antibodies decreases with increasing age.[8]

Pakistan being a developing country, is also endemic with hepatitis B, and 3% population of the country is infected with the virus.[9] In Pakistan the HBV vaccination coverage varies among different parts of Pakistan and in rural areas the vaccination coverage rate is very low[1] therefore preventive measures should be taken against HBV infection.

The EPI in Pakistan has significant and apparent impact on immunization indicators such as measles, tetanus and poliomyelitis eradication at regional and global level.[10] Despite continuous work, efforts and priorities by the Government of Pakistan, the EPI vaccination in Pakistan did not achieve the framed target of 80% protective level among children. Many factors involved in hindrance of the achievement of benchmarks goal of EPI vaccination in Pakistan are lack of awareness, poor management and limited access to immunization etc.[11] Pakistan started HBV vaccination in EPI from 2009.[12] It has been presumed that EPI vaccination against HBV provide protection for long duration of time. There is no follow up data of HBV vaccine response after 5 year of EPI immunization in Pakistan. Therefore, this study was carried out to determine the HBV vaccine efficacy among children who were EPI vaccinated between 2009 to 2016. The purposes of the study were to determine the Sero-prevalence of anti Hbs antibodies in children born after 2010 and vaccinated against HBV through EPI. Since 2009 when EPI HBV vaccination was started in Pakistan, there found no proper evidence regarding HBV vaccination long term protection. It is important and public health concern to determine the exact duration of protection of any vaccine. This study was conducted to determine anti Hbs Antibody level among EPI vaccinated children born between 2009-2016 in urban community of district Peshawar.

Materials and Methods

This was a community based, descriptive cross-sectional study carried out during 2 August 2020 to 30 April 2021, among children born in city Peshawar "between" 2009-2016. The sample size of this study was calculated 184 based on the prevalence of anti Hbs level among healthy population 0.5%.[13] The sampling technique used for data collection in this study was non-probability convenient sampling technique. Ethical approval of the study was provided by the ethics committee of Post Graduate Medical Institute Peshawar institutional research and ethics board with Ref No 11007. This study was conducted among the children whose parents were willing to allow their children to participate in this research. Children having the HBV infection in past were excluded from this study. After taking the written informed consent from the parents a predesigned questionnaire was filled. The content of the questionnaire was about the history of the child's HBV vaccination, demography, vaccination time, place of vaccination and family history about HBV infection etc. After collecting data using questionnaire, trained staff of Pakistan Health Research Council (Research centre Khyber Medical College Peshawar) were deputed for blood sampling. About 3 to 5 ml of blood were collected from each child and was processed to determine the induced immunity of the vaccine against the surface antigen of hepatitis B (HBsAg. For anti HBs titre the collected samples were processed and were proceeded for qualitative anti HBs test through ELISA. Results were collected and entered in data form. The data was analysed using SPSS version 21.

Results

This study included 184 EPI HBV vaccinated children vaccinated "between" 2009 to 2016. Out of 184 children greater proportion 118 (64.1%) were female. Most responders (provided data about the child vaccination history) of this study were the mothers of included children 134 (72.8%). It was observed that most respondents belonged to the middle socioeconomic class 170 (92.4%), and these families have only one earning member 167 (90.8%). The mean age of the study participants was 7.834±2.045 **(Table I).**

Study also showed that most of the studied children (47.3%) were vaccinated from primary health centres. The vaccination records of participated children were confirmed verbally from a total 137 (74.5%) respondents. It was found that among 184

participants 75.5% were vaccinated within last 10 years **(Table II).**

It was observed that only 33 (17.9%) children out of 184 were having protective antibody level against HBV **(Figure 1).** The study found no significant difference in the immune status of the children with respect to the demography age of child p=0.529, gender p= 0.461, place of vaccination p=0.918, economic status p=.0.190 **(Table III).**

Table I : Demographic Status of Study Participants

Demographic Status	Description	Frequency	Percentage
Relation with child	Father	29	15.8
	Mother	134	72.8
	Sibling	21	11.4
	Total	184	100.0
Economic status	High	9	4.9
	Middle	170	92.4
	Low	5	2.7
	Total	184	100.0
Age of child	4 years to 5 years	29	15.8
	6 years to 7 years	52	28.3
	8years to 9 years	63	34.2
	10 years to 12 years	40	21.7
	Mean ±Std	7.834±2.045	
	Total	184	100.0
Gender of child	Male	66	35.9
	Female	118	64.1
	Total	184	100.0
Region	Urban	184	100.0
Disability	No	184	100.0

TABLE II: Description of EPI Vaccination History

Demographic Status	Description	Frequency	Percentage
Place of EPI vaccination	EPI Centre	45	24.5
	Health Centre	87	47.3
	Hospital	51	27.7
	Home	1	.5
	Total	184	100.0
Vaccination confirmation	Verbally	137	74.5
	Card	47	25.5
	Total	184	100.0
Last dose of HBV received	Within 5 years	28	15.2
	Within 10 years	139	75.5
	within 11 to 12 years	17	9.2
	Total	184	100.0
Family HBV infection	No	184	100.0
Anti HBs Ab	Yes	184	100.0
Protective level of anti Hbs Ab	Yes	33	17.9
	No	151	82.1
	Total	184	100.0

Table III: Immune Status of Children with Respect to their Demography

Demographic status	description	Immune status		total	P value
		Immune	Nonimmune		
Age of child	4 years to 5 years	6	23	29	0.529
	6 years to 7 years	6	46	52	
	8years to 9 years	12	51	63	
	10 years to 12 years	9	31	40	
	Total	33	151	184	
Gender of Child	Male	10	56	66	0.461
	Female	23	95	118	
	Total	33	151	184	
Place of vaccination	EPI Centre	7	38	45	0.918
	Health Centre	16	71	87	
	Hospital	10	41	51	
	Home	0	1	1	
	Total	33	151	184	
Economic status	High	0	9	9	0.190
	Middle	33	137	170	
	Low	0	5	5	
	Total	33	151	184	

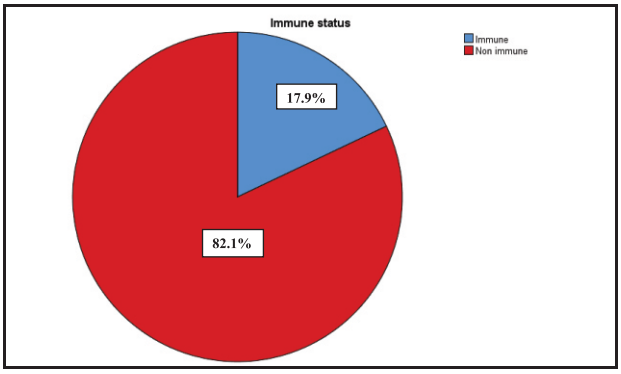

Figure 1: Frequency of Immune Status of Study Participants

Discussion

This study demonstrated the prevalence of HBV vaccination and its effectiveness among children of urban area of district Peshawar vaccinated from 2009 to 2016. The focus of our study was to determine anti Hbs antibodies prevalence among children vaccinated against HBV through EPI. There found no published literatures or findings that justify the long-lasting immunity against HBV after HBV vaccine. In Pakistan, HBV vaccines were included in

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EPI in 2009, therefore the inclusion criteria of this study were set to children born after 2009.

