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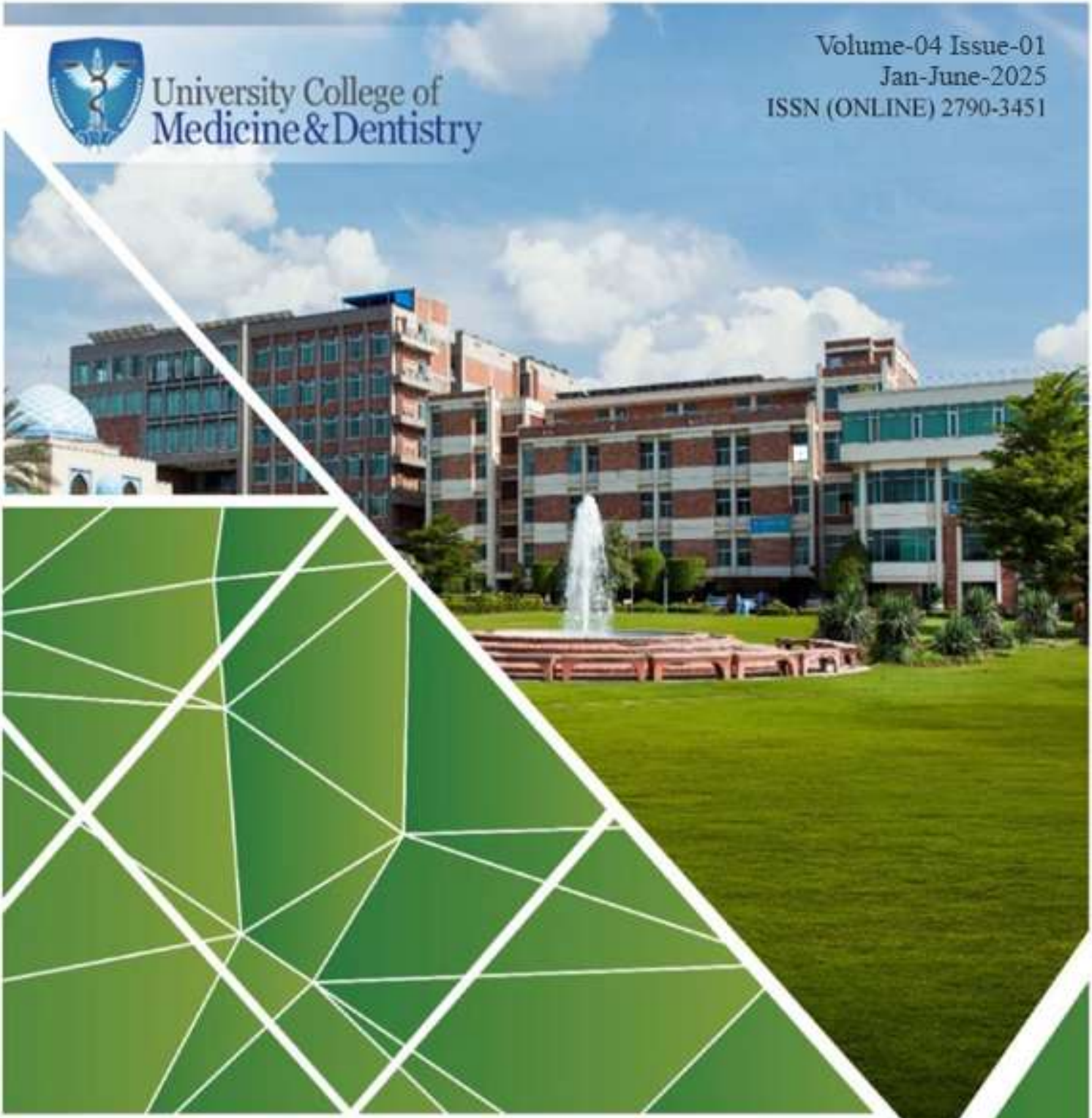

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Editorial

The Rise of Cosmetic Gynaecological Surgeries in Pakistan: Ethical and Cultural Considerations

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As a clinical professor at Michigan State University and chairman of the Department of Obstetrics and Gynaecology at Hurley Medical Center, I have had the opportunity to visit Pakistan frequently. During these visits, I speak at various medical colleges and hospitals, and interact with patients and gynaecologists through my network. Addressing the issue of cosmetic gynaecological surgeries in Pakistan is both a privilege and a responsibility. My training with top Hollywood surgeons has provided me with a clear understanding of how these surgeries involve medical ethics, cultural beliefs, and the evolving healthcare system.

The appeal of cosmetic gynaecological surgeries is driven by societal pressures, personal desires for self-expression, and global beauty standards.[1] As these procedures become more popular, it is important to evaluate their impact on the Pakistani healthcare system. Many women pursue these surgeries to enhance their self-esteem, improve sexual gratification, or gain social acceptance. However, these motivations often conflict with traditional values of femininity and modesty in Pakistan, presenting unique challenges.[2] Additionally, the lack of regulation in the field is a significant concern. Many surgeries are performed in unregulated clinics, which can lead to risks such as infections, scarring, and psychological distress. Therefore, it is essential for healthcare providers to ensure that these surgeries are conducted in accredited facilities by qualified practitioners. Pre-operative counselling is also crucial to ensure that patients fully understand the risks and realistic outcomes of their procedures.

The medical community in Pakistan plays a crucial role in how people view cosmetic gynaecological surgeries. Healthcare providers need to follow well-researched methods and maintain high ethical standards. They should also promote clear and honest communication about these procedures. Ongoing education for medical professionals, creating guidelines for ethical practices, and studying how these surgeries affect people's mental and emotional well-being are important. Additionally, working with community leaders and influencers can help address cultural attitudes towards women's health and body image. While cosmetic procedures are important, they should not overshadow comprehensive gynaecological care, including education on reproductive health, family planning, and preventive services.[3] Empowering women with knowledge about their bodies and health choices is crucial for a well-informed patient population.In conclusion, the rise of cosmetic gynaecological surgeries in Pakistan presents both opportunities and challenges. Healthcare professionals, policymakers, and society must engage in an open and respectful dialogue about these practices. By prioritizing patient safety, ethical standards, and cultural sensitivity, we can help women make informed decisions about their bodies while safeguarding their health and well-being. Let us work together to create a healthcare environment that respects the individuality of every woman, recognizing that true empowerment lies in the values we uphold.

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Original Article

Efficacy of Concentrated Growth Factor with Autograft and Xenograft in Mandible Fractures: A Randomized Clinical Trial

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Abstract

Objective: To evaluate the efficacy of adjuvant therapy with Concentrated Growth Factor (CGF) along with xenograft and autograft in mandible fractures, in terms of bone density gain and healing over the period of 6 months.

Methodology: This was a Randomized Clinical Trial conducted at a public sector tertiary care hospital in Karachi from May 2019 to July 2022. It included patients with mandible fractures requiring bone grafts due to non-union, delayed union, or malunion. The patients were divided into three groups, each consisting of 20 patients. Group A underwent mandibular surgery using autograft alone, Group B received autograft combined with CGF, and Group C received xenograft combined with CGF. The participants were monitored using serial cone-beam computed tomography at the 4th and 6th months post-operatively to evaluate bone healing and bone density. By the end of the study, all cone-beam CT scans were evaluated for bone density.

Results: The results showed a significant increase in bone bulk formation across all three groups between the 4th and 6th month, highlighting the effectiveness of all treatment modalities ($p < 0.001$). However, intergroup comparison revealed that bone density was comparatively higher in groups B and C, where CGF was used as an adjuvant, than in group A. However, the mean difference in bone density over the 6 months period was similar for Group A (-229.2) and Group B (-227.7), while Group C showed a slightly greater mean difference of -237.9

Conclusion: CGF is equally effective with both autograft and xenograft. However, using CGF with xenograft is preferable, as it helps avoid donor site morbidity and reduces patient inconvenience associated with autograft harvesting.

Keywords: Concentrated Growth Factor, xenograft, autograft, Cone Beam Computed Tomography, mandible

Introduction

Road traffic accidents remain the major cause of maxillofacial injuries worldwide, while trauma, assault, and sports causality are also amongst reasons behind fracture of mandible. Any change in mandible orientation due to fracture may cause occlusal discrepancies and difficulty or inability of jaw opening and closing.[1,2] Malunion or nonunion are factors that make healing and restoration of normal functions and esthetics difficult resulting in a defect in fracture line. To reconstruct bony defects, many strategies are taken under consideration. However, indication of reconstruction of a defect is possible if the defect is >5mm but <5cm. [3,4]

Fractured bone healing phenomenon is a complex biological course that involves regeneration and changes in gene expression.[5] It heals by two mechanisms, direct intramembranous and indirect that involves callous formation.[6] Several techniques have been presented to enhance bone healing and tissue regeneration, Platelets are known to stimulate tissue regeneration by releasing several growth factors.[7] The first generation of platelet concentrates consists of Platelet-rich plasma (PRP) and Platelet Rich Growth Factors (PRGF). They stimulate fibrin polymerization with the help of chemical additives such as anticoagulants and thrombin or calcium chloride.[8] The second generation of platelet concentrates, consisting of Platelet-rich fibrin (PRF) and concentrated growth factors (CGF) that are scientifically proven modality for angiogenesis, collagen synthesis and accelerated healing and regeneration.[9] However, platelets drive growth factors are safer to use since they utilize the patient's venous blood to extract platelet concentrates.[10] CGF is used to fill extraction sockets and fill the cavity after cystectomy. CGF has proved to exhibit superior potential in sinus lift procedures and ridge augmentation surgeries. In procedures involving implants, CGF provides membrane support to promote osteointegration.[11]

The defects of mandible fracture should be addressed primarily to provide the patient with dental rehabilitation. The bone healing process depends on the technique acquired to fill the bone defect for early regeneration of bone. CGF is a platelet-derived substance that is believed to have a positive impact on tissue regeneration, angiogenesis, and bone healing. The study evaluated its efficacy of healing by using it as an adjuvant with two other bone graft materials that are xenograft and autograft and to compare it with autograft which is known as a gold standard for to restore the mandible fracture bone defects. The main objective of this study was to compare bone apposition capacity of CGF while using it with bone graft substitutes, that is CGF with autograft, CGF with xenograft and autograft alone over the period of 6 months in mandibular fracture defects.

Methodology

It was a Randomized Clinical Trial conducted at Dow University of Health Sciences and associated hospitals. Simple random sampling technique was used for recruited participants as the criteria for inclusion in any one of the allocated groups. Study population was mostly males since RTA and fractures are more commonly reported in males whilst few females were also reported, however, almost all of the females refused to participate in the study, hence only one female who voluntarily agreed to participate was included. Consent, both written and verbal, was taken from the participants.

The participants were then well informed about the entire procedure and its outcome, both unfavorable and favorable. Once the patient agreed to the terms, the consent was documented with the participant's initials. The next steps after preliminary inclusion were taking detailed systemic history and documenting it over Proforma. The pre-operative radiographs and simultaneous clinical features were then used to assess the type of fracture. The envelop method was utilized for randomization, where 60 envelopes were devised, out of which three groups were made with 20 subjects in each group. However, every subject was asked to pick the envelope and was allocated to their respective group.

Trial registration and ethical approval DUHS (Dow University of Health Sciences) provided the ethical approval for the study and the reference number for ethical approval is IRB-1835/Approval/2020. The study took around 3 years to complete from May 2019 to July 2022. The research protocol was registered with the Protocol Registration and Results System at ClinicalTrials.gov Identifier: NCT05480631 https://clinicaltrials.gov/ct2/show/NCT05 480631. Dates of recruitment and follow-up can be found there as well.

It included patients with mandible fractures requiring bone grafts due to non-union, delayed union, or mal-union. The patients were divided into three groups, each consisting of 20 patients. Group A underwent mandibular surgery using autograft alone, Group B received autograft combined with CGF, and Group C received xenograft combined with CGF. The subjects considered for inclusion were participants aged 18-40 irrespective of gender, while mandible fractures, either symphysis, body or para symphysis having fracture gap size ranging from >5mm to <5cm were included. Subjects with bone disorders, and medically compromised conditions were excluded along with anyone undergoing radio/chemo therapy.

Data Collection Procedure

The participants were allocated to their respective group via envelope method. The fracture assessment was done by detailed history examination and evaluation of radiograph to be categorized into either mal-union, delayed union and/or non-union fracture. The preparation of CGF was done following standardized guidelines, [12] an automated centrifuge machine was used to dispense the CGF.

The surgical procedures started off with taking all the necessary aseptic measures and under general anesthesia, the adequate exposure for better access was done and the exposed part was scrubbed gently. The oral cavity was then scrubbed with pyodine, and the intra-oral assessment was done to plan the incision. Local anesthesia was then injected that contained adrenaline 1:200,000 & xylocaine 2% and incision was made in buccal and/or labial vestibule and full-thickness flap was reflected to get sufficient visibility and access to the fracture site. Necessary measures were taken to avoid insulting mental nerve, and simultaneously bleeding was managed and controlled via cautery, suction and gauze packs to get visibility of fractured bone segments.

Fracture segments were then made devoid of granulation tissue and the defect was assessed for reconstruction. Fracture parts were held close to anatomic position to achieve pre-existing occlusion as accurately as possible. The fracture was secured with mini-plates and desired modality was introduced either autograft which was derived from intra-oral site utilizing grid type cortical bone harvesting from ascending ramus to avoid bone marrow invasion used alone to fill the gap, CGF with xenograft (bovine) or CGF with autograft. The soft tissue was then placed over the bone and secured in placed with the help of resorbable suture that was vicryl 3.0.

Post-Operative Bone Density Assessment Using Cone-Beam CT Scans

All patients underwent post-operative cone-beam CT (CBCT) scans at the 4th and 6th months. A radiology specialist analyzed the grey levels on CBCT to evaluate and record Bone Mineral Density (BMD) from the region of interest, located occlusal to the fracture site. Bone Mineral Density was quantified using Planmeca Romexis 6 software. By the end of the study, all cone-beam CT scans were evaluated for bone density.

Results

Demographic Data

Out of the 64 selected subjects, 20 were assigned to each of the three groups, with 4 patients missing their follow-up visits. The male-to-female ratio was skewed, with only one female participant, indicating that the majority of fracture cases reported between 2020 and 2022 were in adult males. Regarding socioeconomic status and occupation, most participants were either employed or self-employed, while 13 were unemployed.

Clinical Characteristics

Clinical characteristics that were examined as an integral part of the study were fracture site, causes of trauma and the size of the defect. Symphysis fractures were the most frequently encountered ones among all accounting for 60% cases in group A, 50% in group B and 50% in group C. Para symphysis fracture were second most occurring fractures making up 25% of group A cases, 30% of group B and 30% of group C. Body fracture was least found fracture making up to 15% in group A, 20% in group B, and 20% in group C. From the concerning causes of fracture, the most frequent cause was RTA followed by assault and abuse which were the least observed causes of fracture, making up only 1% of all the participants (Table 1)

Table 1: Clinical characteristics of fracture

Clinical Characteristics	A N = 20 (%)	B N = 20 (%)	C N = 20 (%)
Site of fracture			
Body of the mandible	3 (15.0)	4 (20.0)	4 (20.0)
Parasymphysis of the mandible	5 (25.0)	6 (30.0)	6 (30.0)
Symphysis of the mandible	12 (60.0)	10 (50.0)	10 (50.0)
Cause of fracture			
Accident	14 (70.0)	15 (75.0)	13 (65.0)
Fall	3 (15.0)	2 (10.0)	4 (20.0)
Sports injury	2 (10.0)	3 (15.0)	2 (10.0)
Abuse/assault	1 (5.0)	0 (0.0)	1 (5.0)
Defect Size (mm) , Mean ± SD	6.2 ± 1.10	6.3 ± 1.21	5.9 ± 0.74

Comparing bone density within group (Intra-Group Comparison)

Bone density was compared across all three groups between the 4th and 6th months to evaluate whether it increased over time with each individual modality. Groups A, B, and C all demonstrated a significant increase in bone density during this period, with a corresponding p-value of <0.001. However, the mean difference in bone density was similar for Group A (-229.2) and Group B (-227.7), while Group C showed a slightly greater mean difference of -237.9 Hounsfield Units (HU) (Table 2).

Table 2: Comparison of Mean Bone Density at 4th and 6th Months and the Mean Difference Across Groups A, B, and C

Clinical Characteristics	A N = 20	B N = 20	C N = 20
Mean ± SD			
4th	807.8 ± 69.75	1024.7 ± 172.3	1032.8 ± 187.8
6th	1037 ± 150.2	1252.4 ± 194.8	1270.7 ± 193.1
Mean difference (p-value¥)			
6th to 4th Month	-229.2 (<0.001)	-227.7 (<0.001)	-237.9 (<0.001)

Inter-Group Comparison of Acquired Bone Density in Hounsfield Units (HU)

When the inter-group comparison of group A, B and C was done it was revealed that the mean difference between group A and B and group A and C was significant corresponding to p-value <0.001 whilst on comparing group B and C the mean difference was not significant showing close differences that cannot be categorized as significant (Table 3).

Table 3: Inter-group comparison of group A, B and C of acquired bone density.

Months	B vs. A	C vs. A	C vs. B
Mean difference (p-value¥)			
4th	-216 (<0.001)	225 (<0.001)	-8.05 (0.868)
6th	-215.4 (<0.001)	233.7 (<0.001)	18.3 (0.750)

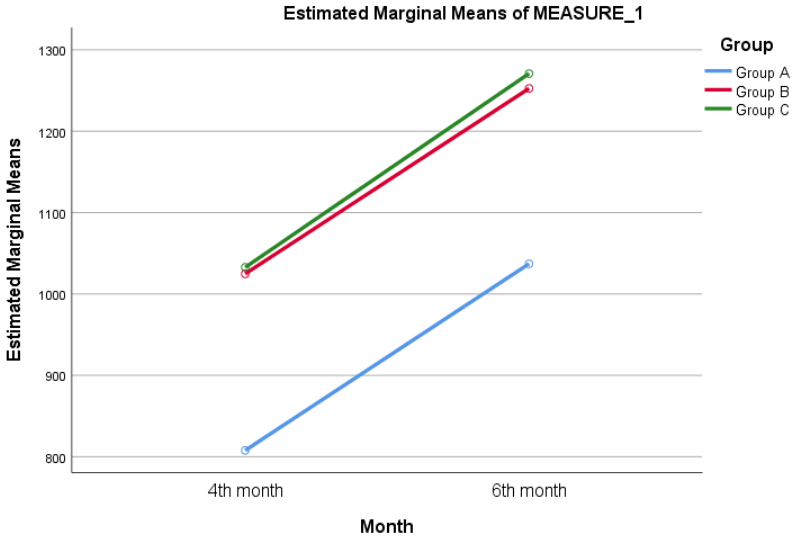

Figure 1. Inter-group comparison of group A, B and C

The results were consistent with another published study in regards of acquiring bone density; however, the pain at donor site was managed via acetaminophen with combination of diclofenac sodium. 3 patients reported with lingering donor site post-operative pain that took three weeks to subside. Thirteen patients reported with post-operative infection which expressed itself via redness, swelling but no draining sinus were formed. Post-operative infections were managed with 1g amoxicillin and 400mg of metronidazole. By the end of the study there were no long-term side effects found in all three modalities.

Discussion

This randomized clinical trial assessed the effectiveness of CGF combined with autograft and xenograft in treating mandibular fractures by measuring bone density improvements and comparing results across the three groups. Over the six-month period, all groups demonstrated significant increases in bone density, with noTable differences observed between the groups.

In terms of demographics, the majority of participants were employed or self-employed, with a smaller portion being unemployed, representing a diverse socioeconomic background. The analysis revealed a predominance of male participants, with only one female participant, aligning with global trends that show mandible fractures are more prevalent in adult males.

Clinically, the mandibular symphysis was the most frequent fracture site across all groups, consistent with the region's anatomical vulnerability. Road traffic accidents (RTAs) were identified as the leading cause of fractures, supporting previous research highlighting RTAs as a major contributor to maxillofacial trauma. Other causes, such as falls and sports injuries, were observed but less common (Table 1).

An intra-group comparison between the fourth and sixth months showed a significant increase in bone density across all three groups ($p < 0.001$), demonstrating the effectiveness of each treatment in promoting bone regeneration. While the differences were modest, Group C (CGF with xenograft) exhibited the largest mean increase in bone density (-237.9 HU), suggesting slightly superior outcomes compared to Groups A and B (Table 2). These findings align with earlier studies emphasizing the osteogenic potential of CGF when combined with grafting materials.

The therapies' effectiveness was further confirmed through inter-group comparisons. Significant differences were observed between Groups A and B, as well as Groups A and C ($p < 0.001$), indicating that combining CGF with either autograft or xenograft leads to greater bone density improvements compared to CGF alone. However, the comparison between Group B (CGF with autograft) and Group C (CGF with xenograft) revealed no statistically significant differences, suggesting similar outcomes for both combinations (Table 3, Figure 1.). These findings highlight the clinical feasibility of xenografts as a viable alternative to autografts, particularly in cases where donor site morbidity is a concern. Furthermore, the results support the use of CGF for critical-sized bone defects to promote effective healing and regeneration. Consensus also provides us with data that supports its use along with other bone graft such as auto-graft, allograft and xenografts.[12, 13] However, the outcomes of this study are aligned with most of the studies that employed similar modality. The use of CBCT also aids i n assessing the bone mineral density in 3 dimensions to generate more accurate and reproducible results. A study conducted by Emad et al, (2012) incorporates the use of PRP within the fracture line and compares the results with that of control group, and the post-operative 3rd and 6th month evaluation over CBCT shows significant difference in cases in terms of elevated BMD in HU.[14,15] CBCT; it is a recent advancement in observing the 3-dimensional aspect of the subject with fewer radiation doses[16.] .Its application to assess the bone density of the maxillofacial region is sufficiently advocated through many studies, especially implant dentistry, orthodontics, and oral surgery.[17]

Xenogeneic bone substitutes have shown better outcomes when used in complicated mandibular fractures, Ekaterina et al. 2022 conducted an experimental study where an angle fracture was complicated with follicular cyst, the pre-operative assessment shows the custic dimension around 2cm. The case was managed with collagenous xenogeneic graft that fills the cystic cavity. Post-operative evaluation was done via plain radiographs; this process enables effective rehabilitation and bone regeneration.[18] The study also advocates the utilization of xenogeneic substitutes in complicated mandibular fractures; however, the current study evaluates its effectiveness of xenogeneic substitutes along with autologous platelets extracts to be assessed on bone mineral deposition levels.

Another clinical trial conducted by Dongdong et al. (2020) in mandible bone defects were assessed over the period of 12 weeks whilst using combination of bone particulates with healing adjuvants. Upon consecutive post-operative visits, it was observed that serum osteocalcin and serum alkaline phosphatase significantly indicated higher bone mineral deposition in subjects where platelet derived growth factor were combined with bone particulates [19].These findings are concordant with the above-mentioned research.[20]

An animal study was conducted by Yilmaz et al. (2018) on rabbits to evaluate the efficacy of CGF to induce proliferation, angiogenesis and healing of bone defects.[21] In this experiment, an intentional fracture at radius diaphysis creating a bone defect of 15mm was made following Masquelet technique, leaving 3mm of sound bone on the edges.[21] The defect was then treated in controls with Masquelet technique alone and in cases the Masquelet technique along with CGF was done. Histopathology and immunohistochemistry analyses revealed that groups treated with CGF exhibited a higher ratio of stem cells, more sTable angiogenesis and vascularization, and the formation of a thicker membrane.[21,22,23] In contrast, bone healing in our study was assessed using CBCT to measure the density of mineral deposition in three dimensions within the region of interest.

An update by Jaime et al. (2017) recommends the use of adjuvant modalities in combination with autogenous bone grafts for managing fractures in atrophic mandibles.[24] The current research also intends to propose the most effective method to reconstruct fracture defects with substitutes with lesser side effects and are accepTable for the recipient. Similarly, Nivedhitha et al, (2019) incorporates CGF after treating the peri-apical lesion with apicectomy and subsequent retrograde filling, the lesion was then filled with CGF squeezed to form membrane. The assessment of the lesion was done via Cone-beam CT pre-operatively and

post-operatively which dictates that the healing and bone deposition was sufficiently good in all 3 dimensions when treated alone with CGF. This research provides evidence for utilizing CBCT as a newer technology to assess bone healing both pre- and post-operatively.[25]

Limitations

Considering the limitations, the results cannot be applicable to larger bone defects that are more than 10mm in greatest dimension. If implant placement is indicted, different evaluations pertaining to bone deposition in Bucco-lingual dimension need to be evaluated. The results are limited to the assessment of bone mineral density in numeric form.

Conclusion

Bone mineral density in the region of interest increased in all three groups when assessed from the 4th to the 6th month post-operatively, demonstrating that all modalities used in the study promote bone density and accelerate healing over time. However, intergroup comparisons revealed higher bone density in groups B and C compared to group A, with similar results observed between groups B and C. This suggests that the combination of xenograft and CGF can effectively support bone healing. Therefore, xenograft with CGF may serve as a viable alternative to autograft, eliminating the need for harvesting autograft and reducing donor site morbidity.

Recommendations

Bone defects reconstruction can be done with either of the available graft and adding CGF can provide speedy healing and bone apposition. Critical size bone defects can easily be treated with CGF mixed with bone power that not only enhances the outcomes but also provide scaffolding effect to the graft. CGF can also be used alone as a membrane in various periodontal procedures. Combining CGF with powdered bone has the same efficacy as of autograft which was thought to be the gold standard for reconstruction. Thus this technique might help in reducing donor site morbidity and creating a second surgical site. Further studies can be conducted that also includes serum levels of osteocalcin and BAP (Bone Alkaline Phosphatases) where CBCT is not inducted or available to assess the healing process efficiency.The future studies can also be done in similar manner by using histomorphometric analysis procedures to avoid the undue exposure to cone beam tomographic rays as done in previous studies.

Authors' Contributions: AHS: Conceptualization, methodology, supervision; TA: Data curation, formal analysis; AR: Investigation, writing—original draft; HFK: Visualization, project administration; AH: Writing—review and editing.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Original Article

One-Year Follow-Up of Morbidity and Mortality in Mechanical Valve Replacement Patients at a Newly Established Cardiac Center in a Developing Country

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Abstract

Objective: To examine the morbidity and mortality rates associated with mechanical heart valve replacement in patients from a developing country at a 1-year follow-up.

Methodology: This retrospective observational study was conducted on the patients who presented with Aortic Valve Replacement (AVR), Mitral Valve Replacement (MVR) and Dual Valve Replacement (DVR), at the Cardiac Surgery Department of Peshawar Institute of Cardiology (PIC). The data of 258 patients who underwent these cardiac procedures was collected between a period of two years i.e., from Jan 2021 till Dec 2022 from the hospital records.

Results: Out of 258 patients, 37 (14.3%) were readmitted within one year of surgery due to complications such as pericardial effusion, pleural effusion, bleeding, endocarditis, hemorrhagic stroke, and stuck valve. The in-hospital mortality rate following the procedure was 2.7%, while the 1-year post-discharge mortality rate was 10.3%, with 14 cases (51.86%) attributed to warfarin-related complications. Within the first year after discharge, the average number of INR (International Normalized Ratio) tests conducted was 8.34 ± 8.268, and the average number of consultations for INR management was 2.53 ± 3.715.

Conclusion: Warfarin-related complications are a major contributor to mortality and morbidity in patients with mechanical heart valves in developing countries. To address this, newly established cardiac centers in the developing world should adopt innovative strategies, such as establishing dedicated warfarin clinics, promoting the use of self-testing devices, and developing remote cardiac care centers to reduce these complications.

Keywords: Cardiac valve replacement, Mitral valve replacement, Aortic valve replacement, Warfarin.

Introduction

The cardiac valve replacement has advanced significantly over the past 50 years and many changes have been made to the material and design of mechanical prosthesis to improve their thrombogenicity, hemodynamic profile and durability, but inspite of this, bleeding events continue to occur and account for 75% of all the complications.[1] Despite of the fact that bio-prosthesis do not require anticoagulant drugs after replacement, their short lifespan means that they are mainly suiTable for older population.[2] Over 100,000 valve replacements are done annually in the United States and 80-90% of these replacements use bio-prosthesis.[1] This strategy was implemented to reduce anticoagulation-related complications, particularly in the elderly population.[3] But rheumatic heart diseases is more common in underdeveloped countries therefore mechanical valve is a choice of prosthesis for younger patients having rheumatic desease.[4] This makes them more prone to develop warfarin related complication like bleeding and thromboembolism.[2]

The prevalence of rheumatic heart disease is 5.7 per 1000 in Pakistan which shows it is very common in developing world.[5] This condition places huge burden of aortic and mitral diseases in young population therefore forcing surgeons to choose mechanical valve rather than tissue valve. Mechanical valves are often chosen in low- and middle-income countries (LMICs) due to their durability, making them a suiTable option for younger patients needing long-term solutions.

Over time, they prove cost-effective by reducing the need for repeat procedures, which is particularly important in regions with limited medical facilities and surgical expertise. Although lifelong anticoagulation is required, warfarin remains widely available and affordable in LMICs.[3] A study reported overall 5-year and 10-year survival rates of 91.8 ± 1.4% and 84.5 ± 2.3%, respectively, in patients who underwent mechanical valve replacement, with freedom from bleeding and thromboembolic complications at 96.2 ± 1.0% and 91.5 ± 2.4% in an Asian population.[6]

Another study identified thromboembolic events and bleeding as the primary causes of mortality and morbidity.[7] Similar findings were observed in a comparable population, where survival rates following mechanical valve replacement were 95.5% at 30 days, 93.2% at 3 months, 87.5% at 1 year, and 82.9% at both 5 and 10 years.[8] There is limited data available on long term follow of these patients undergone mechanical valve replacement in developing world.[4] Our primary objective

was to find out mortality and morbidity rates associated with mechanical valve replacement within 1 year of the procedure, among patients in newly established cardiac center in Peshawar, Pakistan. The secondary objective was to explore different strategies to reduce complications associated with mechanical heart valves in patients from developing countries.

Methodology

This retrospective observational study was conducted from Jan 2021 to Dec 2022. Ethical approval was obtained from the Institutional Review Board (IRB) of Peshawar Institute of Cardiology (PIC) (IRC/24/81). The patients presented for Aortic Valve Replacement (AVR), Mitral Valve Replacement (MVR) and Double Valve Replacement (DVR=AVR+MVR) at the Cardiac Surgery Department of Peshawar Institute of Cardiology (PIC). In addition to that, follow up was conducted on the patients who completed their 1-year follow-up. The inclusion criteria for patients were those who underwent valvular heart surgeries, including AVR, MVR, and DVR, at the same center (PIC) over a two-year period. Patients aged 18 years and above who completed a 1-year follow-up were included.

The exclusion criteria were patients who underwent additional cardiac surgeries alongside valve surgery. The data was collected from Electronic Medical Records (EMR) and Health Management Information System (HMIS). The phone numbers of patients were extracted from the electronic medical records (EMR). Data analysis was performed using Statistical Package of Social Sciences (SPSS) version 23.

Mean ± standard deviation was calculated for variables including age, BMI, Valve size, INR at discharge, number of INR (International normalized ratio) done after discharge in one year, number of INR done after discharge in one year, number consultation for INR management in one year and INR during re-admission.

The overall percentages of male and female patients, operation status, types of valve surgeries and the comorbidities including hypertension, diabetes mellitus, smoking, previous stroke history, chronic renal insufficiency, chronic lung diseases, congestive heart failure and atrial fibrillation was calculated. The occurrence of The New York Heart Association (NYHA) classes was also assessed.

The percentage of the readmitted patients was calculated. Additionally, frequency of different causes of readmission was also analyzed. Similarly, the percentages of the valve related mortalities were also evaluated. Furthermore, the frequency of different valve types used in this study was also determined. To analyze the association of risk factors with post-operative complications, Chi Square test was applied and considered significant at $p<0.05$.

Follow up patients

Further analysis was focused on the follow up patients in which the percentage of mortality was determined. The reasons behind valve related mortality were then further analyzed focusing on the different valve procedures i.e., AVR, DVR and MVR.

Results

258 patients underwent valve replacement during the study duration. All the patients were included in the final analysis. Out of 258 patients, 50.8% were female and 49.2% were male. The Table 1 showed the baseline and clinical characteristics of mechanical valve replacement patients. The mean age of patients was 40.50 years with ±14.137 (Table 1).

Of these patients, 8.9% were operated on emergency bases while 91.1% were operated electively. The surgical procedures performed during the time period were AVR 32.5%, DVR 20.9% and MVR 46.5%. Hypertension was 15.1%, diabetes mellitus and atrial fibrillation were 3.5%, and smoking 3.1% as shown in Table 1. The New York Heart Association (NYHA) class II was reported in 40.7% and class III was in 54.7% patients respectively (Table 1).

Out of these, 37 patients (14.3%) were re-admitted due to various reasons i.e., Pericardial effusion, Pleural effusion, Bleeding, Endocarditis, Hemorrhagic stroke, Stuck valve and Pseudoaneurysm as shown in Figure 1. Using the chi-square test, we checked for the association of risk factors with patients' re-admission and valve related mortality (VRM). Chronic renal insufficiency showed significant association ($P<0.05$) with valve related mortality. Other risk factors, like, hypertension, diabetes mellitus, previous stroke, chronic lung disease, congestive heart failure, atrial fibrillation, peripheral artery disease, chronic liver disease and smoking did not show any strong association with valve related mortality and re-admission.

During this study, SJM mechanical heart valves were implanted in 208 patients, Carbomedics in 36, Medtronic in 11 patients respectively.

Follow up

One-year telephonic follow-up was conducted. Patients were asked about their number of INR done after discharge in one year and number of consultations for the INR management in one year as shown in Table 3. During this one year follow up period, the mortality rate was 10.3% (Table 4). The causes of mortality were bleeding in 7 (2.71%), stuck valve in 2 (0.77%), hemorrhagic strokes in 5 (1.93%), pseudoaneurysm in 2 (0.77%) and unknown reason of deaths were occurred in 11 (4.26%) patients (Table 3).

Mechanical heart valve replacement remains a crucial intervention for patients in developing countries; however, it is associated with significant morbidity and mortality, particularly within the first year. In this study, 14.3% of patients were readmitted due to complications such as pericardial effusion, pleural effusion, bleeding, endocarditis, hemorrhagic stroke, and stuck valves.

The in-hospital mortality rate was 2.7%, while the 1-year post-discharge mortality rate reached 10.3%, with over half of these deaths linked to warfarin-related complications. Limited monitoring, reflected by an average of 8.34 INR tests and 2.53 consultations for INR management within a year, highlights the challenges in anticoagulation management. These findings emphasize the need for innovative approaches, including dedicated warfarin clinics, self-testing devices, and remote cardiac care, to improve outcomes in resource-limited settings.

Table 1: Baseline Characteristics of Patients (n=258)

Characteristics	Mean ± SD	N (%)
Age	40.58 ± 14.137	
BMI	24.1840 ± 5.07281	
Valve size	31.24 ± 10.827	
INR at discharge	1.941 ± 0.9731	
Gender		
Male		127 (49.2)
Female		131 (50.8)
Operation status		
Elective		235 (91.1)
Emergency		23 (8.9)
Valve surgery		
AVR		84 (32.5)
DVR (AVR+MVR)		54 (20.9)
MVR		120 (46.5)
Comorbidities		
Hypertension		39 (15.1)
Diabetes mellitus		9 (3.5)
Previous stroke		5 (1.9)
Chronic renal insufficiency		1 (0.4)
Chronic lung diseases		1 (0.4)
Congestive heart failure		2 (0.8)
Atrial fibrillation		9 (3.5)
Smoking		8 (3.1)
NYHA class		
Class-I		1 (0.4)
Class-II		105 (40.7)
Class-III		141 (54.7)
Class-IV		11 (4.3)

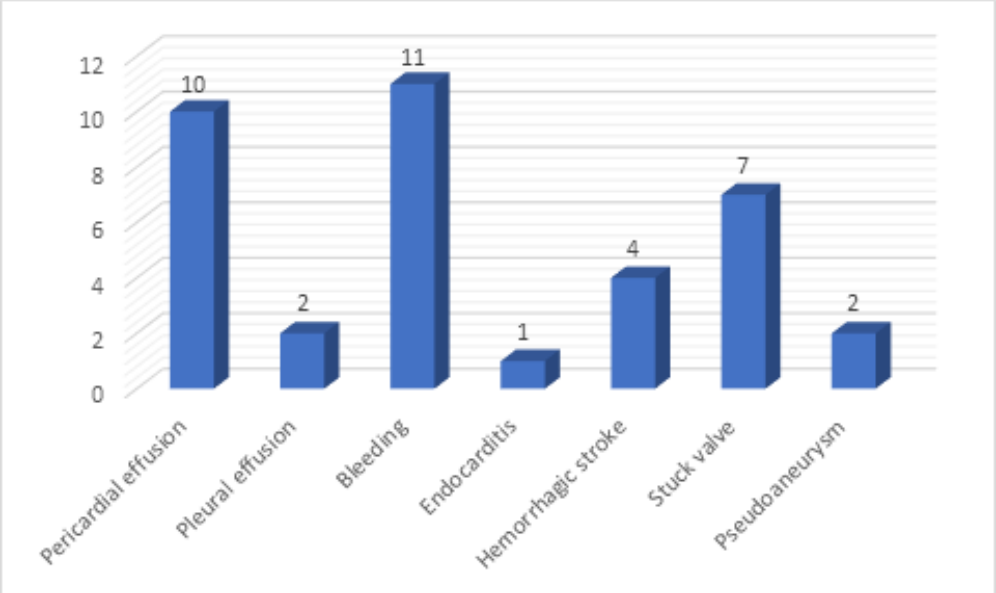

Figure 1: Shows the number of causes of re-admission.

Table 2: Association of risk factors with Readmission and valve related mortality (n=258).

Variables	Hypertension	Diabetes mellitus	Previous stroke	Chronic renal insufficiency	Chronic lung disease	Congestive heart disease	Atrial fibrillation	Smoking
Re-admission	0.430	0.211	0.356	0.682	0.682	0.561	0.778	0.382
Valve related mortality	0.272	0.852	0.649	0.010	0.695	0.580	0.069	0.263

INR checking and number of consultations done at 1 year	
Characteristic	Mean ±SD
No. of INR done after discharge in one year	8.34±8.268
No. of consultation for INR management in one year	2.53±3.715
In-hospital and one-year follow-up mortality	
Mortality	n (%)
In-hospital	7 (2.7)
One year follow up	27 (10.3)

Table 3: Post-operative one year mortality causes and type of surgical procedure.

Mortality Causes	Total mortality, n (%)	AVR only	DVR (AVR+MVR)	MVR only	Warfarin related mortality N (%)
Bleeding	7 (2.71)	3	1	3	
Stuck valve	2 (0.77)	0	1	1	14 (51.86)
Hemorrhagic stroke	5 (1.93)	1	2	2	
Pseudoaneurysm	2 (0.77)	1	0	1	
Unknown reason	11 (4.26)	4	3	4	

Discussion

In last decade there is good advancements in improving quality of mechanical valves in terms of hemodynamic performance and thrombogenicity. But still because of lack of anticoagulation management facilities and poor socioeconomic conditions makes the use of mechanical valve in these population controversial.[9] The selection of mechanical valve prostheses in our study was influenced by several factors, with the primary one being the relatively young age of our population. Younger patients typically need valve that offers long-term durability, and mechanical valves are preferred in this case due to their extended lifespan, which reduces the need for future replacements or surgeries. Second, decision to use mechanical valves may be justified by the limited financial resources as the cost associated with Redo operation after bio-prosthesis would been unaffordable. In developing world valvular diseases are mainly in rheumatic origin showing higher incidence among young patients.[10] In older patients or those requiring long-term valve replacement, bioprosthetic valves and conservative procedures often face early structural deterioration and repair failure over time.[11,12] Consequently, many cardiac surgeons view mechanical valve replacement as a preferable alternative, despite the potential risk of complications, due to its durability and long-term benefits.

As a result, many cardiac surgeons consider mechanical valve replacement a favorable option for many patients, even with the risk of potential complications. Our in-hospital mortality rate, which was 2.7%,(Table 1), was comparable to those from the EACTS and STS databases, which showed that the ranges for AVR and MVR were 4.3% and 6% and 2.9% and 3.7%, respectively.[13,14]. There are limited studies on the long-term follow-up of patients in similar populations; however, one study reported an operative mortality rate of 3.7% in patients who underwent MVR.[15] After a year of follow-up, the mortality rate was 10.3%, which was comparable to many impoverished nations.[16] Among these fatalities, 51.86% were linked to complications associated with warfarin, including bleeding, hemorrhagic stroke, and stuck valve.

In our study, the yearly average number of INR tests was 8.34 ± 8.268, while the average number of consultations conducted per year was 2.53 ± 3.715 (Table 2). The lower

number of consultations compared to the frequency of INR testing may potentially contribute to the higher incidence of warfarin complications. Our group experienced a 14.3% readmission rate, primarily attributed to complications such as pericardial effusion, pleural effusion, bleeding, hemorrhagic stroke, and stuck valve. We believe that these complications can be attributed to the intensity of anticoagulation, inadequate compliance with INR testing, and improper hospital follow-up.

Our data highlight the need to reassess the management strategies for patients on warfarin following mechanical valve replacement in the developing world.[17,18] Introducing changes such as establishing a warfarin clinic with easy phone access, particularly for patients unable to visit from remote areas,[19] introducing safe and effective INR self-testing devices, setting up remote satellite cardiac clinics, and conducting screening campaigns can significantly reduce complications associated with warfarin use.[20,21]

Limitations

Our study has several limitations, including its retrospective design. Additionally, conclusions regarding long-term outcomes, which are essential for this patient population, cannot be drawn due to the small sample size and short follow-up period.

Conclusion

According to our findings, warfarin-related complications significantly contribute to mortality and morbidity among patients with mechanical valves in developing countries. Given this, it's important for new cardiac centers in these regions to adopt more innovative strategies. This may include establishing specialized warfarin clinics, providing INR self-testing devices to patients, implementing remote cardiac clinics, and launching screening campaigns. These initiatives could greatly improve patient outcomes and reduce the burden of warfarin-related complications in this vulnerable population

Authors' Contribution: MT.: Conception and design, data collection, analysis and interpretation, manuscript drafting, critical revision for important intellectual content; AI: Data analysis and interpretation, statistical expertise, manuscript drafting, critical revision for important intellectual content; UUR: Data collection, investigation, manuscript drafting, critical revision for important intellectual content; AQ: Data collection, investigation, manuscript drafting, critical revision for important intellectual content; UQ: Data collection, investigation, manuscript drafting, critical revision for important intellectual content; MW: Data collection, investigation, manuscript drafting, critical revision for important intellectual content.

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Original Article

To Assess the Relationship between Reticulocyte Hemoglobin Content and Iron Status in Hemodialysis-Dependent Patients

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Abstract

Objective: This study aims to evaluate the diagnostic utility of reticulocyte hemoglobin content (RET-He) and its correlation with transferrin saturation (TSAT) and other iron markers for identifying iron deficiency anemia in hemodialysis patients.

Methodology: The study was conducted at Hematology Department of Shaikh Zayed Hospital in Lahore, from March 2022- April 2023. Total 120 patients with chronic kidney disease on hemodialysis were enrolled in this study. Ferritin was determined by chemiluminescence immunoassay. Flow cytometry and spectrophotometry was performed to determine RET-He and iron status including serum iron and Total iron binding capacity (TIBC). Patients of both genders, aged 18-80 and those on hemodialysis for 3 months or more were selected. Patients excluded were those with bleeding from any site in last three months, received oral or parenteral iron supplementation in one month.Results: With 1.5 mg/l as the recommended fluoride level in drinking water, the fluoride concentration ranged from 0.50 to 1.63 mg/l, with a mean of 0.58 ± 0.33 mg/l among individuals with dental fluorosis compared to those without. This difference was statistically significant (p = 0.013). Dental fluorosis was observed in 189 participants (47.3%), of whom 48.8% were male and 39.7% were female.

Results: In this study, 120 hemodialysis dependent chronic kidney disease patients were enrolled. Among them, 65 (54.2%) were males, while 55 (45.8%) were females; 18 years to 80 years was the age range, with 53.48 ± 13.782 years being mean age. Mean RET-He was 29.439 ± 3.51 pg/cell, while mean serum iron was 68.96 ± 38.63 µg/dl, mean TIBC was 224.41 ± 55.109 µg/dl, serum ferritin mean value being 386.91 ± 357.51 ng/ml and mean TSAT was 31.93 ± 18.52%. Sensitivity (Se) was 56.0%, specificity (Sp) was 74.6%, positive predictive value (PPV) 36.8%, negative predictive value (NPV) 86.6% and accuracy of RET-He in diagnosing Iron deficiency anemia was 70.8% respectively.

Conclusion: Reticulocyte hemoglobin content is highly effective in diagnosing iron deficiency anemia in chronic kidney disease patients. Its lower cost compared to traditional markers makes it a valuable tool for clinical practice.

Keywords: Chronic Kidney Disease, Hemodialysis, Iron Deficiency Anemia, Reticulocyte hemoglobin content, Transferrin Saturation.