This study was not a novel study focused on children for determination of immune response against vaccine but similar kind of studies among children were observed in other settings where a similar pattern of immune response against vaccination was observed.[14, 15] The sero-prevalence of anti Hbs antibodies in this study (17.9%) was low as compared to another study conducted in south Korea where protective antibody level was 50%.[16] The target population in Korean study was older and recently vaccinated therefore protective antibody level was high. The efficacy of HBV vaccination was tested among the Egyptian children aged 6 to 11 years where the sero-prevalance was 39.3%.[17] All these studies revealed that the sero-prevalance of anti HBs antibodies declined with the age and duration. The low protective anti HBs antibody level in this study was a clue for public health consideration. More in depth studies regarding post immunization prevalence of anti Hbs Level in multi community level with systemic sampling technique is needed to address the issue. Further studies focusing on the active presence of memory cell for this specific antigen among HBV vaccinated children are needed.

Hepatitis B is endemic with higher rate of endemicity and the immunization against the hepatitis B infection needs a broader vaccination coverage, to cope up with this problem.[18] WHO recommended to introduce HBV vaccination in Expanded Program on Immunization (EPI) to eventually eliminate HBV infection and its chronic long lasting impact. EPI is multinational effort whose goal is to immunize children all around the world against the vaccine preventable diseases d of childhood.[19] All of the participants in this study had completed their three doses of HBV vaccination through EPI. This study results showed that the immune status of the participants is 17.9% which is comparatively very low and with passage of time this protective antibody level further decreases. A previously performed studies in Iran, and Egypt reported that the vaccine induced anti HBs Ag level might decreases with age.[20,21] The results of our study in agreement with other studies revealed that anti Hbs antibodies titter start to decrease after primary vaccination, so there is a need of booster dose which induce or trigger anamnestic immune response against HBV infection.[22] Some studies showed that long term immunity is generated against HBV infection by a booster dose.[23]

The findings of this study were consistence with other studies, demonstrated no significant difference when compared the immune status of children with their gender, economic status and anti HBs antibodies level.[17]

The study was limited to a particular time and due to constrain of budget we selected probability convenient sampling technique which was a major limitation of this study. Due to constrains of budget the anti-Hbs Antibody producing memory cell count using HPLC technique could not be determined, which would determine the exact long-lasting immunity against HBV vaccine.

Conclusion

A very high ratio 82.1% EPI HBV vaccinated children lost protective anti Hbs Ag antibodies level after five years of vaccination. The protective anti Hbs antibodies level after 5 year of HBV vaccination was determined very low and need a booster dose of HBV vaccine after five years of vaccination.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

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ORIGINAL ARTICLE

Prophylactic Use of Tranexamic Acid in Reducing Blood Loss and Preventing Postpartum Haemorrhage in Elective Caesarean Section

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ABSTRACT

Objective: To compare the mean blood loss in women administered pre-operative prophylactic tranexamic acid versus control group undergoing elective lower segment caesarean section.

Study Design: It was an experimental study.

Place and Duration of Study: Study was carried out at Department of Obstetrics and Gynecology at Federal Government Polyclinic Hospital Islamabad from 9th Mar 2021 to 8th Sep 2021.

Materials and Methods: A total of 100 patients were selected who were presented for elective cesarean delivery under spinal anesthesia. Women were equally divided into two groups A & B with 50 patients in each group. Patients in group A were preoperatively given 1gm of tranexamic acid intravenously. Group B did not receive tranexamic acid. Immediately after delivery of neonate both groups received 10 units of oxytocin. All abdominal sponges, gauzes, pads were weighed before surgery and postoperatively and blood from suction container also measured in ml. Postoperatively per vaginal bleeding up to 24 hours were measured by total number of pads used, weighed for dry and wet weight and blood loss measured in ml. Total blood loss was measured. Data analysis was performed through SPSS version 22.

Results: The mean age for Group A and Group B was 29.9years±6.51SD and 28.7years ±5.13SD respectively. The mean age for the total study subjects was 29.3 ±5.9SD. The mean and standard deviation for blood loss after elective lower segment caesarean section in Group A was 576.6ml± 91.59SD and in Group B it was 836.6ml ±91.59SD respectively with 31 %reduction in blood loss in group A. It is clear from the results that blood loss was significant in both the groups with p-value=0.001.

Conclusion: The blood loss is significantly reduced in women undergoing elective lower segment caesarean section by administering pre-operative prophylactic tranexamic acid.

Key Words: *Caesarean, Delivery, Hemorrhage, Postpartum, Tranexamic Acid.*

Introduction

Postpartum hemorrhage is defined by WHO as blood loss which exceeds 500ml after birth but within 24hours of delivery and is responsible for 25% maternal mortality & severe anemia in 12% survivors.[1] Loss of around 45% blood volume results in weakness, sweating, tachycardia and hemodynamic instability. Rise in caesarean section rate worldwide is alarming. It has led to high risk of complications than normal vaginal delivery in the form of either primary or secondary postpartum hemorrhage resulting in increased maternal mortality & morbidity.[2] Pregnancy related causes leads to death of thousands of women worldwide during delivery or in postpartum period. Postpartum hemorrhage stands as a major cause of mortality and morbidity leading to anemia needing red cell transfusion, prolonged hospitalization, and sepsis. In addition to uterine atony, haemostatic equilibrium is shifted towards increased fibrinolysis causing coagulopathy and bleeding due to extensive tissue damage in caesarean.[3,4] Main first line treatment for PPH is oxytocin. Others include ergometrine and misoprostol. Following placental expulsion, fibrinolytic system gets activated resulting in degradation of fibrin and fibrinogen. Rise in plasminogen activators and fibrinogen degradation products causes increased tendency to bleed in postpartum period which lasts up to 10 hours leading

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to more hemorrhage. So, we need other strategies to reduce blood loss in addition to standard utero-tonic agents. There is limited evidence for definitive recommendations of prophylactic tranexamic use in women of all risk profiles undergoing cesarean section.[5,6] Pro-hemostatic drugs such as tranexamic acid provide a complementary biochemical haemostatic effect to well proven uterotonic. Tranexamic acid is a synthetic analog of amino acid lysine. It acts as fibrinolytic agent by competitively binding to lysine receptor site on plasminogen and reduces conversion of plasminogen to plasmin thus preventing fibrin degradation and stabilizing fibrin clot. Tranexamic acid was conventionally used to control peri operative bleeding, reduce hemorrhage & decrease blood transfusion rate in different medical & surgical conditions with resulting decrease in both mortality & morbidity. Recently it's being used in many Gynecological procedures like myomectomy, hysterectomy, cervical & ovarian cancer surgeries & used as 1st line in women with menorrhagia. Although WHO recommended its usage for standard treatment for postpartum hemorrhage within 3 hours of birth but preventive role of this drug in decreasing hemorrhage during & after cesarean has been a conflicting area yet .[7]

The rationale of this study was that uterotonic drugs that are used in routine practice compared to haemostatic agents. Prophylactic usage of tranexamic acid might reduce need of hysterectomy, risk of severe anemia & avoid need for blood transfusion & will help in improving quality of care for women by preventing maternal mortality & morbidity due to postpartum hemorrhage. It is a cost-effective agent with fewer side effects, easy availability, and effective & in developing country like Pakistan where low socioeconomic status prevails, its promising drug. Many international studies are available in literature, but local data is still lacking which could help us in using this favorable drug. So, this study was planned with an objective to find out the mean blood loss and compare it among women receiving prophylactic tranexamic acid with those who do not receive it.

Materials and Methods

It was an experimental study with non-probability consecutive sampling conducted at the department of Obstetrics & Gynecology, Polyclinic hospital, Islamabad. Duration of study was 6 months from 9th Mar 2021 to 8th Sep 2021**.** A total of 100 cases were selected and divided in two groups, 50 in each group; 50 cases in each group were calculated with Confidence level = 95%, Power of study = 90% and mean (SD) for total blood loss i.e., 436.5±118.07 ml with tranexamic acid and 616.5±153.34ml in control group after elective caesarean section. Pregnant women of age 18-40 years, parity <5, gestational age>37 weeks planned for elective lower segment caesarean section under spinal anesthesia were enrolled in the study. Women with heart disease (medical record), renal disorders (creatinine> 1.8mg/dl), diabetes (OGTT>186mg/dl), hypertension (BP>140/90mmH), coagulation disorders (INR>2), and anemia (Hb<10g/dl), requiring blood transfusion, abnormal placentation, polyhydramnios, and multiple pregnancies (on ultrasound) were excluded from study. Moreover, no booked cases and those who were sensitive to tranexamic acid or in whom tranexamic acid is contraindicated and women with history of postpartum hemorrhage in previous delivery were also excluded from study. Informed consent was taken. After taking approval from hospital ethical committee letter No 1/2017-E/C82, 100 women fulfilling selection criteria were enrolled in the study through maternity ward of Department of Obstetrics & Gynecology, Polyclinic hospital, Islamabad. Demographic information (name, age, BMI, gestational age, parity) was noted. Women were randomly divided into two groups. In group A, just before giving skin incision 1gm of tranexamic acid in 10ml of 5% dextrose was given intravenously slowly over 5 minutes. In group B, tranexamic acid was not given preoperatively. In both groups after delivery of neonate 10 units of oxytocin were given. All abdominal sponges, gauzes and pads were weighed before surgery and postoperatively .Blood from suction container was also measured in milli liters. Postoperatively per vaginal bleeding up to 24 hours was measured by total number of pads used, weighed for dry and wet weight and blood loss was measured in milli liters. Total blood loss was measured. Data was entered and analyzed through SPSS version 22. The quantitative data like age, BMI, gestational age and total blood loss was presented as mean and SD. Qualitative variables like parity were

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presented as frequency and percentage. Both groups were compared for mean blood loss by using independent sample t-test. P-value≤0.05 was taken as significant.

Results

The mean age of women in Group A and Group B was 29.9 ± 6.51 years and 28.7 ± 5.13 years respectively. Most of the patients were ≤35 years of age. In group A, 38 (76.0%) were primiparous and 12 (24.0%) were multiparous females. In group B, 35 (70.0%) were primiparous and 15 (30.0%) were multiparous females. The mean BMI of patients in Group A was 28.12 ± 4.45 kg/m^2 and in Group B was 28.72 ± 4.73kg/m^2. Table I

The mean blood loss in Group A was observed as 576.60 ± 91.59 ml and in Group B, the mean blood loss was 836.60 ± 91.59 ml. The difference of blood loss in both groups was highly significant p=0.001. Table II

Table I: Age and Parity of Study Subjects (N= 100)

		Group		Total
		Group A	Group B	
N		50	50	100
Age years)	≤ 25.00	19 (38.0%)	17 (34.0%)	36 (36.0%)
	26.00 - 35.00	21 (42.0%)	26 (52.0%)	47 (47.0%)
	≥36.00	10 (20.0%)	7 (14.0%)	17 (17.0%)
Mean age (years)		29.9 ± 6.51	28.7 ± 5.13	29.3 ± 5.9
Parity				
Primiparous		38 (76.0%)	35 (70.0%)	73 (73.0%)
Multiparous		12 (24.0%)	15 (30.0%)	27 (27.0%)
BMI		28.12 ± 4.45	28.72 ± 4.73	28.42 ± 4.59

Table II: Blood Loss in Both the Groups (N=100)

	Group		p-value
	A	B	
Blood loss (ml)	576.60 ± 91.59	836.60 ± 91.59	0.000

Discussion

Results of our study show that patients in Group A, who received tranexamic acid, their mean blood loss was 576.6ml± 91.59SD compared to 836.6ml±91.59SD group B patients who didn't receive prophylactic tranexamic acid. This value coincides with the 30% reduction in hemorrhage reported by Ahmed & associates in Ismaila Egypt.[3] Another trial conducted in 160 women showed that total blood loss in tranexamic acid recipient group was much less when compared to control group.[8] In another study conducted on 100 females, mean blood loss was significantly lower in study group as compared to control group. The difference was significant with p value <0.057.[9] Finding of these studies are consistent with our study with significant reduction in blood loss in tranexamic acid group.