Introduction

Chronic kidney disease and hemodialysis patients more frequently develop anemia, compromising their normal wellbeing and iron deficiency being the most common cause.[1] Anemia management in hemodialysis (HD) patients can be done with iron status monitoring and by treating iron deficiency.[2] Iron deficiency anemia (IDA) is main hindering factor for response of recombinant human erythropoietin in patients on hemodialysis.[3] Serum ferritin and transferrin saturation (TSAT) are commonly used to judge iron deficiency but they are affected by inflammatory or physiological conditions.[4] Serum ferritin is increased in inflammatory conditions, infectious diseases and in malignancies. TSAT has acute - phase reactivity as transferrin can be increased in inflammation. In chronic disease and nutritional deficiencies, low transferrin level are found due to decreased synthesis.[5]

Various factors lead to high prevalence of anemia in chronic kidney disease. Anemia increase progression of disease and affects survival of chronic kidney disease patients.[6] The importance of anemia avoidance, observance, and treatment in those with chronic kidney disease cannot be overemphasized, as balance must be kept between erythropoiesis stimulation and iron overload among those with chronic kidney disease.[7] In chronic kidney disease, serum erythropoietin is expected to be decreased and is not diagnostically that important. It also doesn't affect the starting dose or dose adjustment of erythropoietin stimulating agents. A low reticulocyte count shows lesser production of red blood cells whereas increased reticulocyte count depicts high destruction of red blood cells or their hemolysis as probable cause.[8] Less production of RBCs is the basic mechanism in anemia of chronic kidney disease, anemia of chronic illness, and in loss of blood.[9] So we should analyze reticulocyte count vigilantly.

Iron deficiency anemia treatment is basic part of chronic kidney disease patient care, and has various advantages like physical activity endurance, better life quality, and lower mortality.[10] Parameters that can directly assess bone marrow iron availability, such as reticulocyte hemoglobin content, have been identified.[11] Hemoglobin in the reticulocyte is assessed by reticulocyte hemoglobin content and it gives idea of iron in bone marrow during erythropoiesis. Reticulocyte hemoglobin is estimated by blood analyzer with software in upgraded

form.[12] Inflammatory conditions don't affect reticulocyte hemoglobin content. It has earlier response to iron treatment and is cost effective.[13] Previous researches indicate we can use reticulocyte hemoglobin content as an alternative test for iron deficiency anemia cases on hemodialysis.[9,10,11] However, there is no local published study on this topic. Owing to lack of local research and the scarcity among existing international literature, current study is performed to study association of reticulocyte hemoglobin with Transferrin Saturation and serum ferritin in those on hemodialysis. These parameters are used to determine iron deficiency anemia. Reticulocyte hemoglobin content is latest parameter, by studying its association with iron status (Transferrin Saturation and Serum Ferritin) we will be able to advise only reticulocyte hemoglobin content to hemodialysis patients. The results of this study will help in better management of such patients in future practices. The aim of the current study is to evaluate the association between RET-He and iron status in hemodialysis patients. To the best of our knowledge, the comprehensive comparison of RET-He with a panel of iron status markers, including serum iron, TIBC, serum ferritin, and calculated TSAT, has not been performed previously.

Methodology

This was a cross-sectional observational study, conducted at Hematology Department of Sheikh Zayed Hospital, Lahore, and its duration was from March 2022 to April 2023. It was approved by Advanced Scientific and Research Board and Ethical Review Committee of University of Health Sciences Lahore, No. UHS/Education/126-20/272. Convenient sampling technique was used to collect samples. The study included patients of both genders with ages 18-80 years and on hemodialysis for three months or more. Patients with significant bleeding from any site in the last three months, including from the gastro intestinal tract caused by uremic environment, concurrent medication or systemic anticoagulation with heparin during dialysis were excluded, those with blood transfusion in last three months, or having inflammatory, infectious disease or any malignancy were excluded from the study. Total 120 patients on regular hemodialysis fulfilling the inclusion criteria were enrolled. Before study, each patient gave informed consent. A sample of 3.5 ml sample was taken in serum separating tube gel vial. Serum ferritin was determined by Chemi luminescence immunoassay while serum iron and Total iron binding capacity was determined by spectrophotometry.

A sample of 3 ml was taken in Ethylene Diamine Tetra acetic Acid and flow cytometry was performed to determine reticulocyte hemoglobin content. Results were analyzed by SPSS v23.0. Quantitative variables like age, hemoglobin, transferrin saturation, serum iron and ferritin were presented as mean and standard deviations. Qualitative variables like gender and iron deficiency anemia were presented as frequency and percentages. Pearson's Correlation was applied to find correlation of reticulocyte hemoglobin content with serum ferritin and transferrin saturation. A 2x2 contingency was generated to calculate sensitivity, specificity, Positive predictive value, Negative predictive value and accuracy.

Data Collection Procedure

Total 120 patients on regular hemodialysis fulfilling the inclusion criteria were enrolled. Before study, each patient gave informed consent. Demographic data was collected by filling out the relevant proforma. Blood samples were taken and RET-He and iron status were measured and their association was made. All the data was collected through a pre designed proforma.

Results

In this study, 120 patients with chronic kidney disease on hemodialysis were enrolled. Among these patients, 65 (54.2%) were males, while 55 (45.8%) were females. Age range in this study was from 18 years to 80 years with mean age of 53.48 ± 13.782 years. Majority of the patients 81(67.5%) had age > 50 years, while 39 (32.5%) patients had age ≤50 years. Among 120 patients, 38 (31.7%) patients showed IDA on RET-He level, while 25(20.8%) showed Iron deficiency anemia on Transferrin saturation level. Mean reticulocyte hemoglobin content was 29.439 ± 3.51 pg, while mean serum iron was 68.96 ± 38.63 µg/dl, mean Total iron binding capacity was 224.41 ± 55.109 µg/dl, mean serum ferritin level was 386.91 ± 357.51 ng/ml and mean TSAT was 31.93 ± 18.52% (Table 1).

There was a positive correlation between Reticulocyte hemoglobin content levels & serum ferritin with Pearson's correlation coefficient of 0.170 with p-value 0.034. Positive correlation was also observed between Reticulocyte hemoglobin content (RET-He) and Transferrin saturation with Pearson's correlation coefficient of 0.302 with p-value 0.001 (Table2). Table 3 shows the comparison of iron deficiency anemia (IDA) detection using RET-He and TSAT, presenting the number of positive and negative cases for each diagnostic method. Table 4 displays the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of RET-He in diagnosing iron deficiency anemia.

Table 1: Comparison of Iron Deficiency Anemia Diagnosis Using RET-He and TSAT Based on Gender and Age

	Gender		Age		Iron deficiency anemia on RET-He		Iron deficiency anemia on TSAT	
Frequency	Male	65	≤ 50 years	39	Yes	38	Yes	25
	Female	55	>50 years	81	No	82	No	95
Percentage	Male	54.2	≤ 50 years	32.5	Yes	31.7	Yes	20.8
	Female	45.8	>50 years	67.5	No	68.3	No	79.2

Table 2: Correlation between RET-He and serum iron and TSAT levels

	Sample size(n)	Correlation coefficient	P-value
Correlation between RET-He level and serum iron level	120	0.170	0.034
Correlation between RET-He and TSAT levels	120	0.302	0.001

Table 3: Identification of iron deficiency anemia on RET-He vs. TSAT

IDA on RET-He	IDA on TSAT		Total
	Positive	Negative	
Yes	14	24	38
No	06	76	82
Total	20	100	120

Table 4: Sensitivity, specificity, PPV, NPV and accuracy of RET-He

Sensitivity	56%
Specificity	74.6%
Positive Predictive Value	36.8%
Negative Predictive Value	93%
Accuracy	70.8%

Discussion

In this study, we explored the usefulness of reticulocyte hemoglobin content as a tool for diagnosing iron deficiency anemia in patients with chronic kidney disease undergoing hemodialysis. Our findings suggest that RET-He is a valuable marker for assessing iron levels, particularly for identifying patients who are not iron deficient, due to its ability to rule out anemia effectively. Compared to conventional markers of iron deficiency, RET-He is simpler, more cost-effective, and provides a real-time reflection of the body's iron status. This highlights its potential to improve the routine management of anemia in hemodialysis patients, offering a practical alternative for clinical practice.

Our findings demonstrated that RET-He had a sensitivity of 56.0%, specificity of 74.6%, positive predictive value (PPV) of 36.8%, and a notably high NPV of 86.6%, with an overall accuracy of 70.8%. While the moderate sensitivity suggests that RET-He may not identify all cases of iron deficiency anemia, its high specificity and NPV indicate that it is particularly reliable in ruling out IDA in this patient population. Additionally, the mean RET-He value (29.44 ± 3.51 pg/cell), when analyzed alongside conventional markers such as mean serum iron (68.96 ± 38.63 µg/dl), total iron-binding capacity (224.41 ± 55.11 µg/dl), serum ferritin (386.91 ± 357.51 ng/ml), and transferrin saturation (31.93 ± 18.52%), provided a comprehensive overview of iron status.

The findings of our study align with previously published research on the role of RET-He in diagnosing IDA among hemodialysis patients. In our cohort of 120 patients, the average age was 53.48 ± 13.78 years, with an age range of 18–80 years. Among these, 38 patients (31.7%) were identified as having IDA based on RET-He (cutoff <28 pg), while 25 patients (20.8%) were diagnosed with IDA using transferrin saturation (TSAT) levels (cutoff <20%) (Figure 1). A positive correlation was observed between RET-He and both serum ferritin and TSAT levels, further validating its role in assessing iron status. The mean values of iron parameters in our study were: RET-He 29.44 ± 3.51 pg, serum iron 68.96 ± 38.6 µg/dL, total iron-binding capacity (TIBC) 224.41 ± 55.11 µg/dL, serum ferritin 386.91 ± 357.51 ng/mL, and TSAT 31.93 ± 18.52%.

Our findings align with those of Sany et al. (2020), who evaluated RET-He in comparison with traditional iron deficiency markers in 50 dialysis patients.[14] Their study reported strong diagnostic performance for RET-He, with an AUC of 0.84 and a cutoff value of 27 pg, yielding a sensitivity of 90.4% and specificity of 80.8%. These results highlight RET-He as a reliable marker for monitoring iron status in hemodialysis patients. Similarly, Dalimunthe (2016) analyzed 72 patients and assessed RET-He's diagnostic ability for iron deficiency using ROC curve analysis. The study reported an AUC of 0.818, a cutoff value of 31.65 pg, and a mean RET-He of 32.96 pg. Using transferrin saturation (cutoff <20%) as a reference, 16 patients (29.6%) were diagnosed with iron deficiency anemia, with RET-He showing a sensitivity of 81.5% and specificity of 61.6%.[15]

Miwa et al. (2010) conducted a study to assess the utility of measuring reticulocyte hemoglobin content (RET-He) in managing iron deficiency among hemodialysis patients.[16]

The study included 217 hemodialysis patients, with RET-He measured using the XE-2100 automated blood cell counter. The mean RET-He value was reported as 32.40 pg. ROC curve analysis revealed an AUC of 0.776, with a cutoff value of 33 pg. The sensitivity and specificity of RET-He for predicting iron deficiency anemia were 74.3% and 64.9%, respectively. Rudiansyah (2020) conducted study in which 181 patients of chronic kidney disease undergoing hemodialysis were selected. Serum iron was correlated to RET-He and transferrin saturation. Mean RET-He was 27 pg and cut off value was 29 pg. Positive correlation of RET-He was found with serum iron (r=0.348, p<0.006) and TSAT(r=0.454, p<0.01).[17]

Elareny (2023) conducted a study involving 200 patients undergoing regular hemodialysis and compared RET-He with traditional markers of iron deficiency.[18] In this study, the mean RET-He was 33.18 pg, serum iron was 84.65 µg/dL, TSAT was 47.53%, and TIBC was 12.76 µg/dL. The area under the curve (AUC) for RET-He was found to be 0.724, with a cut-off value of 31.4 pg. Sensitivity and specificity for RET-He were reported as 71.43% and 71.51%, respectively. These findings are somewhat consistent with those of our study, where RET-He had a moderate ability to predict iron deficiency anemia, with a sensitivity of 56.0% and specificity of 74.6%. The differences in sensitivity between the two studies could be attributed to variations in sample size, patient demographics, or study methodology.

Mehta (2016) conducted a study involving 102 patients and reported significant differences in RET-He levels between two groups: Group A, representing iron depletion, and Group B, reflecting functional iron deficiency.[19] A strong positive correlation was observed between RET-He and serum ferritin levels, highlighting RET-He as a significant predictor of bone marrow iron stores. These findings support the role of RET-He as a reliable marker for diagnosing iron deficiency, consistent with previous studies.

Nassim (2022) reported a significant positive correlation between RET-He and serum ferritin in children with chronic liver disease. The study also demonstrated the diagnostic utility of RET-He in identifying iron deficiency anemia with high sensitivity and specificity.[20] While our study had a lower sensitivity (56.0%) for RET-He, it had a higher specificity (74.6%) (Table 4). The higher sensitivity reported in Nassim's study could reflect differences in patient populations (children with chronic liver disease versus adult hemodialysis patients) and the use of different diagnostic criteria or methods.

Given its lower cost, ease of use, and ability to reflect real-time iron availability compared to traditional markers, RET-He shows significant potential as a practical and efficient tool for the routine diagnosis and management of anemia in hemodialysis patients.

Limitations

It was a single centered study, focusing on a specific patient population, which may not be representative of broader populations. The sample size was relatively small in relation to the larger population affected by iron deficiency anemia. Additionally, other tests such as unsaturated iron binding capacity and soluble transferrin receptors could have been included to enhance the study's scope. As the study was conducted only at Sheikh Zayed Hospital, the findings cannot be generalized to other healthcare settings.

Conclusion

Reticulocyte hemoglobin content is a reliable marker for diagnosing iron deficiency anemia. In the context of the Pakistani population, where iron deficiency is prevalent, it offers a cost-effective and precise method for diagnosing this condition, making it a convenient tool for clinical practice.

Future directions

In the future, we could recommend using reticulocyte hemoglobin content alone to diagnose iron deficiency anemia. This approach would reduce the need for multiple tests, improve the accuracy of identifying iron deficiency, and offer a more cost-effective solution.

Conflict of interest: Authors declare no conflict of interest.

Authors' contribution: SH; Contributed to data collection, flow cytometry and spectrophotometry analysis for determining RET-He and iron status, and the initial drafting of the manuscript; AL; Supervised the data analysis and statistical evaluation of sensitivity, specificity, and accuracy of RET-He in diagnosing iron deficiency anemia. Provided critical revisions to the manuscript for intellectual content; RAS; Assisted in the design and methodology of the study, ensured the validity of laboratory procedures, and contributed to interpreting the findings; MAG; Provided overall supervision and guidance throughout the study. Reviewed and approved the final manuscript for publication.

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Original Article

Histological and Biochemical Alterations Underlying Statin-Associated Pancreatic Toxicity in a Rat Model

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Abstract

Objective: To investigate the histological and biochemical changes in the pancreas associated with simvastatin-induced toxicity using a rat model, focusing specifically on changes in pancreatic weight, vascular congestion, necrosis, fibrosis, and inflammatory markers.

Methodology: A 12-week laboratory-based experimental control trial conducted at the Department of Anatomy of a public sector medical college in Rawalpindi, in collaboration with the National Institute of Health (NIH) Islamabad and Armed Forces Institute of Pathology (AFIP) Rawalpindi from Dec 2021 to Dec 2022. Twenty male Sprague-Dawley rats weighing 250 ± 50 grams, aged 60 ± 5 days were assigned to the control group and another twenty with similar age and weight ranges were assigned to the experimental group. For a duration of 12 weeks, the experimental group was given 60 mg/kg/day of simvastatin orally, whereas the control group was given water and a conventional diet. The following characteristics were measured: body weight, pancreatic weight, biochemical parameters (cytokines, enzymes), and histological alterations (congestion, necrosis, fibrosis). Version 23 of SPSS was used to analyze the data. Qualitative variables were expressed as percentages and frequencies. The statistical significance was defined as $P < 0.05$. Chi-square analyses were used to compare the qualitative factors across the groups.

Results: Compared to controls, the simvastatin group showed significantly increased mean pancreatic weight ($p=0.043$), congestion (55% vs 0%, $p<0.001$), higher levels of CRP ($p<0.030$), IL-6 ($p<0.040$), and TNF-α ($p<0.040$). Trends of mild necrosis (25% vs 5%, $p=0.182$) and interstitial fibrosis (15% vs 0%, $p=0.231$) were observed but not statistically significant.

Conclusion: Simvastatin profoundly impacts pancreatic histomorphology, particularly through increased congestion and inflammatory markers, with potential implications for necrosis and fibrosis development. These findings warrant further investigation into mechanisms of toxicity and close monitoring of patients for pancreatic adverse effects during statin therapy.

Keywords: Simvastatin, pancreatic toxicity, histology, inflammation, congestion, necrosis, fibrosis, cytokines.

Introduction

Statin therapy has revolutionized the dyslipidemia management, however it continues to be a source of concern for its potential side effects.[1] Statins related myopathies are well known and documented, however statin's effect on the pancreas remains unclear.[2] Pancreas controls glucose homeostasis through insulin and glucagon secretion from its endocrine islets. Acinar cells of pancreas provide essential digestive enzymes. Disturbing this intricate balance can have unfavourable consequences for both exocrine and endocrine functions.[3]

There is scarcity of the existing literature suggesting a potential link between statin use and effects on pancreas. Pancreatitis has been attributed to inflammatory reactions, cellular toxicity and accumulation of toxic metabolites.[4] However, this remains unclear as only few studies identified a significant association. Furthermore, the histomorphological basis of this potential risk is not clearly understood, reaching definitive conclusions. The association of statin therapy and related pancreatic toxicity is a complex phenomenon. Some evidences suggest a modest increased risk of acute pancreatitis. Its particularly more evident with higher doses and certain statins.[5] As the precise mechanisms are not fully understood, few of the potential contributors include direct cytotoxicity, disturbance of cholesterol dependent cell signalling, and mitochondrial dysfunction within the pancreatic cells.[6] Despite certain potential risks, cardiovascular benefits of statins outweigh the pancreatic toxicity concerns. It calls for necessary careful risk benefit analysis and of statin therapy.[7]

Despite the growing research on statin associated adverse effects, there remains a significant gap in understanding of the specific histological and biochemical changes that occur in the pancreas following statin exposure. [8]The majority of existing studies have focused on clinical outcomes or in vitro cellular changes, leaving a critical need for in vivo investigations that can clarify the structural and functional alterations in pancreatic tissue. This study aims to address this knowledge gap by providing a comprehensive analysis of pancreatic histomorphology and associated biochemical markers in a rat model of

simvastatin toxicity. Ongoing research is vital to reveal the specific mechanisms underlining statin associated pancreatic toxicity, identify risk factors of patients, and to adopt strategies for ideal mitigation. Future clinical trials can explore statin alternatives for cardiovascular benefits or co-administration of protective agents to decrease pancreatic adverse effects while maintaining a balance of cholesterol lowering efficacy.

This research investigates this critical knowledge gap, identifying potentially important insights into statin-induced histological changes in the rat pancreas. Through a comprehensive histological analysis, we unveil the visual evidence of direct pancreatic toxicity associated with statin exposure. These structural abnormalities, demonstrably disrupting pancreatic physiology, provide a morphological foundation for potential pancreatitis development. The findings of this study hold significant implications for developing therapeutic strategies for patients undergoing long-term statin treatment. By elucidating the histo-morphological landscape of statin-induced pancreatic toxicity, we pave the way for a more nuanced understanding of this potential side effect and, consequently, the development of targeted interventions to mitigate its risk.

Methodology

This novel research study was carried out in the Anatomy Department at a public medical college in Rawalpindi, in collaboration with esteemed research institute National Institute of Health (NIH) Islamabad from Dec 2021 to Dec 2022. Employing a laboratory-based experimental control trial traversing 12-week period, the study scheme was reviewed and permitted by the institutional Ethical Committee on Animal Experiments before commencing (ID AMC/375).

Simvastatin was administered for 12 weeks to two equal groups of forty male Sprague-Dawley rats, each weighing 250 ± 50 grams, aged 60 ± 5 days. Group B was the experimental group and group A was the control group. During the course of the experiment, the rats were euthanized and their pancreases were taken for analysis. The control group (A) was fed a standard diet and water through an oral gavage tube, while the simvastatin group (B) received a standard diet plus 60 mg/kg/day of simvastatin orally every day via a gavage tube. The body weight of all the animals was recorded at the end of the study just before the sacrifice of animals, and the weight of the pancreas was recorded in grams using a digital precision balance.

Histological Parameters

Congestion (increase in blood volume showing presence of RBCs) in the vascular lumen was recorded as present or absent in the pancreatic stroma. Necrosis in acinar cells was accessed at 40X on a semi-quantitative scale using the following criteria of necrosis.[7] Three slides per specimen were observed; Score 0: Not present; Score 1: Mild, less than 25% of the parenchyma involved; Score 2: Moderate, 25–50% of the parenchyma involved; Score 3: Severe, more than 50% of the parenchyma involved Interstitial fibrosis was accessed at 10X on a semi-quantitative scale using criteria modified from sections stained with Masson's trichrome. [8] Mean was taken for the scoring of three slides per specimen. Score 0: No connective tissue between the lobules; Score 1: mild, presence of thick fibrous septa in less than 15% of the pancreatic tissue per slide. Score 2: moderate, presence of thick fibrous septa in 15 to 30% of pancreatic tissue per slide; Score 3: severe, presence of thick fibrous septa or presence of fibrous tissue in the lobules in greater than 30% of pancreatic tissue per slide.

Necrosis in acinar cells was accessed at 40X on the semi-quantitative scale.[7] Three slides per specimen were observed.

Biochemical Parameters

Cytokines Assay and Enzymes Assay (Blood Chemistry Profile) were measured as follows;

Using a commercial kit from Pierce-Endogen (Rockford, IL), the sandwich ELISA technique was used to measure the levels of TNF-α, IL-6, and CRP in plasma. The data are reported as picograms per millilitres of plasma and were obtained using the controls and standards supplied by the manufacturer. Control samples were evaluated alongside experimental samples on separate analysis days in order to watch for any plate-to-plate fluctuation and guarantee uniformity in cytokine values. Serum Amylase was measured using an Amylase colorimetric assay kit of Centronic GmbH/ Germany (LOT GF10201G)). Serum LDH was measured using an LDH colorimetric assay kit of LABLIT (LOT LIQ-1164-CM).

Data Analysis

Data analysis was done by using Statistical Package for the Social Sciences (SPSS) software version 23. Frequencies and percentages were expressed as qualitative variables. $P \leq 0.05$ defined statistical significance.Chi-square tests compared qualitative variables between groups.

Results

Animals in the control group (A) remained active for the entire duration. The mean animal weight just before dissection was 294.18±10.82gm. The mean ±SD weight of the pancreas was 0.750±0.082 gm in control group A. The control group (A) did not display major structural pancreatic changes (Fig 1). None of the animals in the control c showed congested blood vessels. Necrosis was not observed in any of the animals in the control group. Interstitial fibrosis was absent in all animals of the control group. Animals in the experimental group (B) remained active for the entire duration. The mean animal weight of the experimental group just before dissection was 307.64±7.05gm. The change in weight between the groups was statistically significant ($p<0.001$). The weight of the pancreas was significantly higher in experimental group B as compared to control group A ($p = 0.043$). The experimental group (B) exhibited marked pancreatic alterations. The pancreatic tissue showed congestion in eleven (55%) rats of

the experimental group. The frequency of congestion was significantly higher in experimental group B as compared to control group A ($p< 0.001$). In the experimental group, mild necrosis of acinar cells was observed in three (25%) rats while it was observed in 1(5%) rat in the control group. The difference was statistically insignificant ($p=0.182$). In experimental group B, Interstitial fibrosis was present in 3 (15%) rats. The frequency of interstitial fibrosis was higher in experimental group B as compared to control group A but the difference was statistically insignificant ($p= 0.231$). Significant differences were found in CRP, PCT, and IL-6 but not in LDH values between experimental and controls ($P \leq 0.05$).

Discussion

When we compared rats given simvastatin to those that weren't, we found some important differences. Our study revealed that simvastatin, a commonly prescribed cholesterol-lowering medication, can cause noticeable changes in the pancreas of rats.

This aligns with previous evidence that increasing body weight can lead to augmented abdominal organ weight and associated morbidity risks.[9] The specific mechanisms underlying this pancreatic weight increase warrant further investigation but may relate to inflammation and fatty infiltration of the tissue. Findings of this study are important because they give us visual and measurable evidence that statins might affect the pancreas in ways we didn't fully understand before. This information could help doctors better monitor patients taking statins and potentially prevent pancreas-related side effects.

Histological examination revealed structural changes in the experimental group's pancreas. Vascular congestion was observed in 55% of samples, a significantly higher proportion than the control group. Possible explanation for this finding may include local inflammation and acinar cell damage leading to vascular endothelial dysfunction. This is validated by deranged cytokines assay in our results. This may cause vasodilation, increased permeability, and congestion.[10] Another possible explanation can be the release of pro-inflammatory mediators and pancreatic enzymes that activate coagulation cascades.

This can precipitate microvascular thrombosis and congestion.[11]

Similar mechanisms have been proposed to underlie vascular complications in acute pancreatitis, which carry high morbidity if unmanaged.[10] The congestion seen here may indicate early signs of simvastatin-associated pancreatitis.

Though statistically insignificant, mild necrosis affected more experimental samples (Figure 2). The short 12-week study duration likely limited the progression to severe necrosis. However, the increased pancreatic weight and congestion suggest the potential for eventual necrotizing pancreatitis. Necrosis arises from unrelenting cellular insults leading to apoptotic and necrotic death.[12] The trend warrants monitoring with prolonged simvastatin use.

Table 1: Comparison of histological and biochemical parameters between the control and experimental groups

Parameter	Control group A	Experimental group B	p-value
Gross			
Animal Weight (gm)	294.18±10.82gm	307.64±7.05	< 0.001
Pancreas Weight (gm)	0.75±0.094	0.805±0.068)	0.043
Histological			
Congestion	0 (0%)	11 (55%)	< 0.001*
Necrosis	1(5%)	5(25%)	0.182
Interstitial fibrosis	0 (0%)	3 (15%)	0.231
Biochemical			
CRP (mg/ml)	0.4	0.7	<0.030*
Interleukin 6 (pg/ml)	18.5	23.5	<0.040*
TNF-α (pg/ml)	19.5	45	<0.040*
LDH (IU/L)	60	83	0.176

*p-value≤0.05

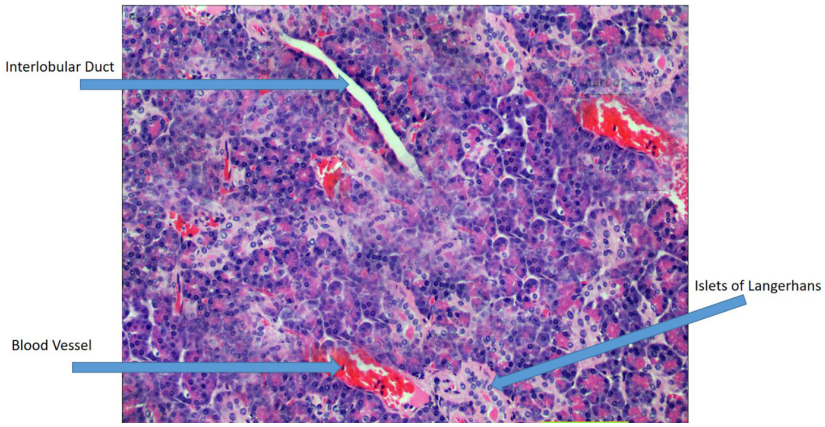

Figure-1: Photomicrograph of a histological section of the pancreas of rat in group B showing necrosis and fibrosis

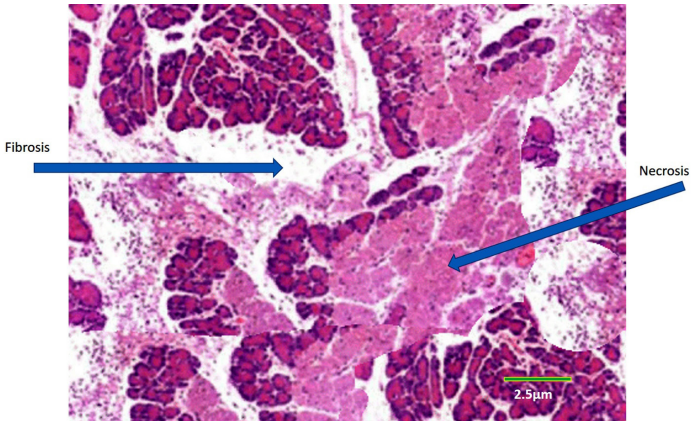

Figure-2: Photomicrograph of a histological section of the pancreas of rat in group B showing necrosis and fibrosis.

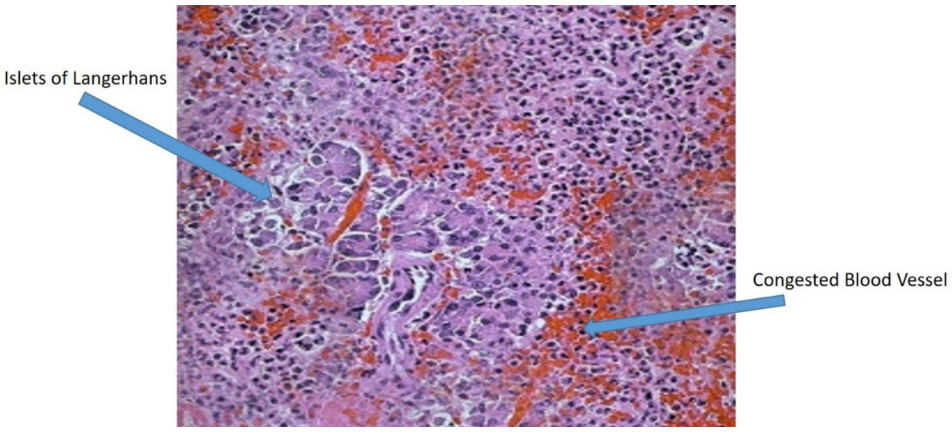

Figure-3: Photomicrograph of a histological section of the pancreas of rat in group B showing congestion

Interstitial fibrosis was not significantly elevated, though human studies link pancreatic fibrosis to aging, obesity, and chronic inflammation.[13] The brief study period may have precluded advanced fibrotic remodeling. However, the inflammation could prime the pancreas for eventual scarring with extended simvastatin exposure. Further studies are needed to characterize long-term fibrosis risk.

From this conversation, it's evident that the structural changes offer clear visual evidence that statins disrupt the microanatomy of the pancreas. The inflammation and fatty replacement are particularly noticeable, as they can disrupt the delicate functions of both the exocrine and endocrine aspects of the organ. Interleukin-6 (IL-6) is a cytokine, a type of signaling molecule that plays a crucial role in the immune response and inflammation. While traditionally associated with immune regulation, recent research has unveiled its involvement in various physiological processes beyond immunity, including metabolic regulation and pancreatic function.[14] Pancreatic beta cells are essential for maintaining glucose homeostasis by secreting insulin, a hormone that regulates blood sugar levels. Any disturbance in the integrity or function of intestinal beta cells can lead to metabolic disorders such as diabetes. Several studies have shown a link between IL-6 and intestinal beta cell health. Chronic low-grade inflammation marked by elevated levels of cytokines such as IL-6 is associated with the development of type 2 diabetes. These inflammatory cytokines can cause beta cell dysfunction and apoptosis, and play a role in the onset and progression of diabetes, particularly IL-6, which is associated with insulin resistance, a state of low cellular response of insulin is related.[15] Insulin resistance is often diagnosed before the onset of type 2 diabetes when elevated levels of IL-6 can disrupt insulin signalling in endothelial cells, causing the body to produce and release excess insulin is activated, and can eventually damage the beta cells IL-6 may also directly affect intestinal function. Some studies have shown that IL-6 can increase or decrease insulin secretion from beta cells, depending on the situation. In some cases, IL-6 can help beta cells grow and survive, suggesting that it may be safe.[16] IL-6 plays a multifaceted role in the inflammatory response in the pancreas. Conditions such as pancreatitis often show increased levels of IL-6, leading to tissue damage and dysfunction. Chronic pancreatitis can lead to loss of pancreatic beta cells and decreased insulin secretion. In addition, genetic studies have identified the association of polymorphisms of the IL-6 gene with insulin metabolism and increased susceptibility to type 2 diabetes, further confirming the association with IL-6 between symptoms and pancreatic function is emphasized. [17]

Elevated CRP levels are a marker of systemic inflammation. In both type 1 and type 2 diabetes mellitus, chronic low-grade inflammation is frequently observed and is linked to higher CRP levels. This inflammation can compromise beta cell integrity by driving oxidative stress, causing cytokine-induced damage, and facilitating immune cell infiltration into the pancreatic islets, as demonstrated in our study. Elevated levels of inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), are commonly observed in chronic inflammatory states and have been implicated in beta cell dysfunction. These cytokines contribute to beta cell impairment through multiple mechanisms: they disrupt insulin secretion pathways, induce endoplasmic reticulum stress, and promote beta cell apoptosis. The derangement of C-reactive protein (CRP) in the context of pancreatic injury reflects a complex interplay of inflammatory mediators, tissue damage, cellular activation, and oxidative stress. Although CRP levels can serve as a useful biomarker for evaluating the severity of pancreatic injury and monitoring the progression of pancreatitis, it is crucial to recognize that CRP elevation is not specific to pancreatic injury and may be elevated in a variety of other inflammatory conditions.[18] Monitoring LDH levels may provide valuable information in the assessment of pancreatic injury or disease. However, LDH is a relatively nonspecific marker of cellular damage, and its interpretation should be considered alongside other clinical and laboratory parameters [19] as evident in our study. In summary, while LDH is not specific to pancreatic tissue, changes in its levels can indicate pancreatic injury or damage, including conditions such as acute pancreatitis, chronic pancreatitis, and pancreatic cancer. Monitoring LDH levels may be useful in the evaluation and management of pancreatic diseases, but it should be interpreted in the context of the clinical presentation and other diagnostic findings. Simvastatin, a widely prescribed cholesterol-lowering medication, is generally well-tolerated. However, there's a potential link between simvastatin toxicity and pancreatic effects which may manifest as biochemical derangements and prompting cautious consideration and individualized treatment approaches.

It is important to note that while animal studies provide valuable insights into the effects of medications like simvastatin, findings in rodents may not always directly translate to humans. Therefore, further research, including clinical studies, is needed to fully understand the effects of simvastatin on pancreatic tissues and its relevance to human health and disease. Additionally, individuals should consult healthcare professionals for personalized medical advice and information regarding the use of simvastatin or any other medication.

Limitations

It's important to note that while animal studies provide valuable insights into the effects of medications like simvastatin, findings in rodents may not always directly translate to humans. Therefore, further research, including clinical studies, is needed to fully understand the effects of simvastatin on pancreatic tissues and its relevance to human health and disease. Additionally, individuals should consult healthcare professionals for personalized medical advice and information regarding the use of simvastatin or any other medication.

Conclusion

This research establishes that statins have a significant effect on the structure of the pancreas. Rats treated with simvastatin displayed noTable alterations, such as increased congestion,

inflammation, and fatty infiltration compared to the control group. Additionally, concerning patterns were observed in terms of necrosis and fibrosis. These findings highlight the need for careful monitoring of pancreatic function in patients undergoing long-term statin therapy and indicate the importance of further research into the mechanisms of statin-induced pancreatic toxicity.

Conflict of Interest

We declare no conflict of interest that could have influenced the work reported in this paper.

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This research project did not receive any funding.

Authors' Contribution

AQ: Study design, concept, data acquisition, manuscript writing; HGK: Manuscript writing, final data approval, analysis, interpretation; MMK: Final manuscript approval, critical review; FU: Critical review, data analysis, interpretation; NM: Microphotograph analysis; KA: Critical review, data interpretation.

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Original Article

Analgesic Efficacy of Transversus Abdominis Plane Block vs Local Infiltration of Lignocaine and Bupivacaine in Post-operative Patients

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Abstract

Objective: To compare the effectiveness of Transversus Abdominis Plane (TAP) block vs Local Infiltration for pain management techniques in patients undergoing laparoscopic lower abdominal surgeries.

Methodology: This cross-sectional study was conducted at the Department of Surgery, Lahore General Hospital, in March 2024. It involved a total of 110 patients, divided into two groups of 55 each, between the ages of 20 to 60 years, diagnosed with indirect inguinal hernia by ultrasound. Chronic smokers, drug addicts, intravenous drug abusers, patients with a history of previous surgeries, with known drug allergies and with complicated hernia were excluded from this cross-sectional study. The Numerical Rating Scale (NRS) was used to see the pain variation and effectiveness of both techniques at 6, 12, 18 and 24 hours.

Results: The mean age in the TAP Block Group was 32.0 ± 9.92 years, and the mean age in the Local Wound Infiltration Group was 34.21 ± 10.01 years. There were 108 (98.18%) male and 2(1.81%) female cases with a higher male-to-female ratio. The results indicated that the TAP Block group consistently required fewer rescue analgesic doses than the local wound Infiltration group at all postoperative time points. At 6 hours, 23.63% of patients in the TAP Block group needed additional analgesia, compared to 38.18% in the Wound Infiltration group, though this difference was not statistically significant. However, at 12, 18, and 24 hours, the TAP Block group showed a significantly lower need for rescue analgesia, with p-values of 0.002, and 0.008, respectively.

Conclusion: In managing postoperative pain of Inguinal Hernia Repair, TAP Block is superior to Wound Infiltration of local anesthetic agent. After TAP Block NRS remains fewer and a smaller number of rescue doses are needed as compared to Wound infiltration.

Keywords: Inguinal hernia, TAP block, Laparoscopic surgery, Lignocaine, Bupivacaine, Post-operative patients.

Introduction

A significant portion of postoperative pain is derived from the surgical incision and visceral areas. Transversus Abdominis Plane (TAP) block first described by Rafi et al. in 2001 is an approach in which local anesthetic is injected into the plane between the internal oblique muscle and the transversus abdominis muscle layers to block the sensory nerve supply to the anterior inferior abdominal wall.[1] The TAP block has demonstrated postoperative pain relief following abdominal surgery, hysterectomy and following cesarean delivery in contrast to no intervention or placebo in prior meta-analysis. Infiltration of local anaesthetic at the site of surgery can help reduce pain after operation as one of the techniques of multimodal analgesia.[2] This easy, risk-free, minimally invasive and cost-effective procedure that is often carried out by the surgeon is regularly done in many centres for postoperative pain relief.[3] In this regard regional anesthesia techniques are well appreciated which provides pain relief with lesser side effects than general anesthesia and systemic analgesics. Of these, the TAP block technique has proven useful in controlling postoperative pain, especially in patients who have undergone abdominal surgeries.[4] TAP block leads to great relief from pain, and patients can move around more comfortably under reduced use of opioids.[5]

After its introduction in the mid-2000, the TAP block has been applied in a variety of different specialties including general surgery, gynaecology, urology and bariatrics. This has been confirmed by so many studies regarding post-operative pain management, and the fact that it is often used because it is easy to perform, and also safe, and may be performed under ultrasound guidance which enhances the accuracy of the block.[6] Nevertheless, the TAP block is not the only regional anesthesia technique applicable in postoperative pain control. Infiltration of anesthetics like Lignocaine and Bupivacaine have been used from time immemorial whereby the anesthetic agents are injected directly on the surgical site to minimize the sensation of pain during surgery.[7] Lignocaine is a shortacting local anesthetic while bupivacaine is a long-acting one, and both are given either alone or in combination to yield good pain relief. Local infiltration is where these anesthetics are directly administered into the tissues around the area of operation with a view of blocking the nerves that transmit pain.[8]

The effectiveness of local infiltration over more complicated regional techniques such as that of the TAP block is debatable. Local infiltration is easy and no specialized tools and personnel are required, hence it is

comparatively economical.[9] However, its effect may be short-lived, potentially necessitating additional doses or the use of supplementary agents to enhance the effects of Lignocaine. In addition, the efficacy of the local infiltration may be influenced by the area of surgery, type of the surgery performed, and the type of technique used.[10] Determination of the relative effectiveness between the TAP block and local infiltration of Lignocaine and Bupivacaine is important in order to compare which method of postoperative pain control is the most effective. It is useful to compare these methods mainly for surgeries of the abdominal wall, in which both techniques are often used. The consequences of making some of these comparisons are crucial in determining clinical practices on pain control measures, resource utilization and ultimately patient care plans.[11] The TAP block is not a new type of analgesia, but more and more researchers have applied this effective interventional technique in managing postoperative pain after abdominal operation.[12]

The objective of this study was to demonstrate the anesthetic technique effectiveness of pain control in patients after laparoscopic lower abdominal surgery by comparing two pain management techniques i.e TAP block and Wound Infiltration block, using an injection of Lignocaine 2% (3 mg/kg) mixed together with Bupivacaine 0.25% (2.5 mg/kg) in combination at the time of surgery.

Methodology

This cross-sectional study was conducted at the Department of Surgery, Lahore General Hospital, Lahore, in March 2024, IRB No.62/24, to compare the effectiveness of two pain management techniques i.e TAP block and wound infiltration block using an injection of Lignocaine 2% (3 mg/kg) mixed with Bupivacaine 0.25% (2.5 mg/kg).in patients undergoing lower abdominal surgery i.e. laparoscopic total extraperitoneal (TEP) or transabdominal preperitoneal (TAPP) laparoscopic surgery. The study involved a total of 110 patients, divided into two groups of 55 each. The Numerical Rating Scale (NRS) was used to see pain relief at 6,12,18 and 24 hours postoperatively and to see the effect of rescue doses. It consists of a segmented numerical scale with 11 points ranging from 0 to 10. Patients are asked to select a matching number to specify the pain intensity they are feeling. A unique benefit of the NRS is that it can be directed verbally, making it an appropriate tool for language, cultural, or cognitive barriers. Patients undergoing laparoscopic surgery for lower abdominal conditions, specifically laparoscopic, total extraperitoneal (TEP) or transabdominal preperitoneal (TAPP) procedures for indirect inguinal hernia, were selected for this study. The inclusion criteria required that patients be between the ages of 20 to 60 years, all patients with indirect Inguinal Hernia diagnosed by ultrasound and all patients who gave consent to surgery. Exclusion criteria included chronic smokers, drug addicts, intravenous drug abusers**,** patients with a history of previous surgeries, patients with known drug allergies**,** and patients with complicated hernia.

Data were collected into two groups: Group A: Patients in this group received a TAP block with an injection of Lignocaine 2% (3 mg/kg) mixed with Bupivacaine 0.25% (2.5 mg/kg). Group B: Patients in this group received local infiltration of the surgical wound with the same mixture of Lignocaine 2% (3 mg/kg) and Bupivacaine 0.25% (2.5 mg/kg). The local anesthetics (LAs) used in this study were Lignocaine and Bupivacaine, which function by reversibly inhibiting nerve transmission. They achieve this by binding to voltage-gated sodium channels within the nerve plasma membrane. These channels are integral membrane proteins that play a crucial role in nerve impulse propagation. By blocking these channels, LAs prevent the initiation and transmission of nerve impulses, thereby providing analgesia. The primary outcome variable was the need for rescue analgesia, measured by the number of doses required postoperatively. This variable was used to assess the efficacy of pain control in both groups. Data were analyzed using SPSS v29. P-values <0.05 were considered significant.

Results

The mean age in this study was 33.10 ± 9.98 years with minimum and maximum ages as 20 and 60 years. The mean age in the TAP Block Group was 32.0 ± 9.92 years with minimum and maximum age of 20 and 51 years and the mean age in the Local Wound Infiltration Group was 34.21 ± 10.01 years with a minimum and maximum age of 20 and 60. There were 108(98.18%) male and 02(1.81%) female cases with higher male-to-female ratio. In the TAP Block Group there were 54 (98.18%) male and 01 (1.81%) female cases while in the Local Wound Infiltration Group, there were 54(98.18%) male and 01(1.81%) female cases. The gender distribution in both groups was statistically the same, p-value > 0.05. (Table 1)

Table 1: Demographic data of participants

Characteristic	Overall (n=110)	TAP Block Group (n=55)	Local Wound Infiltration Group (n=55)
Age (years)			
- Mean ± SD	33.10 ± 9.98	32.0 ± 9.92	34.21 ± 10.01
- Range	20 - 60	20 – 51	20 – 60
Gender			
- Male	108 (98.18%)	32 (98.18%)	30 (98.18%)
- Female	02 (1.81%)	01 (1.81%)	01 (1.81%)
BMI (kg/m²)			
- Mean ± SD	26.5 ± 4.3	26.0 ± 4.1	27.0 ± 4.5
- Range	18.5 - 35.0	18.5 - 34.0	19.0 - 35.0

Characteristic	Overall (n=110)	TAP Block Group (n=55)	Local Wound Infiltration Group (n=55)
American Society of Anesthetists (ASA) Physical Status Classification			
- ASA I	45 (40.9%)	24 (43.6%)	21 (38.1%)
- ASA II	50 (45.4%)	24 (43.6%)	26 (47.2%)
- ASA III	15 (13.6%)	7 (12.7%)	8 (14.5%)
Smoking Status			
- Non-smoker	72 (65.4%)	36 (65.4%)	36 (65.4%)
- Former smoker	25 (22.7%)	14 (25.4%)	11 (20.0%)
- Current smoker	13 (11.8%)	5 (9.0%)	8 (14.5%)

The results demonstrate that patients in the TAP Block Group experienced significantly better pain relief compared to those in the Wound Infiltration Group at all observed time points. At 6 hours postoperatively, 34.54% of patients in the TAP Block Group reported no pain, compared to only 12.72% in the Wound Infiltration Group, with a significant p-value of 0.004. This trend continued at 12, 18, and 24 hours, where the TAP Block Group consistently showed higher percentages of patients with no pain or mild pain (Table 2). The statistical significance of the pain relief in favour of the TAP Block Group was confirmed by chi-square tests at each interval, with p-values all below 0.05, indicating a clear advantage of the TAP Block over wound infiltration for postoperative pain management.