Shah p et. al., in his study took 160 pregnant women who underwent caesarean delivery and were given one gram of Tranexamic acid intravenously. Measurement of blood loss was done during and after the procedure. Women with tranexamic acid showed less blood loss than placebo group with statistically significant difference was found between pre-operative and post-operative hemoglobin levels in Tranexamic acid group than in the control group. Hence tranexamic acid usage in preoperative period decreases blood loss after operative procedure. These findings are consistent with the findings of our study. In a developing country like ours where postpartum hemorrhage is a major threat to the life of the mothers, it seems to be a promising option.[10]

Study conducted by Magann et al in their results reported that 6.7% of caesarean deliveries have postpartum hemorrhage with complication rate of 4.8 %.[11] Jaiparkash in his research gave 1 Gram tranexamic acid before caesarean delivery. Mean blood loss during and after surgery along with side effects were compared with decrease blood loss in study group as compared to control group with no adverse events. It concluded that it is a cheap and easily available drug that leads to significant reduction in blood loss and is suitable in low resource settings[12]All these are in consistent with our study findings.

Meta analysis of 18 randomized control trials was done to study the role of tranexamic acid in decreasing hemorrhage in caesarean delivery. Outcome was compared in women who received intravenous tranexamic acid to prevent hemorrhage after caesarean with placebo group women. The Tranexamic acid group had a 60% decline in risk of postpartum hemorrhage, RR 0.40: 95% CI. There was 68% reduction in women getting risk of severe postpartum hemorrhage (which defined as greater than 1000 ml blood loss) with RR, 0.32; 95% CI & decline in rate of transfusion to 70% with RR, 0.30; 95% CI. No safety concerns were observed about

usage of the antifibrinolytic agent from the 18 RCTs analyzed.[4] All of it is consistent with our study results. Mean blood loss in our study was closer to the research conducted by the Gungorduck et al but higher than research conducted by Gai et al, Gohel et al, Shekavat et al. But in all studies, tranexamic acid use in women statistically decreases the hemorrhage in caesarean delivery and this finding grossly matches with our study.[21-14,15] All of it are in consistent with our study results.

Different studies conducted on incidence of postpartum hemorrhage and role of tranexamic acid in decreasing hemorrhage after caesarean delivery. In research conducted by Gai et al postpartum hemorrhage incidence was much lower in study group when compared to control with a p value of less than 0.05. There was no statistical distinction in postpartum hemorrhage incidence from completion of Caesarean to two hours postpartum between two groups. Research carried out by Gohel et al revealed notable decline of more than 500ml hemorrhage in study group when compared to control in caesarean delivery.[15]

In the study conducted by Joshua M et al, randomized control trial research was done on both surgically & vaginaly delivered women regarding effectiveness of tranexamic acid in preventing postpartum hemorrhage. It revealed that use of tranexamic acid led to decline in post-partum hemorrhage in all cases.[16] These findings are consistent with our study.

Viswanathano and colleagues concluded that direct relation exists between tranexamic acid & decrease in postpartum blood loss. A multicenter randomized double-blind placebo-controlled trial included 4000 women & compared the effect of tranexamic acid in a dose of 1Gram two min after normal vaginal & after prophylactic administration of oxytocin and in all these studies results showed that tranexamic acid has a promising role in decreasing hemorrhage in postpartum hemorrhage. [17, 18] All these studies' results findings are in consistent with finding of our study.

Sentilhes L et al in his research showed biological effect of using tranexamic acid prophylaxis in cesarean with resulting decline in hemorrhage among women who received tranexamic acid compared to group who received placebo.[18]In double blinded randomized controlled trials, not only significant decline in blood loss(Amount of intraoperative blood loss was significantly less in the tranexamic group 2232 ± 1204 ml compared to the placebo group 3405 ± 1193 ml with p value 0.002) with use of tranexamic acid was shown but also significantly less frequency of hemorrhage, decline in need for uterotonic agents, reduced need for hysterectomy, reduced risk of severe anemia and less need for blood transfusion was also shown. [3,19-21]

There are several limitations to our study. It is underpowered in detecting adverse outcomes of this agent and identifying specific risk factors for PPH in certain patients. It was not powered to detect potentially meaningful differences in the risk of severe maternal complications. In addition to this, maternal satisfaction on day 2, psychological status at 2 months, quality of life and mother–infant relationship were not explored. Further studies are required to validate the role of TXA in women at high risk of PPH.

Conclusion

The blood loss is significantly reduced in women undergoing elective lower segment caesarean section by administering pre-operative prophylactic tranexamic acid. So Tranexamic acid can be used as prophylaxis before caesarean section for decreasing blood loss during surgery.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Role of Zinc Supplementation in Preterm Neonates with Sepsis

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ABSTRACT

Objective: Objective of the study was to assess the role of zinc in addition to antibiotics in reducing mortality & morbidity in preterm neonatal sepsis.

Study Design: Prospective randomized controlled trial.

Place and Duration of Study: Neonatal unit of Department of Pediatric Medicine, Jinnah hospital Lahore. The study duration was 10 months, from 1st January 2021 to 31st October 2021.

Materials and Methods: We enrolled 260preterm babies who had clinical findings of sepsis and positive blood investigations fulfilling the preset criteria. The intervention group was given zinc sulfate monohydrate at a dose 2mg/kg/day orally 2 times a day for 10 days with empirical antibiotics while the control group received empirical antibiotic treatment (Ampicillin & Amikacin) only without addition of zinc. Blood samples were withdrawn for laboratory investigations like complete blood count, CRP & blood culture & sensitivity from the two groups at days 0, 2, 5 & 10 of start of intervention. We compared both groups with the help of a predefined sepsis score including both clinical and laboratory data. Percentages were calculated to measure the outcomes in both groups to show the difference of CRP level and mortality. Demographic variables including weight in kilograms and age of gestation in weeks were mentioned in mean ± SD (standard deviation).

Results: Only 34% of blood cultures were organism positive, including Staphylococcus aureus, E.coli, Klebsiella Acinetobacter, Streptococcus, Pseudomonas and Candida. CRP levels before start of zinc therapy were comparable in both groups; while at day 5 and day 10 of zinc therapy, there was a relative decline in blood CRP level in intervention group. Mortality was 19% in the group with zinc addition as compared to the other group(25%) with no zinc supplementation.

Conclusion: Zinc supplementation along with antibiotics decreases morbidity (septic shock, seizures, organ dysfunction, metabolic acidosis, respiratory distress/apnea, feeding issues) and mortality in preterm babies with neonatal sepsis.