Table 2: Numeric Rating Scale (NRS) postoperatively at different time intervals for both groups

Time (Hours)	Pain Intensity (NRS)	TAP Block Group (n=55)	Wound Infiltration Group (n=55)	Total (n=110)	Chi-square Test	P-value
6 Hours	0 = No Pain	19 (34.54%)	07 (12.72%)	26 (23.63%)	0.028	0.004
	1-3 = Mild Pain	24 (43.63%)	26 (47.27%)	50 (45.45%)		
	4-6 = Moderate Pain	11 (20%)	18 (32.72%)	29 (26.36%)		
	7-10 = Severe Pain	01 (1.8%)	04 (7.27%)	05 (4.54%)		
12 Hours	0 = No Pain	24 (43.63%)	13 (23.63%)	37 (33.63%)	0.044	0.009
	1-3 = Mild Pain	23 (41.81%)	23 (41.81%)	46 (41.81%)		
	4-6 = Moderate Pain	7 (12.72%)	18 (32.72%)	25 (22.72%)		
	7-10 = Severe Pain	01 (1.8%)	01 (1.8%)	02 (1.8%)		
18 Hours	0 = No Pain	31 (56.36%)	21 (38.18%)	52 (47.27%)	0.018	0.004
	1-3 = Mild Pain	22 (40%)	21 (38.18%)	43 (39.09%)		
	4-6 = Moderate Pain	2 (3.63%)	12 (21.8%)	14 (12.72%)		
	7-10 = Severe Pain	0	1 (1.8%)	1 (0.9%)		
24 Hours	0 = No Pain	28 (50.9%)	14 (25.45%)	42 (38.18%)	0.003	0.001
	1-3 = Mild Pain	25 (45.45%)	30 (54.54%)	55 (50%)		
	4-6 = Moderate Pain	2 (3.63%)	11 (20%)	13 (11.81%)		
	7-10 = Severe Pain	0	0	0		

The results indicate that the TAP Block group consistently required fewer rescue analgesic doses than the Wound Infiltration group at all postoperative time points. At 6 hours, 23.63% of patients in the TAP Block group needed additional analgesia, compared to 38.18% in the Wound Infiltration group, though this difference was not statistically significant. However, at 12, 18, and 24 hours, the TAP Block group showed a significantly lower need for rescue analgesia, with p-values of 0.002, 0.002, and 0.008, respectively. This suggests that the TAP Block is more effective in providing sustained postoperative pain relief.

Discussion

Our study aims to review the analgesic outcome of two different techniques so that patients have a better experience of inguinal repair surgery. This study intended to evaluate the efficiency of two pain management techniques—TAP block and Local Wound Infiltration—in patients undergoing laparoscopic lower abdominal surgery for indirect inguinal hernia. Conducted at the Department of Surgery, Lahore General Hospital, in March 2024, this cross-sectional study involved a sample size of 110 patients, with 55 patients in each group, aged 20 to 60 years. Patients were divided into two groups to receive either the TAP block or local wound infiltration. Pain variation and technique effectiveness were evaluated using the Numerical Rating Scale (NRS) at 6, 12, 18, and 24 hours post-surgery. Results demonstrated that the TAP block group had a constantly lesser need for rescue analgesics at the majority time points postoperatively, showing noteworthy differences at 12, 18, and 24 hours, thus demonstrating the superiority of TAP block over local infiltration for managing postoperative pain in inguinal

Table 3: Comparison of rescue analgesic doses required postoperatively at different time intervals for both groups:

Time (Hours)	Rescue Analgesic Doses Required	TAP Block Group (n=55)	Wound Infiltration Group (n=55)	Total (n=110)	Chi-square Test	P-value
6 Hours	Yes	13 (23.63%)	21 (38.18%)	34 (30.9%)	0.099	0.074
	No	42 (76.36%)	34 (61.81%)	76 (69.09%)		
12 Hours	Yes	7 (12.72%)	21 (38.18%)	28 (25.45%)	0.002	0.002
	No	48 (87.27%)	34 (61.81%)	82 (74.54%)		
18 Hours	Yes	2 (3.63%)	13 (23.63%)	15 (27.27%)	0.002	0.002
	No	53 (96.36%)	42 (76.36%)	95 (86.36%)		
24 Hours	Yes	2 (3.63%)	11 (20%)	13 (11.81%)	0.008	0.008
	No	53 (96.36%)	44 (80%)	97 (88.18%)		

In the TAP Block Group, 38 (69%) didn't require any rescue analgesic dose, 10 (18%) required a single dose, 7 (13%) required 2 doses in the first 24 hours postoperatively, while no patient required 3 or 4 doses in first 24 hours post operatively. In the Local Wound Infiltration Group 20 (36%) didn't require any rescue analgesic dose, 17 (31%) required a single dose, 7 (13%) required 2 doses, 9 (16%) required 3 doses and 2 (4%) in first 24 hours postoperatively. P-value = <0.001 which is statically significant.(Table 3, Figure 1)

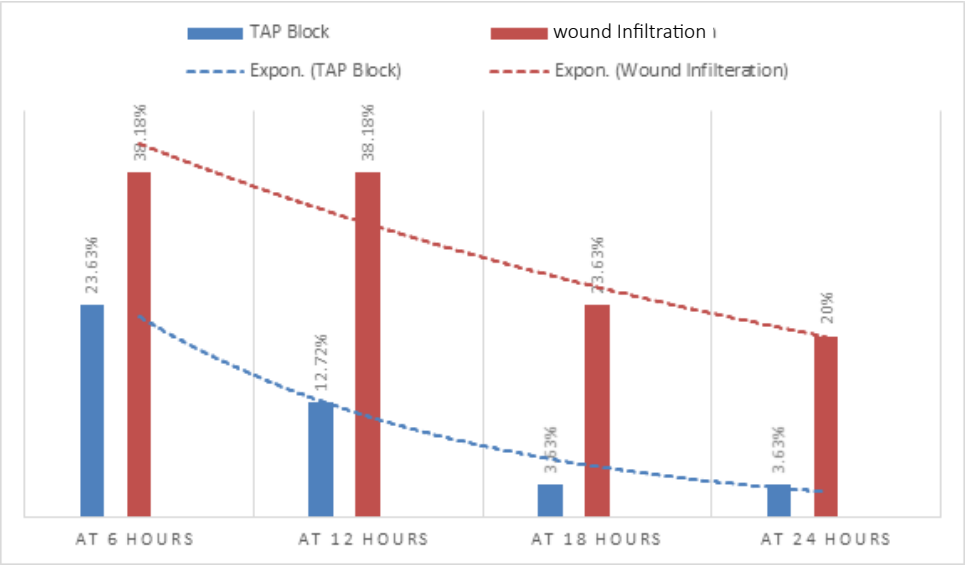

Figure 1: Comparison of rescue analgesic doses at different time intervals between both groups.

hernia repair. Postoperative pain management plays a vital role in the early mobilization and recovery of the patient. Achieving this without the side effects of oral/injecTable analgesics is also a challenge to be faced by surgeons. Wound infiltration with LA is a predominant technique used to manage postsurgical pain. In previous years, there was increasing corroboration in the favor of effectuality of TAP block in a number of abdominal operations.[13,14]

In our study, it is evident that the numeric rating score in the TAP Block group remained significantly less as compared to that of wound infiltration with the local anesthetic group with less need for rescue analgesic doses.(Table 2) Compared to another study the pain-relieving ability of TAP block after cesarean delivery performed under spinal anesthesia varies depending upon whether or not intrathecal morphine is utilized as a postsurgical pain reliever.[15] When intrathecal morphine isn't utilized, TAP block, contrasted with placebo, is related to lesser post-operational morphine utilization and pain count, increased duration to 1st pain killer shot, decreased rate of after effects, and increased patient contentment. Likewise, local anesthesia injection in the incision, contrasted with placebo, is linked with decreased morphine utilization and decreased rate of nausea after cesarean delivery.[16] In line with these findings, this study has confirmed that post-operative pain management using a TAP block is more effective than using local wound infiltration with Lignocaine and Bupivacaine. (Table 3) (Figure 1) The demographic characteristics in both studies suggested a comparable age, gender distribution, BMI, as well as ASA physical status which precludes the baseline patient factors as the reason for the differences in the pain outcomes reported by the study.[17] (Table 1)

The TAP block proved to have better pain relief outcomes at all the postoperative time intervals as evidenced by the enhanced percentage of patients who complained of no pain or mild pain as compared to the Local Wound Infiltration Group. Decreased by 72% in the Local Wound Infiltration Group, ($p = 0.004$). It was also evidenced at 12, 18, and 24 hours of the procedure where TAP Block Group had better scores in their pain relief than the Local Wound Infiltration (Table 3) Group with p-values less than 0.05.[18] These findings agree with previous studies that have also noted that the TAP block provided a longer duration of Analgesia with reference to abdominal surgeries. The TAP block involves the nerves that are involved in the anterior abdominal wall thus avoiding pain from the surgical site. Nonetheless, similar to patient-controlled thigh infiltration, local wound infiltration gives the first release of pain and lasts for a shorter period resulting in reinjection or rescue analgesia.[19]

The requirement for rescue analgesia once again proves the emergence of more effectiveness from the TAP block.[20] At 6 hours the total rescue analgesic consumption also did not show much variation between the two groups but the TAP Block Group used a smaller number of doses on a rescue basis. That is why over time the difference became distinctive. When compared to the Local Wound Infiltration Group the TAP Block Group used significantly fewer rescue analgesic doses at 12, 18 and 24 hours with p values of 0. 002, 0. 002, and 0. 008, respectively.[21]

Limitations

The following are weaknesses that should be taken into consideration when analysing and interpreting the results of this research study. The number of patients was relatively small, and the study was conducted at a single centre, which modifies the transferability of the results. The blinding was not conducted properly and this might have resulted in biases; the short duration of follow-up did not enable the identification of other results like chronic pain and overall recovery. Other shortcomings of the study include inconsistency in the methods of conducting surgeries as well as dependence on self-report of pain. The study also did not compare the TAP block with other analgesic techniques like epidural or spinal anesthesia, nor did it assess the cost-effectiveness or broader aspects of postoperative care and rehabilitation.

Conclusion

In managing postoperative pain of Inguinal Hernia Repair, TAP Block is superior to Wound Infiltration of local anesthetic agent. After TAP Block NRS remains fewer and a smaller number of rescue doses are needed as compared to Wound infiltration.

Conflict of Interest: The authors declare no conflict of interest.

Authors' Contributions: MSA contributed to the initial conception and design of the study, wrote the initial draft and supervised the project; MK was primarily involved in the acquisition of data, including overseeing the patient selection criteria and ensuring proper randomization protocols; SM conducted the statistical analysis; AA focused on literature review; QF was responsible for organizing patient follow-up assessments, monitoring post-operative pain levels, and documenting patient-reported pain outcomes; MR contributed to the ethical and administrative aspects of the study, ensuring compliance with institutional review requirements and obtaining informed consent from participants.

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Original Article

Exploring the Link between ABO Blood Groups and Obesity among Young Adults

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Abstract

Objective: To explore the link between the ABO blood groups and obesity among young adults of Hyderabad district, Sind, Pakistan.

Methodology: This cross-sectional study was conducted from February 2021 to January 2022, and included 582 randomly selected participants, including 301 males and 281 females, aged between 18 to 40 years, from various institutions of district Hyderabad, including students, faculty members, and employee of universities, colleges, hospitals. A simple random sampling technique was used for the collection of data. Before induction, verbal consent was taken from all the participants. Data was collected by a self-structured questionnaire including sociodemographic characteristics. A brief history was taken relevant to the parameters of the study followed by measuring Body Mass Index, waist circumference, and waist-hip ratio. BMI was categorized with South Asian standards. Data collected through structured questionnaires and anthropometric parameters were analyzed by SPSS version 20.

Results: In this study, the data of 582 participants were included out of 600 participants, as the remaining 18 could not provide complete data. The mean age in male participants was 27.83 ± 5.478 and in females was 22.27 ± 4.730. The average BMI in male participants was 25.81 ± 5.08 and in females was 24.00 ±4.90. Overall, 205 B blood group participants were found obese, which included 111 male participants and 94 female participants, followed by blood 197 group O participants, 130 A blood group participants, and 50 AB group individuals. In total, there were 536 Rh positives, and only 42 Rh negatives. Individuals with blood group B and Rh-positive status were identified at being greater risk of developing higher BMI, waist-hip ratio, and waist circumference.

Conclusion: The evidence found in this study proved the positive association of the types of blood groups with BMI, waist-hip ratio, and waist circumference.

Keywords: ABO blood group, Obesity, Waist circumference, Waist-hip ratio.

Introduction

The relationship between ABO blood groups and obesity has been investigated in numerous studies with conflicting results. While some studies suggest an association between specific blood types particularly O and B with a higher prevalence of obesity, others indicate that factors such as ethnicity and gender play more significant roles.[1] Obesity is a complex medical problem defined by the World Health Organization as the abnormal and extreme deposition of fats in the body that has negative impacts.[2]

The most common causes of obesity are increased intake of food, physical inactivity, and genetic predisposition.[3] However, it may be caused by endocrine disorders, medications, or mental disorders. Obesity is a prevenTable condition by a combination of changes in social life and personal choices. It can be treated through healthy food and exercise.[3]

Obesity is a prevenTable cause of death around the world, with a higher prevalence in children and adults. According to WHO, urban areas of Pakistan have a burden of obesity ranging from 22 to 40%.[4] A study reported that approximately 600 million adults and an estimated 100 million children were found obese in 195 countries in 2015.[5] Young adults aged between 18 to 40 years are at critical life stages where lifestyle habits are mostly stiff making it a vital time for preventing obesity.[6] A sedentary lifestyle and consumption high-calorie diet and processed food have been found to be key contributors to obesity.[7]

The conventional factors of obesity, such as the imbalance between intake of calories and expenditure of energy, are well understood.[8] The ABO blood group system has been previously associated with various metabolic and cardiovascular conditions.[2,9] These blood groups influence biological processes such as inflammation, lipid metabolism, and insulin sensitivity; all of these play major roles in the development of obesity.[9]

Research conducted in the local population that focuses on a specific region is more valuable for gaining insights into genetic, environmental, and cultural factors that affect both obesity and the distribution of the ABO blood groups. Therefore, this study aims to find out the frequency of the ABO blood group with obesity among young adults aged between 18 to 40 years, from Hyderabad, Sindh, Pakistan.

Methodology

After approval from research ethics committee letter No: DRGS/1601, University of Sindh, this cross-sectional survey was conducted to record the relationship of the ABO blood groups with obesity in the young population aged between 18 to 40 years, living in district Hyderabad. Verbal consent was taken from all the participants. The study was conducted from February 2021 to January 2022. The sample size was calculated by Rao-soft online calculator, Random Sampling was used to collect data. A total of 600 individuals were contacted finally 582 participated in this study, the response was 97 %, and the remaining 18 (3%) of individuals refused to provide necessary information Questionnaires were filled by all authors while collecting data in hard copies.

In this study, participants were healthy and had no illnesses that could have significantly changed either their lifestyle habits or physiological measures. Individuals who participated were selected on the criteria to achieve close to accurate results. Participants included knowing their blood groups, without any cardiovascular diseases, non-pregnant, non-smoker, and non-addict. Participants who were not residents of district Hyderabad, who were > 40 years of age, diagnosed with any heart disease, pregnant, active smokers, a genetic disorder linked with obesity, conditions including hypothyroidism, polycystic ovary syndrome or Cushing syndrome linked with obesity and drug addicts, were excluded from this study.

Physiological Variables: There were two types of physiological variables taken into account; those that were physically measured, including;

Anthropometric Measurements: including height, weight, waist circumference, and hip circumference were measured with a balanced beam scale, porTable stadiometer, and flexible, non-stretchable measuring tape.

Basal Metabolic Index (BMI) is a measure used to assess an individual's body weight with relevance to their height. BMI was calculated by dividing the weight in kgs of individuals by their height in meters. Individuals were classified as underweight, normal or optimal, overweight, and obese, depending upon the BMI range they fell in, and calculated with formula: weight in kgs/ (height in meters).[2] The normal South Asian range of BMI is >23 kg/m^2.[10] Waist Circumference refers to the measurement of the distance around a person's waist. It is typically measured at a point just above the hip bone and below the rib cage. The normal South Asian range of waist circumference is ≥ 90 cm (Male), and≥ 80 cm (Female).[11]

Statistical Analysis

Data was analyzed with a statistical package for the social sciences (SPSS Version 23.0). Descriptive statistics (mean, standard deviation, frequencies) were calculated for the baseline characteristics. Chi-square was used to assess the association between the ABO blood group and the prevalence of increased blood pressure. Logistic regression analysis was performed to determine the odds ratio, accounting for confounders such as age and BMI, in order to assess the strength of the association between ABO blood groups and elevated blood pressure. A p-value of less than 0.05 was considered statistically significant.

Results

Basic characteristics of participants including, age, BMI, mean waist circumference, mean waist-hip ratio, mean blood sugar fasting, and mean systolic and diastolic blood pressure are shown in Table 1.

Table 1: The basic characteristics of participants

Variable	Male (n=301)	Female (n=281)
Distribution of the Participants' Blood Group		
A	72	58
B	111	94
AB	22	28
O	96	101
Age	27.83 ± 5.478	22.27 ± 4.730
Body Mass Index (BMI)	25.81 ± 5.08	24.00 ±4.90
Blood Sugar Fasting (BSF)	104.25 ± 36.42	90.31 ± 19.65
Systolic Blood Pressure (SBP)	122.60 ± 13.38	113.22 ± 16.65
Diastolic Blood Pressure (DBP)	83.38 ± 8.762	76.31 ± 9.49
Waist Circumference	90.11 ± 13.327	73.25 ± 12.644
Waist Hip Ratio	0.7342 ± 0.442	0.9203 ±0.2713

Table 2 indicates that participants with B blood group were established more vulnerable to develop increased BMI. Rh-positive subjects were also found in increased BMI category, Waist circumference and Waist hip ratio.

Table 2: The association of ABO blood group with BMI, waist circumference, and waist hip ratio

Variable	**Normal Weight < 23 Kg/m²**		**Increased Weight > 23 Kg/m²**		**(P-Value)**
Body Mass Index	N	%	n	%	
O (197)	177	89.84	20	10.15	(0.000)
A (130)	116	89.23	14	10.76	(0.778)
B (205)	155	75.60	50	24.39	(0.001)
AB (50)	43	86	7	14	(0..692)
Rh +ve (536)	449	83.76	87	16.23	(0.000)
Rh -ve (46)	42	91.3	4	8.69	(0.236)
Waist Circumference	Normal < 102 cm (Males) 80 cm (Females)		Increased > 102 cm (Males) 80 cm (Females)		(P-Value)
O (197)	178	90.35	19	9.64	(0.000)
A (130)	113	86.92	17	13.07	(0.013)
B (205)	167	81.46	38	18.53	(0.000)
AB (50)	43	86	7	14	(0.048)
Rh +ve (536)	459	85.63	77	14.36	(0.000)
Rh -ve (46)	42	91.3	4	8.69	(0.004)
Waist Hip Ratio	Normal < 90 cm (Males) 85 cm (Females)		Increased > 90 cm (Males) 85 cm (Females)		(P-Value)
O (197)	111	56.34	86	43.65	(0.000)
A (130)	60	46.15	70	53.84	(0.000)
B (205)	85	41.46	120	58.53	(0.000)
AB (50)	21	42	29	58	(0.000)
Rh +ve (536)	253	47.2	283	52.79	(0.000)
Rh -ve (46)	24	52.17	22	47.83	(0.000)

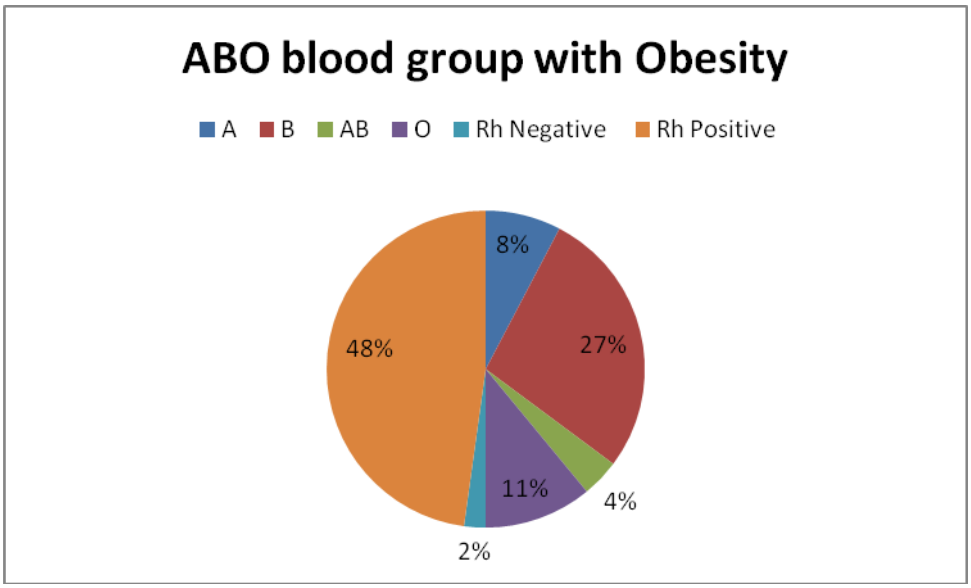

Figure 1: Association of ABO blood group with Obesity, showing that B blood group have higher tendency to develop obesity

Discussion

This study was conducted to explore whether a person's blood group could be a risk for obesity. As obesity is a growing global health concern, especially in younger populations, identifying any potential biological marker like blood group, could aid in predicting the risk of obesity and developing personalized prevention strategies. The findings in our study suggest that participants in the B blood group were prone to develop obesity followed by A and AB blood group participants. Waist circumferences were found increased in B blood group participants followed by AB and A blood group participants. The waist-hip ratio was also found higher in participants in the B blood group followed by AB and A blood group participants. In this study, the mean body mass index of subjects was 24.945 ± 5.0765, however, no significant gender-wise difference was found in body mass index. In this study, blood group B had a higher prevalence of increased body mass index followed by A, O, and AB blood group, and subjects with Rh D positive were more prone to develop obesity compared to Rh D negative. This finding indicates that participants with B blood group might be genetically prone to develop obesity than other blood groups.

A study from India on 200 medical students by Bhattacharyya et al. found in consistent with our result that blood group B participants were more prone to develop obesity than other blood groups.[12] Another Malaysian study on the Punjabi population of Selangor, conducted by Kumeshini et al. showed agreement with our findings.[13] Parveen et al. conducted a study on 181 medical students of Karachi which were inconsistent with our findings and determined that blood group A had a higher prevalence of increased BMI.[14] This difference might be due to the reduced sample size of the study conducted in India and Karachi.