Key Words: *Infections, Low-Birth Weight, Newborns, Prematurity, Zinc.*

Introduction

Sepsis in newborns is defined as a systemic inflammatory response with clinical features of infection happening in the initial 4 weeks of life. Neonatal sepsis usually presents as fulminant infection without focus (septicemia). It may become localized to involve joint(arthritis) or meninges (meningitis), lungs (Pneumonia), urinary tract (UTI) gut (enteritis), and skin (cellulitis).[1] Sepsis of neonates is very dangerous and diverse condition. Pathogenic organisms and certain host factors i.e., age of gestation, maternal factors like anemia, infection, and environmental factors also worsen the sepsis of newborns.[2] Newborn infants are more prone to bacterial infection because of their weaker immunity; and preterm babies, therefore, are even more susceptible.[3]

Sepsis is a major cause of neonatal mortality in the world. According to World Health Organization neonatal sepsis adds a huge health burden in poor socioeconomic states.[4]

Preterm neonates have poor zinc stores in their body as compared to the full-term newborns because fetuses acquire around 60%of their total body zinc during the last trimester of pregnancy. Preterm infants are also deficient in zinc because of their poor intake, immature digestion and absorption and extra body losses as compared to term babies.[5]

Certain micronutrients like zinc play an important role in modifying immune reactions, therefore their

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deficiency can increase susceptibility to infection. Low zinc levels may disturb immunity by contributing to atrophy of lymphoid tissue, poor hypersensitivity reaction of skin, decreased activation of human B and T lymphocytic population and impaired chemotaxis of monocytes and nutrophills.[6]

In one study, neonates with sepsis were given zinc with routine antibiotic regimens. The results showed marked reduction in the levels of hematological markers of septicemia including inflammatory cytokines and serum calprotectin levels.[7] It is previously known from available data that zinc supplementation has been found to cause decreased chances of infections especially diarrhea, pneumonia, and skin diseases. Zinc as a supplementation therapy can also be used in neonatal sepsis.[8]Another study revealed that preterm neonates suffering from late onset sepsis showed improved clinical and laboratory findings when zinc was added to their regular treatment of sepsis.[9]

Advanced technology is being focused on specific immunometabolism of early human life and identifying the factors that might influence the susceptibility and risk of infection. In this context, certain metabolic agents such as zinc are currently being evaluated both as a prophylactic agent & as treatment for neonatal sepsis.[6]

Materials and Methods

It was a prospective clinical study. Written informed consent was taken from parents and guardians. We enrolled 260 preterm babies less than 37 weeks of gestation, with the diagnosis of sepsis taking predefined clinical and laboratory parameters. Diagnosis of sepsis was made according to these parameters shown in **Table-I.**

Any preterm baby fulfilling clinical and laboratory criteria with score> 4 was considered septic. Sepsis scoring was done upon admission & reassessed on day2,day5, and day10 of starting the treatment. Permission to conduct the study was obtained from the institutional Ethical Review Board (Letter attached).

All neonates with gross structural congenital anomalies, gastrointestinal bleeding, hypoxic ischemic encephalopathy, intracranial hemorrhage, respiratory distress syndrome & inborn errors of metabolism were excluded.

Table I: Clinical Criteria for Neonatal Sepsis

Clinical criteria for neonatal sepsis	Score>4 =positive sepsis
• General: pallor, petechiae, bruises or jaundice	1
• Cardiovascular system: tachycardia or bradycardia,	1
• Poor perfusion, or shock	1
• Variability in temperature (hypothermia or hyperthermia)	1
• Respiratory system: moaning, grunting, intercostals/subcostal retractions, apnea, or cyanosis.	1
• Central Nervous system:	1
• Hypotonia, hypertonia, lethargy, irritability or seizure, bulging/ tense anterior fontanelle.	1
• Gastrointestinal system: abdominal distension, hepatosplenomegaly	1
Laboratory Criteria for Neonatal Sepsis	
• White blood cells (WBC) count<5000/uL or>20,000/uL	1
• Absolute neutrophil count <1500 • Platelet (PLT) count<150,000/uL	1 1
• CRP >5mg/dl.	1
• Positive blood culture	1

Enrolled neonates were divided into 2 groups. Group 1 was named Intervention group (n=130) and group 2 as control group (n=130). Patients were enrolled in the Neonatal Intensive Care Unit of Jinnah hospital Lahore from January 2021 to October 2021. After written informed consent from parents/guardians, we started with detailed history of baby and mother, then a precise clinical examination was performed by residents and senior registrars and documented as daily vitals, anthropometry, and systemic assessment. Both groups had laboratory examinations in the form of Complete blood count (CBC) including (leukocyte and Platelet count),C reactive protein (CRP) and blood cultures before starting treatment. C-reactive protein (CRP) was measured quantitatively and a level >5 mg/ml was considered positive.

In group 1,neonates with sepsis were given zinc as 2 mg/kg /day twice daily of zinc sulfate monohydrate suspension per oral for 10 days in addition to

antibiotics as per the routine protocol, i.e., ampicillin, cefotaxime, and amikacin. In group 2, neonates with sepsis were not administered zinc but only received antibiotics. Zinc was given orally or through the orogastric or nasogastric tube by staff nurse on duty daily for the set time. Data was analyzed using the statistical software SPSS version 21. Results were obtained in the form of percentages and standard deviations.

Results

Total 260 preterm neonates were kept in this clinical trial.130 in group 1(intervention group) and 130 in group 2(control group).After data collection and analysis, we found no difference between the two groups in their gestational age (weeks),sex, weight in (kg), and mode of delivery.(Table II)

Table II: Comparison of Demographic Variables Among the 2 Groups (n= 260)

Variable	Control Group N (%)	Intervention Group N (%)
Sex:		
Male(n)	62 (47.7%)	59 (45.3%)
Female(n)	68 (53.3%)	71 (54.6%)
Birth weight(kg) mean ± SD	1.91 ± 0.74	1.87± 0.93
Mode of delivery:		
C-section(n)	48 (37%)	51 (39%)
NVD(n)	82 (63%)	79 (60.7%)
Gestational age Mean ± SD	33.5 ±2.43weeks	32.6 ±4.67 weeks

The initial CRP levels were comparable in both groups. Whereas, after administration of zinc therapy, there was quite a significant difference noted in the results of CRP levels on day 2, day 5 and day 10 of zinc therapy. A rapid decline of levels of CRP was noted in the Group 1 who received zinc sulfate with antibiotic regimen than the other group with antibiotics only.(**Table-III**)

Mortality was also compared in both groups, which was relatively higher in the babies who did not receive zinc supplements (25%) than the sample of babies with addition of zinc as intervention(19%). (**Table-III**).

Among all 260 blood samples drawn for culture and sensitivity, only 38% were organism positive, while 72% blood culture reports showed no growth. Most isolated organisms among positive culture reports were Staphylococcus aureus, E coli, Streptococci, Klebsiella, Acinetobacter, Pseudomonas and Candida.

Table III: CRP level & Mortality Rate in the two Groups

Variable		Control group Mean ± SD	Intervention group Mean ± SD
CRP *(mg/dl)*	Before	23±10.23	29.3±8.7
	At day 2	17.8±14.6	21.5±9.9
	At day 5	10.7±4.5	13.2±5.8
	At day 10	4.3±1.3	2.5±1.7
Mortality: *n (%)*		32 (25%)	23 (19%)

Discussion

Our study indicated that supplementing zinc (oral zinc sulfate monohydrate 2mg per kg per day) for 10 days markedly improved the rate of recovery from sepsis in most of the neonates recruited in the intervention group(n=130).

Among total 260 of babies, intervention was performed in 45%males and %54% female babies in comparison to 47.7% males and 53.3% females in control group.so there was no significant difference in sex distribution of two groups. Similarly, the mode of delivery in neonates in control and invention groups was comparable as SVD born babies were 63% and 60% in control and intervention groups respectively.

Mean CRP levels at the commencement of intervention were quite high in both groups. But the serial measurements of CRP in both groups at intervals imply significant decrease in the morbidity in terms of low CRP values and less mortality due to neonatal sepsis, i.e 25% and 19% in control vs intervention group respectively.

On day 1, mean CRP in control group was 23+-10.3 and in intervention group was 29.3+-8.7,which were found to fall at mean of 2.5+-1.7 in group I and 4.3+- 1.3 in group II at the 10th day of treatment with zinc supplementation. The rate of fall of CRP levels in infants with Zinc supplementation was 93% as compared to 82 % in the control group.

In other studies, supporting our findings, Chopani R et al, in 2021 used zinc sulfate in neonates with sepsis and found better outcomes of Neonatal sepsis in the form of weight gain, less need of total parenteral nutrition and better feed tolerance[18]. Our results were also in accordance with those of Banupriya et al. in an RCT 2018, who found a comparative low death rate and a higher mental quotient, among

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neonates supplemented with zinc compared to the babies without Zinc[7]. Premature babies have weak immune system, poor feeding abilities and hypoglycemia due to low glycogen store so have high risk of neonatal infections.[14] Laura G et al revealed that there is particular micronutrients found to be deficient and ultimately increasing the chances of infections in neonates. We can reduce the burden of neonatal sepsis and its treatment cost if these cheaper micronutrients can be replaced in newborns.[17]

In a trial by Ali SM et al, zinc was recommended as an adjunct therapy for septic neonates because it drastically decreased the time of recovery as the mean clinical recovery time in zinc group was 104.20 ± 16.61 hours and that of placebo group it was 111.46 ± 19.43 hours ,which was in favor of our results.[16]

In consistent with our findings, Heba GA et al, in a randomized controlled trial demonstrated a decrease in morbidity and mortality when extra doses of Zinc were administered to premature babies admitted in neonatal ICU.[21]

However, Kefle et al concluded that there was need to shift on higher order antibiotics and average length of hospital stay was also same even with addition of Zinc[19].Same was the conclusion by Mehta et al's RCT, which also confirmed no statistical significance for zinc supplementation in reducing death rate in septicemic neonates.[11]

According to Irfan O et al, A significant reduction in neonatal mortality rate with Zinc in neonatal sepsis was recoded as in our study. However, no significant effect was noted on length of hospital stay for septic infants.[20]

This huge variability in clinical, pathological, and statistical significance implies that further large-scale trials should be performed to reach a firm conclusion. There is a need to enhance the generalizability and validity of the recommendation for addition of zinc sulfate as adjuvant therapy in the management of neonatal sepsis.

Limitations:

In our study, the outcome was measured in terms of CRP only & other reliable acute phase reactants were not entertained. Compliance was poor because of the enteral route of zinc administration especially in cases with GERD, emesis after the dose was given, and gastrointestinal bleed. Neonates were not prescreened for an underlying zinc deficiency before the start of treatment. Other factors in deteriorating or improving sepsis in neonates were not entertained. Also, babies with early and late onset sepsis were not separately evaluated.

Conclusion

Oral zinc therapy as a supplement to antibiotics is beneficial in improving infection and decreasing mortality in preterm neonates with sepsis.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Comparison of Perioperative Outcomes : Conventional Milligan Morgan Hemorrhoidectomy Versus Ligasure Assisted Hemorrhoidectomy

Adil Shafi[1], Mumtaz Ahmad Khan[2], Salman Habib Abbasi[3], Saira Mahmood[4], Muneeb Ullah[5], Muhammad Faisal Murad[6]

ABSTRACT

Objective: Outcomes based comparison between Milligan Morgan hemorrhoidectomy and ligasure assisted hemorrhoidectomy.

Study Design: Experimental Interventional.

Place and Duration of Study: Surgery department of Holy Family Hospital between December 2021 and May 2022. Duration of study is six months.

Materials and Methods: After informed consent, 44 patients were enrolled and equally divided in two groups. Sample size was calculated in context to another local study. The Group A underwent ligasure assisted hemorrhoidectomy while Group B underwent conventional Milligan Morgan hemorrhoidectomy. Comparison between the groups was done for operative time, postoperative pain, analgesia requirement and duration of hospital stay. Data analysis was done using Statistical Package for Social Sciences (SPSS) version 23.

Results: Patients had mean age of 36.56 ± 11.9 years with male dominance 31 (70.5%). Group A had lesser operative time in minutes when compared to Group B (11.64 ± 1.94 vs 19.55 ± 2.28, p<0.001). Postoperative pain calculated using numeric rating scale was less severe in Group A versus Group B at 12 hours (4.55±1.26 vs 6.91±0.87, p<0.001) and at 24 hours (3.00±1.07 vs 4.41±1.05, p<0.001). 90.5 % patients were discharged in 12 hours in Group A while only 4.5% were discharged in 12 hours in Group B. Overall hospital stay was more in Group B (p<0.001).

Conclusion: Hemorrhoidectomy using ligasure for pedicle coagulation is better than Milligan Morgan hemorrhoidectomy in terms of operative time, postoperative pain and duration of hospital stay.