The distribution patterns of BMI differ within and between populations around the world. These changing patterns of BMI in different populations are recognized and related to changes in socioeconomic status.[15] Both overweight and obesity are considered to be harmful to a person's health and several studies reported the link of higher BMI with the development of certain diseases.[16] Increased body weight is related to an increased risk factor for the development of various diseases and clinical disorders including coronary artery disease, hypertension, stroke,[17] malignancies, diabetes type II,[18] liver diseases,[19] asthma, allergies,[20] and psychological problems.[16] Some studies conducted around the world found an insignificant relationship between the ABO blood group with body mass index.[21-25] These variable findings concerning the relationship of the ABO blood group with body mass index may be due to local factors, which change population phenotype, or may be due to sampling size difference rather than actual genetic influence.

In our study, waist circumference was found normal in 501 (86.08%) subjects and increased in 81 (13.91%) subjects. Waist circumference was increased in subjects with B blood group followed by O, A, and AB blood group subjects (Table 2). However, Rh-positive subjects had increased waist circumference compared to Rh-negative subjects. Many studies proved the association of blood groups with different diseases, yet it is not clear whether its role is big or small related to lifestyle and heredity. However, the concept of fitness has changed. Several studies showed that body mass index is not the correct parameter of health or obesity. It is the amount of body fat, which determines the health condition of the individual. Waist-hip ratio was normal in 277 (47.59%) subjects and increased in 305 (52.40%) subjects. Waist Hip Ratio was increased in B blood group subjects followed by A, AB, and O blood group subjects. Subjects with Rh-positive were found to have an increased waist-hip ratio compared to Rh-negative subjects. Behera et al. [26] conducted a study that found a relationship between blood group with waist-hip ratio and males, indicating AB and Rh-negative blood group individuals were prone to develop increased waist-hip ratio, while in females, AB and Rh-positive were found more prone.

Limitations

Geographic and ethnic variability including ABO blood group distribution, and obesity prevalence can vary significantly by region and ethnicity. Confounding factors like obesity are dependent on diet, physical activity, socioeconomic status, and environmental influences. The cross-sectional study can only show indication, not causation. The study focuses on young adults, the findings may not be generalizable to another age group.

Conclusion

This study concluded that participants having the B blood group are more susceptible to developing obesity. This association indicates a possible genetic tendency that may relate to environmental and lifestyle factors, increasing the chances of obesity in this population. The observed increased incidence of obesity among B blood group individuals may be associated with differences in metabolic processes, such as lipid metabolism and insulin sensitivity, which are influenced by blood group antigens.

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Conflict of Interest: The authors declare no conflict of interest.

Authors' Contributions: SAS designed the study and did the write up; NAY, MMM did data collection; KRL and AAU critically analysed the results; SFM supervised the project and gave final approval.

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Original Article

Parental Awareness of Thalassemia Transmission and the Impact of Consanguineous Marriages: A Cross-Sectional Survey

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Abstract

Objective: To determine the frequency and relationship between consanguineous marriages and the awareness of thalassemia transmission among parents of thalassemic children.

Methodology: A cross-sectional study was conducted from Oct 2019 to Feb 2020 in Hyderabad, Sindh, Pakistan. Three hundred and eleven thalassemic children families were included in the study using a convenient purposive sampling technique. After informed consent, the parents were interviewed and a proforma was filled out. Performa had questions about personal information, family information, and thalassemia awareness. Data was entered in SPSS version 21. Qualitative data was measured in frequencies.

Results: Among Three hundred and eleven thalassemic families, 26.4% didn't know consanguineous marriage causes thalassemia; 72.3% of participants weren't tested for thalassemia; 98.7% didn't consult a doctor before marriage; only 1 % of participants did prenatal genetic testing after pregnancy; 86.8% of the parents' marriages were consanguineous. In 31.5% of these 311 children, the mother was her husband's first cousin (daughter of spouse's father's sister). 16.4% of mothers were daughters of their spouse's father's brother, 15.8% of the spouse's mother's brother, and 23.5% of the spouse's mother's sister. Most couple who had thalassemic children don't consult with a doctor nor do they go for genetic testing before marriage.

Conclusion: Consanguineous marriage is common among parents having a thalassemic child. Urgent policies should be advised and implemented for the proper education of thalassemic families at the earliest.

Keywords: Consanguinity, Consanguineous Marriages, Thalassemia.

Introduction

The name Thalassemia stems from two Greek words, "Thalassa," meaning floating sea, and "Emia," meaning blood.[1] Thalassemia is a monogenic hereditary disorder that is almost spread all over the globe.[1] Thalassemia is solely a genetically transmitted disease caused by the mutation or damaging hemoglobin synthesis on the alpha or beta globin chain. Researchers have calculated that 2.5 billion people have the variant gene for B-thalassemia and that around seventy thousand affected homozygous are born yearly.[2] About 3 to 10 percent of the global population has the variant gene associated with B-thalassemia.[3] Many nations are heavily impacted by Thalassemia, major or mild.[4]

Several circumstances can influence the rate at which beta-thalassemia worsens. Consanguinity, increased birthrate, lack of education, resources and awareness, all play a role in the increase in the incidence of Thalassemia.[5] The most significant risk factor for this rise in the rate is consanguinity.[5] The Latin prefix "con" means "common," and the noun "sanguine" refers to "blood," hence the word "consanguinity" is derived from these two concepts. In a consanguineous marriage, both partners share a common ancestor. It has to do with their biological and genetic forebears. First-cousin, second-cousin, and third-cousin marriages are all examples of consanguineous unions. Consanguineous marriages can arise for several causes, some of which are more stable than others. Consanguineous marriages are widely encouraged on both the local and national levels. There are more elements at play, such as social pressure for intracast marriage, illiteracy rate, poor socioeconomic condition, and lack of awareness. Consanguineous weddings are on the rise, and this may be attributed to families wanting to preserve their traditions by marrying within the same immediate family.[6]

Consanguineous marriages are the most serious concern internationally. Around 80-90 million beta-thalassemia carriers are prevalent owing to intermarriages. Thalassemia is more frequent in nations where consanguineous marriages occur.[7] There is a significant disparity in the rates of consanguineous marriages that occur between distinct communities or networks throughout the world, and there is also a significant

disparity in the rates of consanguineous marriages that occur between various groups and ethnic communities that reside inside the same country. The rate of consanguineous marriage may vary greatly from one generation to the next, depending on factors such as religion, customs, race, and geology. Among significantly impacted locations where this genetic condition is found include the Middle East, North Africa, Asia, Pakistan, and India.[8] About 4,000 to 5,000 children with Thalassemia are born in thalassemic carrier families in Pakistan every year.[9]

Pre-marital screening has decreased the birth prevalence of Thalassemia patients.[10] Comprehensive screening programs, accurate recognition and mentoring of at-risk couples, and pre-birth detection of the parents are all promising strategies for reducing mortality and spreading Thalassemia in countries where it is prevalent. Although testing for carrier status and parental diagnosis of beta-thalassemia has been available in Pakistan for over ten years, its usage has been limited due to low rates of awareness and high costs.[11] Despite the Sindh Provincial Assembly passing the Thalassemia Prevention and Control Bill 2013 on Sept 19, 2013, there is still a lack of parental education contributing to this disease's spread.[12] No extensive study on Consanguinity and Thalassemia has been done in Sindh, the second most populous province of Pakistan. We have conducted our study intending to determine the Parental Awareness of Thalassemia Transmission and the Role of Consanguineous Marriages in the district of Hyderabad, Sindh, Pakistan.

Methodology

This descriptive cross-sectional study was conducted from Oct 2019 to Feb 2020 at thalassemic center in Hyderabad, Sindh, Pakistan, after getting approval from the institutional ethical committee via letter no DRGS/3613. A total of Three hundred and eleven thalassemic children's parents were included in the study using a convenient purposive sampling technique. The sample size of 202 families was calculated using openEpi software, keeping a 95% confidence interval. Our sample size exceeded the required sample size. All parents who gave consent for the study were included, those who didn't give consent or children accompanied by their guardians were excluded from the study.

A self-structured Proforma having questions related to personal information, family information, and thalassemia awareness was made and checked by two subject experts. The performa was initially pilot-tested on parents of ten thalassemic children. The cronbach's alpha was 0.74. The validated performa was then distributed among the three hundred and eleven thalassemic children's parents. After getting informed consent, the questionnaire was filled out by interviewing parents of every registered thalassemic child. In order to ensure the confidentiality of the participants, the interview of the parents were done in a separate room furthermore the provided data was accessible only to the principal investigator. SPSS version 23.0 was used for both analysis and data entry. Qualitative data such as gender, relationship, and consanguineous marital history, were expressed in terms of frequencies and percentages.

Results

A total of 311 different families eligible for the study registered at the two thalassemic centers in Hyderabad were initially approached. All agreed to participate in the study so the response rate was 100%. The mean age of the children was 131.75 + 63.97 months. A higher prevalence of β-thalassemia was found in male children (n = 177, 56.9%) than in female children (n =

Table I: Distribution of ß-thalassemia children according to gender and number of thalassemic children born from thalassemia carrier families

Gender	Frequency	Percentage (%)
Female child	134	43.1
Male child	177	56.9
Number of Total Children in family	Frequency	Percentage (%)
≤2	90	28.9
>2	221	71.1
No of Thalassemic children in family	Frequency	Percentage (%)
≤2	273	87.8
>2	38	12.2

134, 43.1%). Seventy-one percent of all thalassemic children belonged to families with more than two children. 87.8% of the thalassemic children have either no sibling or one other thalassemic sibling. At the same time, 12.2% of thalassemic children have more than two other thalassemic siblings (Table I). Forty percent of the parents had a thalassemic sibling. Seventy percent of the parents said that they knew consanguinity has a role in Thalassemia., but only one percent of the parents consulted their doctors for Thalassemia before marriage, and twenty-seven percent of the parents tested themselves for thalassemia carrier status. Eighty-seven percent of the parents had a consanguineous wedding. Of 311 families, 149 had paternal consanguineous marriages, while 121 had maternal consanguineous marriages (Table 2) (Fig 1,2,3).

Table 2: Awareness regarding Thalassemia and Consanguinity among parents of Thalassemic patients

Variable	Yes		No	
	Frequency	Percent (%)	Frequency	Percent %
1. Any of your Siblings have Thalassemia?	126	40.5	185	59.5
2. Do you know that consanguinity has role in Thalassemia?	219	70.4	92	29.6
3. Do you have a Consin marriages	270	86.8	41	13.2
4. Have you consulted with doctor before marriage?	4	1.3	307	98.7
5. Have you tested yourself for the Thalassemia trait?	86	27.7	225	72.3
6. After pregnancy did you go for prenatal genetic testing	3	1	308	99
Frequency of Thalasemmia among paternal, maternal, and no direct relation				
	Frequency	**Percent (%)**		
Paternal	149	47.9		
Maternal	121	38.9		
No direct relation	41	13.2		
Frequency among direct relatives of paternal, maternal, and no direct relations				
Father's sister (Phupho)	98	31.5		
Father's brother (Chacha)	51	16.4		
Mother's brother (Mamoo)	49	15.8		
Mother's sister (Khala)	73	23.5		
No relation	40	12.9		

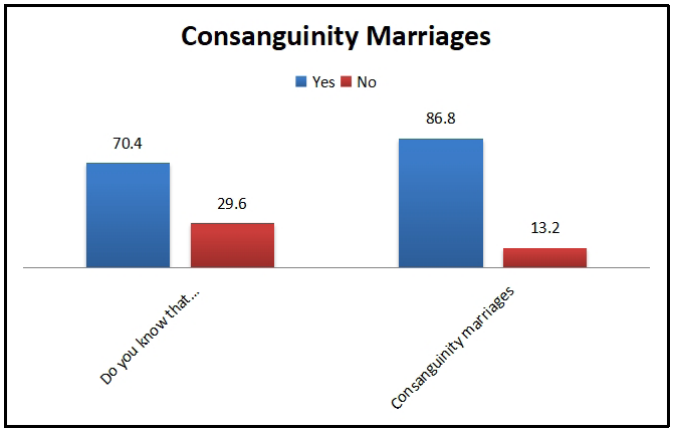

Figure 1: Frequency of Consanguinuous Marriages among families

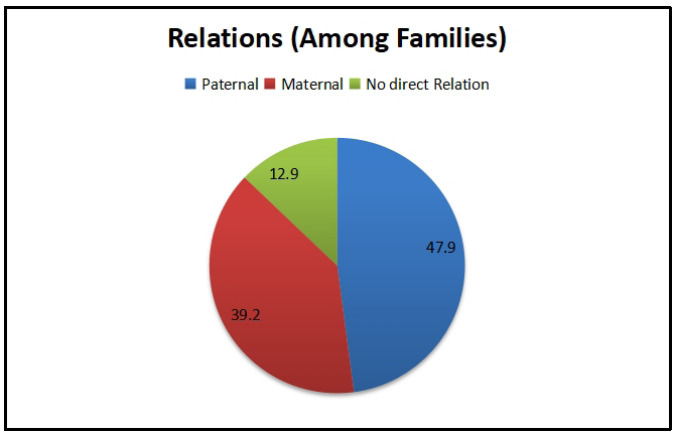

Figure 2: Distribution of Relationship among Families (paternal and maternal)

Discussion

Thalassemia is a global issue, and Consanguinuous marriages are the most severe concern internationally. The increase in consanguineous marriages in underdeveloped countries is worrisome. It is associated with an increase in the prevalence of Thalassemia. Despite advancements in health sciences, thalassemic families are still unaware. Our study showed that the incidence of Thalassemia in consanguineous marriages has increased, and families still lack awareness.

Among Three hundred and eleven thalassemic children families, 29.6% didn't know consanguineous marriage causes thalassemia (Table 2; Figure 1). 72.3% of participants weren't tested for thalassemia, and 98.7% didn't consult a doctor before marriage. only 1 % of participants did prenatal genetic testing after pregnancy(Table 2). 86.8% of the parents' marriages were consanguineous (Figure 1). In 31.5% of these 311 children, the mother was her husband's first cousin (daughter of spouse's Father's sister). 16.4% of mothers were daughters of their

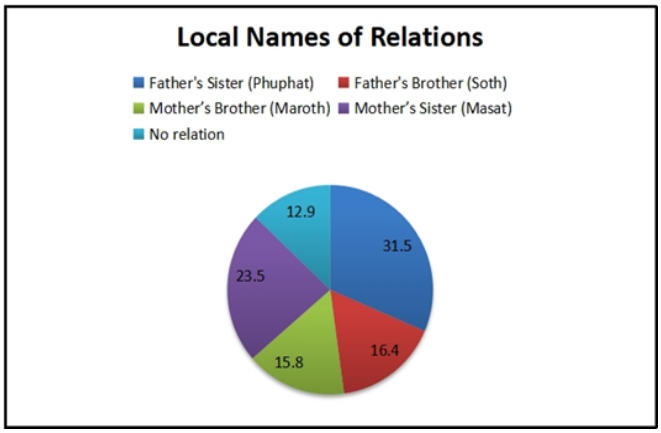

Figure 3: Distribution of Relatio ship among Families with local Names

spouse's Father's brother, 15.8% of the spouse's mother's brother, and 23.5% of the spouse's mother's sister(Table 2; Figure 3).

Our data represents that 86.8% of the β-thalassemia carrier are born with consanguineous marriages(Figure 1). It is in accordance with literature.It has been reported that 25%–60% of all marriages from Arab Regions are consanguineous.[13] According to statistics, first-cousin marriages make up about 31% of all consanguineous marriages, which have a 42 percent overall prevalence in Lebanon.[14] According to a study by Khan et al, 74% of thalassemic parents in the KPK province of Pakistan had consanguineous marriages.[15] A study by Ishaq et al showed that consanguineous marriages are associated with Thalassemia in 81.7% of the cases.[16]

Our study shows that Thalassemia is more prevalent in males than females. A study conducted t in district Dadu, Sindh, which showed the prevalence of Thalassemia as 54.76% in males.[17] Our current study showed the prevalence of Thalassemia as 56.7 % in males and 43.1% among females(Table 1). Several studies have reported that the male gender is more affected by Thalassemia than the female gender.[15, 17-18] Why males are at higher risk of getting Thalassemia needs to be investigated.

Our study showed that despite having a thalassemic child almost 30 % of the parents don't know that consanguineous marriage is associated with Thalassemia which is quite worrisome. Moreover, only about 1 % of the parents consulted their doctor for Thalassemia before marriage and after marriage during pregnancy for prenatal screening. This lack of awareness is a burning issue in our locality. Previous studies have shown that the main non-biomedical reason that causes families to experience severe social, economic, and psychological issues is a lack of knowledge and awareness regarding Thalassemia.[19] The amount of knowledge and education of the families affected by the disease determines awareness of and attitudes

toward screening procedures for the treatment of the disease.[20] Failure to recognize the inheritance patterns has a significant negative physical and social impact on the affected patients and their families in the form of Thalassemia.[21]

This lack of awareness dates back to ancient times, a sufficient degree of public education and awareness combined with a trained general society attitude regarding these thalassemia concerns has shown to be an effective countermeasure to the spread of Thalassemia.[22] Abu shosha et al concluded that to effectively manage and prevent Thalassemia, one must have a thorough understanding of beta thalassemia major.[23]

Surprisingly, in our study 71.1% of families have more than two children, and of those families, 87.8% suffer from thalassemia after the disease was diagnosed in their first kid. However, among families with thalassemia patients, there is still a significant risk of the presence of asymptomatic carriers and the transmission of the disease to new generations of susceptible children. It will take a significant amount of work to eradicate this genetic condition since the overall number of people suffering from thalassemia is dramatically on the rise in our population. In these kinds of situations, increasing knowledge and encouraging premarital testing may be a great assist in reducing the risk of thalassemia being passed down from parent to child. It was also a concerning finding of this investigation that just a few people, 27.7 percent, had an understanding of the relevance of prenatal screening in cases when the two guardians are carriers.

Lack of understanding about the causes and treatment of beta thalassemia major not only makes the condition worse but also negatively affects the social and psychological well-being of parents of sick children.[24,25]

Several nations, like Greece, Italy, Cyprus, and Iran had a considerably larger burden of thalassemia than Pakistan had, yet they were able to effectively remove it from their society. For a considerable amount of time, these nations have not reported any new cases of thalassemia major among their newborns. At the same time, these nations have created great healthcare services to effectively manage thalassemia patients who are already a part of their populations.[26-29] On the other hand prevalence of thalassemia in Pakistan is still increasing. One of the reasons for this increase is the lack of awareness regarding Thalassemia and consanguinity. Education regarding these issues is the need of the hour among thalassemic families in specific and in public in general. Moreover, our higher authorities should take strict and prompt measures for thalassemia awareness.

Conclusion

Most couples who had thalassemic children don't consult with a doctor nor do they go for genetic testing before marriage. Consanguinary marriage is common among parents having a thalassemic child. Further, the paternal relation is at high risk as compared to the maternal. Prevalence of thalassemia in Sindh region of Pakistan is alarmingly high. One of the reasons for this increase is the lack of awareness regarding Thalassemia and consanguinity. Education regarding these issues is the need of the hour among thalassemic families in specific and in public in general. Moreover, our higher authorities should take strict and prompt measures for thalassemia awareness.

Limitations

Our study has a few limitations. We recruited the families who were visiting the two thalassemia centers presently working in Hyderabad city only. All those families who were not visiting these centers or were not having any treatment or staying at their homes were not included in the study.

Conflict of Interest: The authors declare no conflict of interest.

Author contributions: AMM: Conception & design,acquisition of data, analysis & interpretation of data, Final approval of the version to be published; ZAL, JW,FI, NS & RKA: Drafting the article and revising it critically, Final approval of the version to be published. All authors agree to to be accounTable for all aspects of the work related to the precision or reliability of the article.

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Original Article

Association of Raised C-Reactive Proteins with Prolonged ICU Stay in Children with Bronchopneumonia: A Cross-Sectional Study

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Abstract

Objective: To study the association of raised CRP with prolonged ICU stay in children with bronchopneumonia at Ghurki Trust Teaching Hospital, Lahore, Pakistan.

Methodology: This cross-sectional study was conducted in Paediatric Intensive Care Unit of Ghurki Trust Teaching Hospital, Lahore, Pakistan, for a duration of six months (June 2023 to December 2023). Out of 127 children admitted into ICU, 82 met the inclusion criteria, aged 2-60 months, diagnosed with bronchopneumonia. Upon admission, blood sample was taken for CRP levels and these levels were correlated with ICU stay, TLC count, O2 dependency, and antibiotics duration of the patients. Patients were divided into five groups based on CRP counts. CRP counts less than 0.3 mg/dL were taken as normal. CRP counts from 0.4-0.9 mg/dL were taken as mild, 1-10 mg/dL were considered moderate, 11-49 mg/dL were considered marked, and ≥50 mg/dL were considered severe.

Results: Out of 82 patients, 45 (54.88%) were males and 37 (45.12%) were females. This study found that raised CRP was present in 73 (89.02%) out of 82 children ($p<0.04$). Amongst 73 (89.02%), 08 (10.96%) patients had mild elevation of CRP, 36 (49.32%) had moderate elevation, 22 (30.14%) had marked, 07 (9.59%) had severe elevation. Moreover, a direct relation was observed among CRP and ICU stay (3.82±3.12), O2 requirements (3.72±3.07), TLC (13.36±5.18), antibiotic treatment duration (9.52±3.94) of broncho pneumonic patients.

Conclusion: Higher CRP levels significantly result in longer ICU stays and higher oxygen requirements in children with bronchopneumonia.

Keywords: Bronchopneumonia, Creactive proteins, Paediatric Intensive Care Unit, World Health Organization.

Introduction

In numerous developing countries, pneumonia is the most prevalent cause of mortality among children under the age of five.[1] It is a contributing factor to sepsis or mortality.[2] Approximately 30% of community-acquired pneumonia cases develop into severe pneumonia because of delayed detection and treatment.[3] Furthermore, compelling data indicates a rise in severe pneumonia cases.[4] Severe pneumonia is characterized by the need for admission to an intensive care unit and often leads to death.[5] Prompt and efficient therapy for pneumonia is essential. The World Health Organization (WHO) advises using established therapies for moderate and severe pneumonia cases.[6] Nevertheless, the unavailability of suiTable medications and equipment in developing nations still needs to be improved. Moreover, severe pneumonia contributes to the continuation of mortality rates related to nosocomial infections.[7] To decrease the death rate and enhance prognosis, diagnosing pneumonia promptly before it reaches a severe stage is crucial. Various organisms cause pneumonia; however, it is challenging to pinpoint the specific infections responsible. Determining moderate and severe pneumonia primarily relies on the clinical manifestation and physical assessment.[8] The predictability of the clinical course and prognosis of pneumonia may be enhanced through an integrated assessment of the clinical symptoms and CRP levels. The diagnostic significance of the CRP level in patients with a significant risk of pneumonia is unknown. The role of clinical signs, inflammatory markers, and symptoms in predicting the onset of severe pneumonia remains uncertain.

Therefore, it is necessary to conduct a comprehensive investigation on a large population to validate the diagnostic precision of CRP regarding clinical signs and symptoms in predicting the occurrence of severe pneumonia. Severe pneumonia can result from bacterial, viral, or combination illnesses.[9] This study aims to show the association and direct link of increasing CRP with increasing hospital stay primarily and the TLC, O_2 and antibiotics duration.

Methodology

This cross-sectional study was undertaken

Table I: Patients demographic variables with mean age and mean weight

Sr. No.	Gender	Frequency (%)	Mean Age (months) (Mean ± SD)	Mean Weight (Mean ± SD)
01	Male	45 (54.88%)	9.97±8.12	7.34±2.81
02	Female	37 (45.12%)	9.54±10.00	6.92±3.08
03	Total	82	10.06±11.52	7.45±3.47

at the Department of Paediatric Medicine, Lahore Medical and Dental College / Ghurki Trust Teaching Hospital, Lahore, following authorization from the Ethical Review Committee of LMDC/GTTH (Ref No.2023/06/R-03). Non-probability consecutive sampling technique was used to select patients admitted to the hospital. Sample size was calculated using WHO sample size calculator (version 1.1) having 95% confidence interval, anticipated population proportion of 0.79, and absolute precision of 0.09.[10] Out of 127 children admitted into PICU, we enrolled 82 patients fulfilling the inclusion criteria within the given time frame of 21st June 2023 to 21st December 2023. Diagnosis was established based on tachypnea (respiratory rate>50/min), signs of respiratory distress (intercostal and subcostal recessions) and radiological findings in form of chest X ray.[11] The respiratory rate thresholds established by WHO for the identification of children with pneumonia are as follows: Infants under 2 months of age: For children aged 2-12 months, a respiratory rate of 60 breaths per minute or higher is considered normal. For children aged 1-5 years, a respiratory rate of 50 breaths per minute or higher is considered normal.

For children aged 1-5 years, a respiratory rate of 40 breaths per minute or higher is considered normal.[12] Those with malnutrition, suspected viral etiology, primary immune deficiency, congenital heart disease and chronic lung pathology were excluded from study. Informed consent was taken from parents of the patients. Demographic data (including name, age, gender, and weight) was collected. Upon admission, a blood sample was collected from each patient and sent to the Ghurki hospital laboratory for analysis; CRP levels were measured and correlated with ICU stay, TLC count, O_2 dependency and antibiotics duration of the patients. To do so, patients were divided into five groups based on CRP counts. CRP counts less than 0.3 mg/dL were taken as normal. CRP counts from 0.4-0.9 mg/dL were taken as mild, 1-10 mg/dL were considered moderate, 11-49 mg/dL were considered marked, and ≥50 mg/dL were considered severe.[13] The data analysed using the Statistical Package for the Social Sciences, version 27 (SPSS).

Results

During the study period, 127 patients, with the clinical diagnosis of bronchopneumonia, were admitted in the Paediatrics Department of Ghurki Trust Teaching Hospital, Lahore. Out of 127, 82 patients with the clinical diagnosis of bronchopneumonia, fulfilling the inclusion criteria, participated in the study. The admission mean age was 10.06±11.52 months ranging from 02 to 60 months, respectively. Out of the 82 patients, 45 (54.88%) were males and 37 (45.12%) were females with male to female ratio of 1.2:1. Their mean weight at the time of admission was 7.45±3.47 as given in Table I.

Signs of respiratory distress (intercostal and subcostal recessions) and increased respiratory rate thresholds were recorded in all children. Among clinical characteristics, cough, fever, diarrhoea and pleural effusion were taken under consideration. Patients' clinical characteristics are given in Table 2. In this study, we found that CRP was noticeably raised in 73 out of 82 neonates accounting for 89.02% of total patients ($p<0.04$). Out of 73 (89.02%), 08 (10.96%) patients had mild elevation of CRP, 36 (49.32%) had moderate elevation, 22 (30.14%) had marked, 07 (9.59%) had severe elevation. Patients who showed a noTable rise in CRP levels had longer stays in the paediatric intensive care unit, with an average duration of 5.86±1.77 days. Furthermore, these patients exhibited elevated levels of total leukocyte count (TLC), with an average of 19.47±6.28. In addition, they exhibited a higher reliance on oxygen, with an average duration of 5.57±1.90 days. These individuals also necessitated extended durations of antibiotic treatment, with an average length of 11.86±4.95 days (Table 3).When a graph was plotted between CRP levels and ICU stay, O_2 requirement, TLC, and antibiotic treatment duration of broncho pneumonic patients, a direct relation was observed as dshown in graph 1 below. It means raised CRP not only increases ICU stay, but also increased TLC, duration of antibiotic treatment, and O_2 requirement in broncho pneumonic children.

Discussion

This study examines the association between increased levels of C-reactive protein (CRP) and extended hospitalizations in the paediatric intensive care unit among children with bronchopneumonia at Ghurki Trust Teaching Hospital in Lahore. During a six-month study including 82 patients, it was discovered that elevated levels of CRP are strongly linked to longer hospitalizations in the paediatric intensive care unit, increased need for oxygen, higher total leukocyte count (TLC), and longer durations of antibiotic treatment (Table 3). The study highlights the significance of CRP as an indicator for the seriousness of bronchopneumonia and its potential function in directing clinical treatment.

Bronchopneumonia is prevalent in children, particularly newborns and young children due to developing respiratory

Table 2: Clinical characteristics of broncho pneumonic children

Sr, No.	Groups	Patients with raised CRP (n=73)	Cough (n=60)	Fever (n=63)	Diarrhoea (n=31)	Pleural Effusion (n=51)
01	Normal	09	00	00	00	00
02	Mild	08	05 (62.50%)	07 (87.5%)	02 (25%)	03 (37.5%)
03	Moderate	36	31 (86.11%)	31 (86.11%)	11 (30.56%)	27 (75%)
04	Marked	22	18 (81.82%)	18 (81.82%)	14 (63.64%)	15 (68.18%)
05	Severe	07	06 (85.71%)	07 (100%)	04 (57.14%)	06 (85.71%)
06	Total	82	60	63	31	51

system, variation in pathogens and underdeveloped immune system lower levels of antibodies, and impaired function of respiratory epithelial cell cilia. Consequently, this can lead to a swift progression of diseases.[14] Hence, timely detection plays a crucial role in the medical administration of bronchopneumonia. The conventional approach to diagnosing pneumonia involves identifying a fresh infiltration on chest radiographs and recently developed respiratory signs and symptoms.[15] Primary care physicians depend exclusively on the patient's health record and physical examination for diagnosis. Empirical evidence has shown that assessing clinical symptoms and signs is inadequate for diagnosing pneumonia. Several variables need to be considered to forecast the progression of severe pneumonia. Prior research has examined the diagnostic importance of pneumonia. At the same time, further studies have suggested that pneumonia is linked to the severity of the disease and the likelihood of death in patients who are hospitalized with pneumonia.[16] Nevertheless, there has been no reported correlation between CRP and severe pneumonia, as far as we know. However, this study investigated that mild, moderate, marked and severely increased levels of CRP can enlengthen number of ICU admission days. The study findings revealed that individuals with severe pneumonia had greater CRP levels than those with mild pneumonia. This suggests that the continuous increase in serum CRP levels may be linked to the patient's health and the progression of severe pneumonia. One of the studies demonstrated that measuring CRP levels could provide more insight into distinguishing pneumonia from other lower respiratory tract infections.[17] Elevated CRP levels demonstrate positive predictive values (PPVs) of up to 97%. The high positive predictive values suggest that it may be reasonable to initiate therapy for pneumonia in children with elevated levels without waiting for the results of chest radiography.[18] This study had a total of 82 individuals diagnosed with bronchopneumonia, with 45 being male (54.88%) and 37 being female (45.12%). The average

Table 3: Mean values of dependant variables based on independent CRP variable

Sr. No.	CRP Category	Patients	ICU Stay (Mean ±SD)	TLC	O_2 dependency (days)	Days of Antibiotic Treatment (Mean±SD)	p value
1	Normal	09	2.00±2.35	9.08±3.79	1.56±1.81	7.78±1.79	0.12
2	Mild	08	1.88±3.48	11.05±2.75	2.14±3.67	7.50±3.12	0.37
3	Moderate	36	3.19±2.47	12.04±4.10	2.97±2.40	9.36±3.56	0.31
4	Marked	22	4.91±3.69	14.43±5.61	4.86±3.63	9.77±4.29	0.41
5	Severe	07	5.86±1.77	19.47±6.28	5.57±1.90	11.86±4.95	0.11
	Total (excluding normal)	73 (89.02%)	3.82±3.12	13.36±5.18	3.72±3.07	9.52±3.94	0.04

age of patients was 10.06±11.52 months, and the average weight was 7.45±3.47 kg (Table 1). The male-to-female ratio was 1.2:1, suggesting a somewhat greater occurrence in men. The considerable variation in average age (10.06±11.52 months) indicates that bronchopneumonia can affect a wide range of ages among children. The average weight of 7.45 kg accounts for the presence of newborns and young children. Nair et al., 2013 also reports a greater prevalence of respiratory illnesses in male children. The study conducted by Nair et al. also emphasizes the susceptibility of newborns and young children to respiratory infections as a result of their growing immune systems and respiratory anatomy.[19] Amongst 73

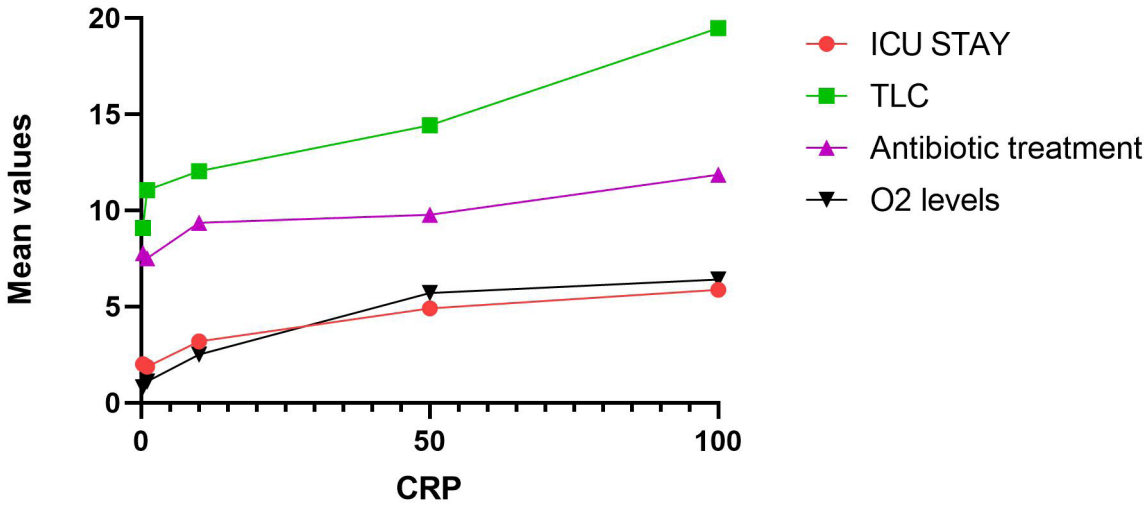

Figure 1: A direct relation observed between CRP levels and ICU stay, TLC, Antibiotic treatment, O_2 levels of mild, moderate, and severe patients

patients, 82.19% (60 patients) experienced cough, 86.30% (63 patients) had fever, 42.47% (31 patients) had diarrhoea, and 69.86% (51 patients) had pleural effusion (Table 2). The prevalence of these symptoms differed throughout the CRP categories (mild, moderate, pronounced, severe). The elevated occurrence of cough and fever aligns with the characteristic manifestation of bronchopneumonia. Diarrhoea was infrequent but noTable, and a considerable percentage of individuals exhibited pleural effusion, suggesting serious respiratory impairment. The association between symptoms and elevated CRP levels underscores the function of CRP as an indicator of the seriousness of the disease. Comparable findings observed by Holter et al. in 2015 demonstrated that severe pneumonia cases commonly exhibit symptoms such as cough, fever, and other clinical indications.[20] Holter et al. also discovered a positive correlation between these symptoms and elevated levels of inflammatory markers, such as CRP, which suggests the presence of a more severe form of the disease.[20] The study identified a noTable increase in CRP levels in 73 out of 82 patients, which accounts for 89.02% of the total. Patients exhibiting a significant increase in CRP levels experienced extended stays in the paediatric intensive care unit lasting an average of 5.86±1.77 days. These patients also had higher TLC levels, averaging at 19.47±6.28. Additionally, they displayed a greater dependency on oxygen, with an average duration of 5.57±1.90 days. Furthermore, these patients required longer courses of antibiotic therapy, lasting an average of 11.86±4.95 days (Table 3). An important connection ($p<0.04$) was found between CRP levels and the dependent variables mentioned.

The data indicates a correlation between elevated CRP levels and the severity of the disease, as seen by longer stays in the intensive care unit, greater total leukocyte count, increased need for oxygen, and prolonged use of antibiotics. This suggests that CRP can function as a dependable indicator for forecasting the seriousness of an illness and determining the appropriate level of treatment. Comparable findings may be seen in the studies conducted by Koster et al. in 2013,[21] as well as in the research conducted by Pepys and Hirschfield in 2003.[22] Koster et al. established that CRP serves as a good indicator for the diagnosis and evaluation of the seriousness of lower respiratory tract infections. Pepys and Hirschfield highlighted the significance of CRP in detecting severe infection and its ability to forecast clinical outcomes.[22]

Moreover, the graph illustrates a positive correlation between elevated CRP levels and the duration of ICU stay, TLC, oxygen need, and duration of antibiotic treatment (Figure 1). The visual data presented corroborates the statistical findings, highlighting a direct correlation between elevated CRP levels and the escalating severity of bronchopneumonia, hence requiring more aggressive medical measures. The significance of CRP as a predictive tool in the management of paediatric bronchopneumonia is emphasized by this relationship. A study conducted by Schuetz et al. in 2013 found similar findings, showing a correlation between CRP levels and the severity and prognosis of systemic infections, such as respiratory infections. Schuetz et al. emphasized that CRP could serve as a valuable tool for informing treatment choices and forecasting clinical outcomes in patients with severe illnesses.[23]

Limitations of the study

The study involved a limited sample of 82 patients from a single institution, and this limits the generalizability of the results. The small sample size used in this study may not accurately reflect the larger population, which limits the capacity to apply the findings to a wider context. The study utilized CRP levels as the main biomarker for evaluating the extent of bronchopneumonia. Nevertheless, CRP levels can be altered by diverse causes that are not connected to pneumonia, hence potentially compromising the reliability of CRP as the single indicator of illness severity.The diagnosis process of bronchopneumonia may have been affected by a certain level of uncertainty, particularly when distinguishing between bacterial and viral causes, due to the dependence on clinical signs, symptoms, and radiological findings.

Conclusion

Higher CRP levels significantly result in longer ICU stays, higher O_2 requirement, raised TLC, and increased duration of antibiotic treatment in children with broncho pneumonia.

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Original Article

Evaluating Communication Practices between Dentists and Dental Technicians

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Abstract

Objective: To evaluate the effectiveness of current communication practices and the understanding of technicians regarding written prescriptions.

Methodology: This Questionnaire based cross-sectional study was conducted in Lahore, from Aug 2023 to May 2024, to assess communication quality between dentists and dental technicians. The sample consisted of 50 dental technicians currently employed in ten different private and public dental laboratories in Lahore, Punjab. The selection of participants was carried out using non-probability convenient sampling. Undergraduate students pursuing dental technology were excluded from the study to maintain a focus on experienced professionals who actively participate in dental restoration processes. Data were collected using a modified standardized questionnaire, including items on demographics and communication quality. Data was collected, reviewed for completeness, and analyzed using SPSS v24.

Results: Most dental technicians (n=38, 68%) possess a BSc degree in dental technology with work experience ranging from 1 to 45 years. Communication preferences varied notably across workplace settings. About 46% (n=23) of the technician favored direct communication. There was a significant difference in communication modes between these settings (p=0.001), with a preference for personal visits, particularly among technicians from teaching institutes (n=23, 88.5%). The majority (n=42, 84%) reported positive receptivity from dentists, and 62% (n=31) indicated that communication was encouraged, particularly in teaching institutes. Issues regarding blank prescription cards were mixed, with 36% (n=18) never receiving them and 50% (n=25) consulting clinicians in such cases. Only 36% (n=18) of technicians felt they received sufficient information.

Conclusion: Most technicians prefer direct communication from dentists, particularly in teaching institutes, compared to those in commercial labs who favor phone calls. A major concern was the lack of sufficient information and blank patient prescriptions from dentists. Addressing these gaps through standardized protocols, modern digital tools, and enhanced training can improve patient outcomes.

Keywords: Communication, Dentist, Dental technicians, Prescription card.

Introduction

Dentistry is a challenging field that requires meticulous clinical and laboratory procedures. For successful outcomes in this discipline, it is crucial to maintain close communication between dental practitioners and technicians. Although dental technicians do not interact directly with patients, they play a vital role in fabricating prostheses based on the specifications provided by dental practitioners.[1] Effective communication between dentists and technicians is essential for creating high-quality and aesthetically pleasing prostheses. By employing advanced communication techniques, practitioners can ensure that the final restoration not only looks visually appealing but also performs optimally and replicates the missing structure precisely.[2] It is imperative for dentists to articulate their requirements clearly to the technicians. Effective communication, particularly through prep guides, significantly improves the quality of zirconia crowns and overall prosthetic treatments.[3] Despite the importance of collaboration in dental treatments, communication gaps can lead to errors in prosthesis fabrication, such as color mismatches, sizing issues, and anatomical inaccuracies.[4,5] These errors compromise patient care, increase treatment time, and incur additional costs. Traditional communication, like handwritten prescriptions and phone calls, often lacks clarity and detail, resulting in misunderstandings.[6, 7] Studies show that work authorization forms can improve communication, but they must include sufficient space and diagrams.[8,9] Modernizing communication methods and training is essential to reduce errors and enhance care quality.[7, 10]

Dental technicians often face ethical concerns when receiving poor quality impressions and records from dentists, which can hinder effective collaboration and lead to decreased treatment quality.[11] The introduction of digital communication tools and standardized forms has been seen as a way to improve clarity and reduce ambiguities, yet adoption varies widely and is often incomplete.[12] Effective communication ensures that prostheses meet both functional and aesthetic standards, crucial for patient satisfaction and clinical success. However, persistent gaps in communication can lead to errors in prosthesis fabrication, unnecessary costs, and increased treatment times, negatively affecting both patient outcomes and professional efficiency.[4] Given the shift towards digital technologies in dentistry, understanding the dynamics of current communication practices and identifying areas for improvement is essential for optimizing workflows and enhancing the overall quality of dental healthcare services.[13] The aim of this study is to assess

the effectiveness of communication practices between dentists and dental technicians and to understand how these practices impact the quality of dental prostheses and patient outcomes.

Methodology

This cross-sectional observational study was conducted over a period from August 2023 to May 2024, after the approval of the Institutional Review Board of de' Montmorency College of Dentistry (No. 1764/DCD), and the participating institute (IRB FMH÷92/07/24iRB 1192) and laboratories, focusing on assessing the quality of communication between dentists and dental technicians within the context of private and public dental laboratories in Lahore.

The sample consisted of 50 dental technicians currently employed in ten different dental laboratories across Lahore. The selection of participants was carried out using non-probability convenient sampling. Undergraduate students pursuing dental technology were excluded from the study to maintain a focus on experienced professionals who actively participate in dental restoration processes. Data collection was performed using a modified version of a standardized questionnaire originally developed by Juszczyk et al. adapted to better fit the local laboratory conditions.[14] This self-administrated questionnaire was designed to capture detailed information regarding the clarity and comprehensiveness of written instructions on work authorization forms and the overall quality of communication between dental practitioners and technicians. The questionnaire consisted of 14 close ended questions and two sections. The first sections involve demographics, while the second section has items targeting quality of communications and lucidity of the written instructions from the dentist to the technician. The questionnaire was validated and later pilot tested on 5 subjects and underwent several revisions before it was finalized. Prior to distributing the questionnaires, informed consent was obtained from all participants to ensure ethical standards were maintained. After participants completed the questionnaires, they were immediately collected and reviewed for completeness. Any forms found to be incompletely or incorrectly filled were promptly returned to the participants for correction on the spot, ensuring the integrity and completeness of the data before analysis.

The data collected during this study was systematically recorded and subsequently analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 24, by IBM Corporation, USA. Initially, descriptive statistics were employed to determine the frequencies and percentages of the responses, providing a foundational understanding of the data distribution and primary trends within the dataset. Statistical analysis included the application of chi-square tests to explore the associations between the quality of written communications and the perceived effectiveness of interactions between dental technicians and dentists. A p value of less than or equal to 0.05 was taken as significant.

Results

A total of 50 technicians responded, the response rate was 100%. The demographical data, educational qualification, work experience and specialization areas of the respondents is tabulated in Table 1. Minimum age of technician started from 20 years and maximum age was 65 years. Mean age of technicians was 29.4±11.22. The technicians had different qualification levels and were distributed into four groups i.e. Graduate with BS in Dental Technology, B.Sc Dental Technology, F.Sc with diploma in Dental Technology, and Matriculation with diploma in Dental Technology.. The demographical information of the participants, work experience and areas of specialization are exhibited in Table 1

Table 1: Demographic and Professional Profile of Participants

Demographics	n	%
Gender		
Male	42	84
female	8	16
Qualification		
BS Dental Technology	3	6
B.Sc Dental Technology	38	68
F.Sc	0	0
Matriculation	9	18
Workplace Type		
Teaching Institute	26	52
Commercial Laboratories	24	48
Specialization		
Crown and Bridge	20	40
General Dental Technician	14	28
Prosthodontics	12	24
Orthodontics	4	8

The results revealed that communication preferences among dental technicians varied by workplace setting (Table 2). Technicians in teaching institutes favored direct communication with clinicians, while those in commercial laboratories often preferred indirect channels. Personal visits were the preferred communication method overall, though phone calls were more common in commercial settings (Table 2). Most technicians reported positive clinician attitudes, including receptiveness to input and encouragement of communication. However, issues arose with handling blank prescription cards, as well as dissatisfaction regarding the sufficiency of information provided by dentists (Table 2).