Key Words: *Hemorrhoidectomy, Ligasure, Milligan Morgan, Operative time, Pain.*

Introduction

Hemorrhoids are enlarged anal cushions that are filled with blood vessels and need subsequent management.[1,2] They can either be external, internal or mixed based on origin from dentate line.[2,3] Internal hemorrhoids are classified into four grades based on reducibility and prolapse.[4,5] Intense pain, excessive bleeding, perianal soiling, prolapse and hematoma formation are among the common reasons why patients seek treatment.[3,6] Contributing factors to hemorrhoids include obesity, lifting heavy weights, prolong sitting and straining, pregnancy, constipation and low fiber diet.[7] Hemorrhoidectomy is conventionally performed by Milligan Morgan technique in which pedicle is ligated at the base and the distal part is then excised out.[8] In ligasure assisted hemorrhoidectomy, ligasure is used to seal mucosal edges and divide the pedicle.[9] Postoperative pain varies with the type of procedure performed. Usually, anal canal remains painful for two to four weeks. If this postoperative pain can be reduced, patient can be mobilized early and quicker rehabilitation can be achieved.[10] A meta-analysis shows that ligasure assisted technique leads to less postoperative pain, decreased length of hospital stays and more patient comfort. Again, the operative time is markedly reduced by ligasure method as the procedure is relatively robust.[9] Rationale of this study was to ascertain if ligasure assisted hemorrhoidectomy is superior to conventional Milligan Morgan hemorrhoidectomy in terms of surgical operative time, postoperative pain and duration of hospital stay.

Materials and Methods

This experimental interventional research was carried out in surgery department at Holy Family Hospital, Rawalpindi after ethical review board

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approval (Reference No. M-26/63/RMU). Study duration was six months from Dec 2021 to May 2022. After fulfilling the selection criteria and written informed consent 44 patients were enrolled. Sample size was calculated using a local reference study.[11] The sample size calculated was 44 patients (22 in each group). Patients above 18 years with American Society of Anesthesiologists (ASA) I or II and grade III or IV hemorrhoids were included. Exclusion criteria included those with ASA III or more, Grade I or Grade II hemorrhoids, obstetrical patients, morbidly obese, those unfit for spinal anesthesia or those having thrombosed hemorrhoids. Anesthesia evaluation was done one day prior to surgery and standard fasting of six hours to solids and 2 hours to clear fluids was applied. Patients were divided by simple random sampling method in to two equal groups; Group A (Ligasure assisted haemorrhoidectomy) and Group B (Milligan Morgan haemorrhoidectomy). On the day of surgery, all patients were given kleen enema in morning. During surgery hemorrhoidal bundles were identified and followed by either conventional ligation or vessel sealing by ligasure. Paraffin gauze was left inside the anal canal and removed postoperatively at six hours. All surgeries were performed by either one of the two specified consultants. Duration of surgery in minutes was noted by principal author. To assess pain the patients were asked to rate the pain using numeric pain rating scale (NRS) of 0 to 10 at 12 hours and 24 hours postoperatively. Collected data included age, gender, ASA group, operative time, postoperative pain, and duration of hospital stay. Mean and standard deviation was calculated for quantitative variables such as age, numeric pain rating score, hospital stay and operative time. Categorical data like gender, ASA group and required analgesia were documented in frequency and percentages. Analysis of the collected data was done using Statistical Package for Social Sciences (SPSS) version 23. An Independent t-test was used for comparing numeric data and Chi square test was used for comparing categorical data, between the two groups. 95% confidence level was taken for all statistical tests in the study. P value of less than 0.05 was considered statistically significant.

Results

The mean age of the patients was 36.70 ± 11.82 years with 31 (70.5%) males ranging from 19 years to 65 years. Demographic details with respective groups and p values are given in Table I.

Table I: Description of Demographic Variables in Group A and Group B

Variable		Total	Ligasure (Group A)	Conventional (Group B)	P-value
		Mean ± SD / Count (%)	Mean ± SD / Count (%)	Mean ± SD / Count (%)	
Age		36.70 ± 11.82	35.36 ± 12.61	37.81 ± 11.33	0.508*
Gender	Male	31 (70.5%)	16 (72.7%)	15 (68.2%)	0.500**
	Female	13 (29.5%)	6 (27.3%)	7 (31.8%)	
ASA	I	40 (90.9%)	20 (90.9%)	20 (90.9%)	0.697**
	II	4 (9.1%)	2 (9.1%)	2 (9.1%)	

*Independent t test ** Chi-square
ASA – America Society of Anesthesiologists

Group A had less operative time, lesser pain score at 12 hours and 24 hours and shorter length of hospital stays in hours as compared to Group B. These results were found to be statistically significant (p value < 0.05). Comparative details between Group A and Group B outcome variables are detailed in table II.

Table II: Comparison of Outcome Variables in Group A and Group B

Variable		Group A	Group B	P-value
		Mean ± SD / Count (%)	Mean ± SD / Count (%)	
Operative time in Minutes		11.64 ± 1.94	19.55 ± 2.28	<0.001*
Hospital Stay	Daycare (12 hours)	20 (90.9%)	1 (4.5%)	<0.000**
	1 Day (24 hours)	2 (9.1%)	19 (86.4%)	
	2 Days (48 hours)	0 (0.0%)	2 (9.1%)	
Pain at 12 hours (NRS)		4.55 ± 1.26	6.91 ± 0.87	<0.001*
Severity at 12 hours	Mild	8 (36.4%)	0 (0.0%)	<0.001**
	Moderate	14 (63.6%)	7 (31.8%)	
	Severe	0 (0.0%)	15 (68.2%)	
Pain at 24 hours (NRS)		3.00 ± 1.07	4.41 ± 1.05	<0.001*
Severity at 24 hours	Mild	17 (77.3%)	2 (9.1%)	<0.001**
	Moderate	5 (22.7%)	19 (86.4%)	
	Severe	0 (0.0%)	1 (4.5%)	
Inj Paracetamol requirement		1.68 ± 0.56	3.55 ± 1.60	0.007*
Inj Ketorolac requirement		0.13 ± 0.35	1.45 ± 1.22	0.004*

*Independent T test ** Chi-square

Discussion

Mean age in our study was comparable to a study done in Iraq.[12] 70.5% patients were male in our study and this male predominance was also seen in local

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and international studies.[13,14] This may be because male gender is more predisposed to physical exertion, that contributes to hemorrhoids. Many techniques have been employed for hemorrhoidectomy in context to improving postoperative outcomes and decreasing complications, but none is found to be superior over the other.[15] Therefore, modification of surgical approach has become an area of focus for surgeons especially with development of novel technologies such as ligasure, harmonic scalpel, thunderbeat etc.[16] Ligasure assisted hemorrhoidectomy is a relatively new technique, though relatively expensive, but it is found to have reduced operative time and postoperative complications.[17,18] The operative time in our research was less in the ligasure assisted hemorrhoidectomy group when compared with traditional Milligan Morgan group by 8 minutes (p value < 0.001). A comparative study conducted in Iran also reported that operative time was lesser in ligasure hemorrhoidectomy compared to Milligan Morgan group (p value < 0.001).[17] The Egyptian study reported operative time similar to our study which was less in ligasure group.[18] A study carried out by Peker et al, reported that ligasure group had lesser operative time as well as quicker return to work in these patients.[19] An Italian study have also reported shorter operative time with use of energy devices.[20,21] Significant number of patients were discharged on the same day in ligasure assisted hemorrhoidectomy group in comparison to traditional Milligan Morgan group (p value <0.001) comparable to a study conducted in Baluchistan.[22] Pain after surgery and its severity was also much less in ligasure assisted hemorrhoidectomy group at both 12 hours (p value < 0.001) and 24 hours (p value < 0.001). This was also seen in study done at Karachi.[23] This correlates with the analgesia requirement that was less in ligasure group (p value for paracetamol = 0.007 and p value for ketorolac = 0.004). International data also reports lesser need for analgesia on 1st postoperative day and 2nd postoperative day with ligasure appraoch.[17] Similarly a Pakistani study reported lesser postoperative pain as well as reduced analgesia requirement with ligasure technique as compared to conventional method.[1,24]

Limitations of Study

This study did not address short- and long-term complications of the procedure as well as the time taken by the patients to get to normal life. Use of ligasure adds cost burden to the patient and remains a hurdle in cost effective management of hemorrhoids, especially in developing country like ours.

Recommendations

Future research prospects should also compare long-term outcomes with added variables like experience of performing surgeon, comorbid conditions, cost effectiveness and complications.

Conclusion

Hemorrhoidectomy using ligasure for pedicle coagulation is better than Milligan Morgan hemorrhoidectomy in terms of operative time, postoperative pain and duration of hospital stay.

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DISSERTATION/THESIS BASED ARTICLE An article based on dissertation/thesis submitted as part of the requirement for a postgraduate degree (M. Phil, FCPS, MS) can be sent for publication after it has been approved by the institution's ethical review board/committee and the college/university evaluation committee/board. The data should not be more than five years old. Thesis/dissertation-based articles will be assessed by proper review process. Once accepted for publication, disclosure will be made that 'it is a Dissertation based article.'

GENERAL ARCHIVAL INSTRUCTIONS

The manuscript should be typed in MS Word. Each manuscript should include a title page (containing email address, cell numbers, institution, and postal address of the corresponding author), abstract, key words, text, acknowledgements (if any), references, tables (each table, complete with title and footnotes) and legends for illustrations and photographs. Each component should begin on a new page. Sub-headings should not be used in any section of the script except in the abstract.

TEXT ORGANIZATION

All manuscripts except Short Communication and Letter to the Editor should be divided into the following sections.

ABSTRACT

Abstracts of original article should be in structured with following sub-headings:

- Objective
- Study Design
- Place & Duration of Study
- Materials & Methods
- Results
- Conclusion

Four elements should be addressed: "why did you start?", "what did you do?", "what did you find?" and "what does it mean? “.” Why did you start?" is addressed in the objective. "What did you do?" constitutes the methodology and could include design, setting, patients or other participants, interventions, and outcome measures. "What did you find?" is the 'results', and "what does it mean?" would constitute the conclusions. Please label each section clearly with the appropriate sub-headings. Structured abstract for an original article, should not be more than 250 words. At least 3 key words should be written at the end of the abstract. Review articles, case reports and others require a short, unstructured abstract. Commentaries do not require an abstract.

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Write this section with references as per following instructions:

1. Give background information about the subject matter and the issues your study intends to address. Only strictly pertinent references should be cited, and the subject should not be extensively reviewed.
2. Describe what is known (in the literature) and what is not clear about the subject with reference to relevant literature thus identifying the literature gap.
3. You write the rationale (justification) of your study.
4. Finally, you mention the objective of your study

MATERIALS AND METHODS

Methodology is written in past tense.

Follow this sequence **without headings:**

- Study design
- Place and Duration of Study
- Sample size
- Sampling technique
- Mention about permission of the ethical review board and other ethical issues addressed.
- Inclusion and Exclusion Criteria
- Data collection procedure-
- Type of data: parametric or nonparametric
- Data analysis: including Statistical Software used, and statistical test applied for the

calculation of p value and to determine the statistical significance. Exact p-values and 95% confidence interval (CI) limits must be mentioned instead of only stating greater or less than level of significance. All percentages must be accompanied with actual numbers.

RESULTS

These should be presented in logical sequence in the text, tables, and illustrations. All the data in the tables or illustrations should not be repeated in the text; only important observations should be emphasized or summarized. No opinion should be given in this portion of the text.

DISCUSSION

This section should include the author's comments on the results. Write in present tense, active voice except for results, which are written in past tense. It should be written in following sequence:

- First, very briefly summarize, Interpret and discuss main results and don't merely repeat the results.
- Discuss key studies relevant to your study.
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- Suggest future work if necessary.

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Conclusion should be provided under a separate heading. It should be in congruence with the objective. No recommendations are needed under this heading.

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Tables and illustrations should be merged within the text of the paper, maximum number of tables and illustrations should not exceed four, and legends to illustrations should be typed on the same sheet. Tables should be simple and should supplement rather than duplicate information in the text; tables repeating information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 ½" x 11' paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If abbreviations are used, they should be explained in footnotes and when they first appear in text. When graphs, scattergrams, or histograms are submitted, the numerical data on which they are based should be supplied. All graphs should be made with MS Excel and be sent as a separate Excel file even if merged in the manuscript. For scanned photographs the highest resolution should be used.

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- Cover Letter

- JIIMC Checklist
- JIIMC Conflict of Interest Performa
- JIIMC CopyRight and Undertaking Agreement
- IRC Certificate
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Template of these files is available in the download section.

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CORRIGENDUM

In the article titled **"Utility of iRat as a Tool to Identify Low Academic Performers in 1st Year MBBS with High Scores in Pre-Medical Examination,"** published in the June 2023 edition of the Journal of Islamic International Medical College(JIIMC) **VOL. 18, no. 2**, there is a correction to be made in the authorship.

The name of the sixth author is corrected as follows:

From: Madiha Imran to Madiha Ali

The corrected authorship should now read as follows:

Sana Malik, Atteaya Zaman, Saima Saleem, Saima Mumtaz Khatak, Anbreen Aziz, Madiha Ali

Sincerely,

JIIMC