Table 2: Comparison of communication quality and modes between technicians in teaching institutes and commercial laboratories

Variables	n(%)	Teaching Institutes n(%)	Commercial Laboratories n(%)	X^2	p-value
Preferred Communication Method with Dentists					
Direct communication	23(46)	13(50)	10(41.7)	66.14	<0.001
Through lab manager	10(20)	1(3.8)	9(37.5)		
Through practice manager	8(16)	8(30.8)	0(0)		
Through collection manager	9(18)	4(15.4)	5(20.8)		
Current Communication Method with Dentists					

Variables	n(%)	Teaching Institutes n(%)	Commercial Laboratories n(%)	X^2	p-value
By phone	13(26)	1(3.8)	12(50)		
Using lab prescription card	9(18)	2(7.7)	7(29.2)	75.08	<0.001
Personal visits	28(56)	23(88.5)	5(20.8)		
Is Communication Welcomed by Dentists?					
Yes	42(84)	24(92.3)	18(75)	53.83	<0.001
No	8(16)	2(7.7)	6(25)		
Is Communication Encouraged by Dentists?					
Yes	31(62)	20(76.9)	11(45.8)	56.22	<0.001
No	19(38)	6(23.1)	13(54.2)		
Do Dentists Act on Technician Suggestions?					
Yes	45(90)	25(96.2)	20(83.3)	53.32	<0.001
No	5(10)	1(3.8)	4(16.7)		
Are Technicians Expected to Follow Instructions Strictly?					
Yes	5(10)	2(7.7)	3(12.5)	51.32	<0.001
No	45(90)	24(92.3)	21(87.5)		
Handling of Blank Patient Work Prescriptions					
Accept and proceed with the work	3(6)	2(7.7)	1(4.2)		
Consult clinicians for guidance	25(50)	11(42.3)	14(58.3)	52.87	<0.001
Reject the work offered	4(8)	3(11.5)	1(4.2)		
Sufficiency of Information Provided by Dentists					
Yes	18(36)	11(42.3)	7(29.2)	51.95	<0.001
No	32(64)	15(57.7)	17(70.8)		

Discussion

This study evaluated communication practices between dentists and dental technicians in Lahore, focusing on technicians' understanding of written prescriptions. Conducted from August 2023 to May 2024, the research surveyed 50 experienced dental technicians working in private and public dental laboratories. The findings revealed a preference for direct communication, especially among those in teaching institutes, while technicians in commercial labs favored phone calls. Most technicians reported positive communication from dentists, but concerns were raised about insufficient information and the handling of blank prescription cards. The study highlights the need for standardized communication protocols and better information-sharing practices to enhance the quality of dental care and patient outcomes.

The demographic composition of the participants in this study reflected a predominant male presence (Table 1). However, a significant disparity was observed in the average age of technicians, 29.4 years in the current study versus 45.6 years in previous studies, suggesting a younger workforce in Lahore's dental laboratories. A concerning finding was that 18% of technicians lacked formal education in dental technology, a reflection of the deficiency of regulatory oversight in Pakistan.[15,16] Moreover, the impact of educational background on communication was evident, with technicians from less educated backgrounds feeling their input was less valued. This emphasizes the critical role of education in enhancing communication skills within the dental field.[8]

Communication patterns varied significantly, with 46% of technicians preferring direct communication with clinicians (Table 2), a stark contrast to the 87% observed in the United Kingdom.[9] This discrepancy could stem from different organizational structures and the perceived effectiveness of communication skills and management in different cultural contexts.[17] The qualifications of technicians markedly influenced their interaction with clinicians, where higher qualified individuals reported more positive responses to their suggestions.[17,18] Regarding the handling of prescriptions, 64% of technicians reported receiving blank prescription cards, mirroring findings from earlier studies like Juszczyk et al.[14] This recurrent issue underscores a global challenge in dental practice, where inadequate written instructions compromise the quality of dental prostheses.[19] Historical and contemporary studies

consistently reveal that poorly completed work authorization forms and unclear instructions are prevalent issues that hinder effective communication between dentists and technicians.[5,19,20]

A study in Casablanca revealed that traditional communication methods like written prescriptions and phone calls still dominate, but often lead to misunderstandings due to incomplete or unclear instructions.[21] This underscores the need for improved communication training and the adoption of modern technologies, also including the standardization of work authorization forms and the integration of modern communication technologies.[21, 22] In the present study, most respondents preferred direct communication through personal visit and phone call, underscoring a need for the introduction of modern technology and fast and effective communication through digitizing the system by involving the web and phone applications. Moreover, it is imperative to integrate communication skills into the curriculum of dental education and to provide continuing education opportunities for practicing professionals. By fostering a deeper understanding of each other's roles and enhancing interaction skills, the dental industry can improve the quality of care delivered to patients and reduce the incidences of miscommunication that lead to clinical errors.[23, 24]

Limitations

The limited sample size owing to the small number of qualified technicians is one of the limitations of the study, therefore, the findings cannot be generalized to the broader population. Moreover, a larger and diverse sample is recommended for future studies. The present study not only highlights the existing gaps in communication between dentists and dental technicians, but also suggests that improving these interactions through education, regulatory measures, and technological advancements could significantly enhance the outcomes of dental treatments. To improve dentist-technician communication, adopt digital tools like exocad for precise case sharing and cloud systems for real-time updates. Provide training on material science for dentists and occlusal principles for technicians. Incorporate workshops and VR simulations to enhance collaboration, ensuring better workflow, accuracy, and patient outcomes.

Conclusion

The study highlights significant differences in communication preferences between technicians in teaching institutes and commercial laboratories, with the former favoring direct communication and the latter relying more on phone calls. Key concerns include insufficient information from dentists and unclear handling of blank prescription cards, emphasizing the need for clear guidelines and improved collaboration to enhance care quality.

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Original Article

Psychosocial Resilience and Quality of Life in Patients with End-Stage Renal Disease Undergoing Hemodialysis: A Cross-Sectional Study

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Abstract

Objective: To evaluate psychosocial resilience and quality of life (QOL) in patients with end-stage renal disease (ESRD) undergoing hemodialysis at a private hospital in Punjab, Pakistan.

Methodology: This cross-sectional study included 191 ESRD patients undergoing hemodialysis at a private center in Lahore, Pakistan, from January to December 2022. Eligible participants were aged 18 or older, diagnosed with ESRD, and receiving regular hemodialysis. Exclusion criteria included acute kidney injury, incomplete medical records, cognitive impairments, or psychiatric disorders. Resilience was measured using the Connor-Davidson Resilience Scale (CD-RISC), and quality of life (QOL) was assessed with the WHOQOL-BREF™ questionnaire. Demographic and clinical data were also collected. Data were analyzed using SPSS version 25.0, with descriptive statistics, one-way ANOVA, and post hoc Bonferroni correction. A p-value of <0.05 was considered statistically significant.

Results: The study involved 191 hemodialysis patients with a mean age of 53.4 ± 14.2 years, 45% male and 55% female. Common co-morbidities included hypertension (85%), diabetes (65%), and cardiovascular disease (40%). The mean duration of ESRD was 5.6 ± 3.2 years, with 70% undergoing hemodialysis three times per week. Most patients (60%) had higher education, while 15% had no formal education, and 70% were married. Resilience, measured by the CD-RISC, had a mean score of 45.27 ± 8.35, and QOL, measured by the WHOQOL-BREF™, had a mean score of 51.71 ± 6.30. Both scores were significantly lower than population norms ($p = 0.029$ for resilience, $p = 0.001$ for QOL), indicating considerable psychological challenges.

Conclusion: ESRD patients on hemodialysis experience low levels of psychosocial resilience and quality of life, highlighting the need for targeted interventions to improve these critical aspects of patient well-being.

Keywords: End stage renal disease, Resilience, Hemodialysis, Quality of life, Social support.

Introduction

End-Stage Renal Disease (ESRD) is the final stage of chronic kidney disease, where the kidneys have lost nearly all their ability to perform essential functions, such as filtering waste and maintaining fluid and electrolyte balance.[1] Patients suffering from ESRD experience physical, emotional, and psychological health impact. Recent resilience index, mental health, and QOL studies in ESRD patients show that particular psychosocial aspects can improve treatment results. Resilience impacts mental health, QOL, and psychological strain in ESRD and other chronic disease patients every day.[1] Resilient ESRD patients are less depressed and more dialysis-ready. Social support is a crucial resilience factor. Having strong social networks and community ties positively impacts individuals in several ways.[2,3]

Additionally, social support plays a crucial role in influencing the quality of life of individuals with ESRD.[4] Researchers found that patients with stronger social support experienced better mental health and fewer depressive symptoms.[5] Many studies have explored the relationship between social connections and quality of life, consistently demonstrating that improved interpersonal interactions contribute positively to patient health.[6,7] Dialysis patients complain of weariness more often, affecting QOL and physical function.

This study adds to existing literature by examining how sleep disturbances and resilience levels influence depression, anxiety, and both physical and mental health in patients with ESRD. These factors are critical in understanding the overall well-being of ESRD patients and offer insights into potential interventions to improve their quality of life. Dialysis patients, as assessed using the Pittsburgh Sleep Quality Index, often experience poor sleep quality.[7] Treatment for ESRD patients who wake up at night may include cognitive-behavioral therapy or sleep hygiene counseling. Resilience, psychology, and quality of life in ESRD patients are more complex than initially imagined. Dialysis is the next step for patients with physical and emotional issues. It shows that resilience minimizes these risks to improve mental health and life.[2]

Up to one-third of ESRD patients suffer from depression and anxiety, making psychosocial status a key factor in QOL.[8] This study highlights how resilience and social support can help ESRD patients

manage mental and emotional issues and improve their quality of life. Dialysis patients often exhibit signs of poor mental and physical health, including fatigue, sleep disturbances, and restricted food intake, leading to both physical and psychological deterioration.[9] Dialysis patients exhibit signs of lower mental and physical health, including fatigue, poor sleep, and restricted food and physical and psychological deterioration symptoms. Furthermore, dialysis patients are particularly affected by exhaustion, which impacts their QOL and physical function.[10]

This study adds to the existing literature by exploring how sleep disturbances and resilience levels influence depression, anxiety, and both physical and mental health in ESRD patients. These factors are critical for understanding the overall well-being of ESRD patients and offer potential pathways for interventions to enhance their quality of life. Dialysis patients, as assessed using the Pittsburgh Sleep Quality Index (PSQI), frequently report poor sleep quality. Treatment for ESRD patients who wake up at night may include cognitive-behavioural therapy or sleep hygiene counselling. The resilience, psychological well-being, and quality of life of ESRD patients are more complex than previously thought. Dialysis, as a treatment for patients with physical and emotional challenges, can be optimized by addressing resilience, which reduces the risk of mental health issues and improves overall life quality.

Both locally and globally, there is a scarcity of studies assessing resilience and QOL specifically in hemodialysis patients, limiting a comprehensive understanding of the psychological impact of this treatment modality. This study used two tools, the Connor-Davidson Resilience Scale (CD-RISC)[11] and the WHOQOL-BREF™,[12] to measure resilience and quality of life in hemodialysis patients. The CD-RISC is a 25-question scale that looks at how well patients can handle stress and challenges. The WHOQOL-BREF™ is a 26-question survey that checks different aspects of life, including physical health, mental well-being, relationships, and living conditions.[12]

Both tools are effective in understanding the overall impact of chronic kidney disease on patients' resilience and quality of life. By focusing on this patient group, the research provides valuable observations into how resilience impacts their mental and physical health outcomes. Based on the findings, it is anticipated that targeted therapeutic and psychological interventions will enhance individualized care and improve the quality of life for hemodialysis patients. The primary goal of this study is to better understand the psychological factors influencing ESRD patients, with a particular focus on resilience and quality of life, to inform more effective patient care strategies and improve patient outcomes in this underrepresented population.

Methodology

This cross-sectional observational study aimed to assess psychosocial and physical resilience in patients with ESRD undergoing hemodialysis. Data were collected from 191 ESRD patients at a private Hemodialysis Center in Lahore, Pakistan, from January to December 2022. Ethical approval was obtained from the Institutional Ethics Committee (GAUS/MDEC/D10/0083). Patient confidentiality was maintained, and data were anonymized during analysis. Written informed consent was obtained from all participants before enrollment.

The study included 191 patients diagnosed with ESRD and undergoing regular maintenance hemodialysis. Participants had a disease history ranging from 6 months to several years and were receiving ongoing treatment at the Hemodialysis Center. The mean follow-up duration for the participants was two weeks, providing a representative sample for assessing psychosocial and physical resilience in this specific treatment group. Eligibility for the study required patients to be aged 18 years or older, diagnosed with ESRD, and undergoing hemodialysis. Participants were required to voluntarily sign informed consent and to have the cognitive and physical ability to complete the study assessments. Exclusion criteria included patients with acute kidney injury, incomplete medical records, cognitive impairments, or psychiatric disorders that would hinder the completion of the study questionnaires. These criteria helped minimize bias and ensure that the collected data were as accurate as possible.

Data Collection Tools

Psychosocial resilience was measured using the Connor-Davidson Resilience Scale (CD-RISC),[11] a 25-item Likert scale that assesses resilience, with higher scores indicating greater resilience. Quality of Life (QOL) was assessed using the WHOQOL-BREF™ questionnaire,[12] which consists of 26 items across four domains: physical health, psychological health, interpersonal relationships, and the physical environment. Items were rated on a Likert scale, with higher scores indicating better quality of life. These tools provided valuable insights into the psychosocial and mental health status of the participants.

Procedure

Participants were consecutively recruited during their routine hemodialysis sessions. After explaining the study's objectives, patients were asked to self-complete the one time questionnaire, CD-RISC to assess resilience and WHOQOL-BREF™to measure the QOL , with trained research assistants present to ensure consistency and minimize scoring variability. Demographic information such as gender, age, co-morbidities, clinical characteristics, duration of ESRD, and type of treatment were also collected for analysis.

Data were analyzed using SPSS version 25.0. Descriptive statistics were reported as mean ± SD for continuous variables and frequencies with percentages for categorical variables. Differences between the study variables were assessed using one-way ANOVA. A post hoc analysis with the Bonferroni correction was performed to identify specific group differences. A p-value of <0.05 was considered statistically significant.

Results

The mean resilience score, as measured by the Connor-Davidson Resilience Scale (CD-RISC), was 45.24 ± 8.35, indicating low levels of resilience among the participants. The QOL, assessed through the WHOQOL-BREF™ scale, had a mean score of 51.72 ± 6.30, reflecting significant

impairment in overall quality of life (Table 2). Statistical analysis revealed that the resilience score was significantly lower compared to established population norms (p-value = 0.029). Similarly, the QOL score was also significantly lower compared to general population expectations, with a p-value of 0.001. These results highlight the significant psychological and emotional challenges faced by individuals on hemodialysis, emphasizing the need for targeted interventions to improve both resilience and quality of life. This Table provides a clear overview of the key statistics for the hemodialysis patients (n=191), including the resilience score and quality of life.

Table 1: Socio-Demographic and Clinical Characteristics of Hemodialysis Patients

Demographic Parameter	**Frequency (%) / Mean ± SD**
Total Sample Size	191
Age	Mean = 53.4 ± 14.2 years
Gender	45% Male, 55% Female
Co-morbidities	
- Hypertension	85%
- Diabetes	65%
- Cardiovascular Disease	40%
Duration of ESRD	Mean = 5.6 ± 3.2 years
Frequency of Hemodialysis	3x/week: 70%, 2x/week: 30%
Education Level	
- No formal education	15%
- Primary/Secondary school	25%
- Higher education	60%
Marital Status	70% Married, 20% Single, 10% Divorced
Employment Status	35% Employed, 65% Unemployed

Table 2: Resilience and Quality of Life Scores in Hemodialysis Patients

Variable	**Hemodialysis Patients (n=147)**
Resilience Score (CD-RISC)	45.24 ± 8.35
Overall Quality of Life (WHOQOL-BREF)	51.72 ± 6.30
P-value	0.029

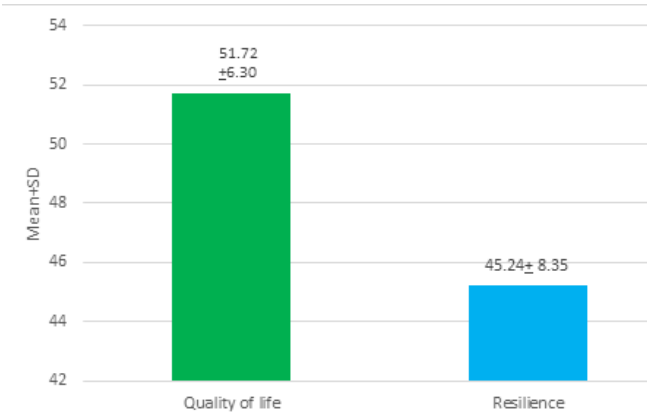

Figure 1: Resilience and Quality of Life Scores in Hemodialysis Patients

Discussion

This study aimed to assess the psychosocial resilience and overall QOL in a cohort of 191 patients undergoing hemodialysis for ESRD. The findings highlight the considerable challenges faced by these patients, both physically and psychosocially. The resilience scores of hemodialysis patients were notably low, which aligns with well-documented evidence suggesting a decline in psychological well-being due to the physical and functional impairments imposed by hemodialysis treatment. Factors like fatigue, dependency on dialysis schedules, and the continuous nature of therapy contribute significantly to the emotional and psychological toll experienced by these patients.

The socio-demographic and clinical characteristics of the patient population provide valuable context for understanding the resilience and QOL scores observed in this study. The mean age of the patients was 53.4 ± 14.2 years, representing a predominantly middle-aged group (Table 1), consistent with the known prevalence of ESRD in this age range.[13] Advancing age often contributes to physical frailty, psychological challenges, and reduced adaptability to chronic illnesses, which can negatively affect resilience and QOL. The gender distribution showed a slight predominance of females (55%) over males (45%) (Table 1). While ESRD affects both genders, female patients may experience greater psychological distress, such as anxiety and depression, due to societal roles, family responsibilities, and physical limitations imposed by hemodialysis.[12,14] These factors could partially explain the lower resilience and QOL scores among this group.

Hypertension (85%) and diabetes (65%) were the most prevalent comorbidities, which aligns with their established roles as primary risk factors for ESRD. The burden of multiple comorbidities, including cardiovascular disease (40%), complicates clinical management, contributes to fatigue and physical discomfort, and increases psychological stress—key factors that can impair both resilience and QOL.[13] Educational attainment was another critical factor, with 40% of patients having no formal education and 45% completing only primary or secondary schooling (Table 1). Lower educational levels can hinder understanding of the disease, treatment adherence, and access to health information.[15] This limited health literacy may contribute to increased psychological distress and reduce patients' ability to develop coping mechanisms, ultimately impacting resilience and QOL.

Furthermore, the high proportion of married patients (70%) suggests that marital support plays a role in managing chronic illness. However, it may also pose emotional and practical challenges, especially in the presence of functional limitations caused by ESRD. In summary, the patients' middle age, gender differences, high prevalence of comorbidities, and low educational attainment collectively highlight the multifaceted challenges faced by this population. Addressing these factors through targeted interventions, such as health education, mental health support, and social assistance programs, may help improve both resilience and QOL among hemodialysis patients.

The mean duration of ESRD was 5.6 ± 3.2 years, suggesting that most patients have been undergoing hemodialysis for a prolonged period (Table 1). Chronic exposure to the physical and emotional demands of frequent hemodialysis sessions can diminish patients' ability to cope effectively with their condition. Studies have shown that prolonged treatment duration is associated with psychological burnout, reduced social engagement, and increasing feelings of helplessness, which negatively affect resilience.

Regarding the frequency of hemodialysis, 70% of patients underwent treatment three times per week, while 30% received it twice per week. Patients requiring more frequent sessions often experience greater disruption to their daily lives, including reduced opportunities for employment and social activities. This time-consuming nature of hemodialysis imposes significant lifestyle restrictions, contributing to poorer QOL and resilience. The prolonged duration of hemodialysis treatment makes it increasingly difficult for patients to adjust psychologically. The frequent sessions and associated physical discomforts diminish psychological resilience, as patients face the ongoing burden of treatment with limited prospects for improvement in their condition. Chronic hemodialysis induces both physical and emotional exhaustion, exacerbating feelings of helplessness and reducing the ability to cope effectively with the demands of treatment.[16] Psychological stress, including anxiety, depression, and social isolation, is prevalent among hemodialysis patients, further contributing to the observed low resilience scores. Moreover, the physical intrusion of the procedure, coupled with long-term dependency on dialysis, results in decreased autonomy and a sense of loss, thereby diminishing the ability to adapt to these challenges.

In terms of overall QOL, the scores of hemodialysis patients were significantly low (Table 2, Figure 1). This finding is consistent with previous studies documenting poorer QOL among dialysis patients.[1,7] The study participants reported diminished physical and psychological well-being, as reflected in the physical and psychological domains of the WHOQOL-BREF™ questionnaire (Table 2, Figure 1). These results confirm earlier findings that dialysis patients often suffer from fatigue, pain, restricted mobility, and social disengagement due to the time-consuming nature of dialysis.[6,7,8] The frequent treatment sessions, which can span several hours multiple times a week, contribute to the loss of social interactions, decreased mobility, and dissatisfaction with their quality of life.

The psychosocial impact of these physical limitations is profound. Hemodialysis patients often experience social withdrawal and reduced opportunities for social engagement, which are essential for maintaining mental well-being.[17] The inconvenience and discomfort associated with dialysis, coupled with the psychological burden of managing a chronic illness, result in a significant reduction in QOL. These findings are consistent with studies where dialysis patients report lower QOL compared to other patient populations, including those with kidney transplants.

The psychological burden on hemodialysis patients is substantial and is reflected in both the lower resilience and QOL scores observed in this study. Patients undergoing hemodialysis not only struggle with the physical aspects of their condition but also with the emotional and psychological challenges associated with the treatment. Despite medical advancements, the chronic nature of kidney failure and the need for lifelong treatment often lead to feelings of hopelessness and anxiety about the future. The repeated cycles of dialysis, combined with the uncertainty of future health, contribute to the erosion of mental resilience.

Therefore, healthcare providers must address not only the physiological aspects of dialysis but also the psychological needs of these patients. Implementing interventions focused on mental health support, including counseling and stress management techniques, could help improve resilience and QOL in these patients. The study results suggest that healthcare strategies should encompass both medical and psychosocial interventions. Psychological support, such as counselling, social support programs, and stress management interventions, should be integrated into the care plans for hemodialysis patients. Education on coping strategies and the importance

of mental well-being could also empower patients to better manage the psychological challenges associated with their treatment.

The resilience scores, measured by the Connor-Davidson Resilience Scale (CD-RISC), revealed a mean score of 45.27 ± 8.35, suggesting a moderate level of resilience among the hemodialysis patient population (Table 2, Figure 1). This is consistent with literature showing that chronic illness, particularly ESRD, severely impacts a patient's ability to cope with ongoing stressors.[2,3,4,5]Resilience plays a crucial role in managing the psychological and emotional challenges of prolonged treatments like hemodialysis. The relatively low resilience scores in this study may reflect the emotional toll of managing a chronic illness, frequent hospital visits, and the physical limitations imposed by kidney failure.

The overall QOL scores, measured by the WHOQOL-BREF™ questionnaire, showed a mean of 51.71 ± 6.30 (Table 2, Figure 1). This score suggests that although patients on hemodialysis report poor quality of life overall, there is variation in QOL, with some patients managing better than others. The physical limitations imposed by hemodialysis, coupled with frequent hospital visits and associated costs, likely contribute to the lower QOL scores. In particular, the physical domain, which includes energy, pain, and mobility, is significantly affected in ESRD patients, consistent with findings in this study. Chronic kidney disease and its treatment, including hemodialysis,[18] result in multiple physical challenges such as fatigue, muscle weakness, and cardiovascular problems, all of which can reduce overall QOL.

Furthermore, the socio-economic challenges faced by many patients in this study, including unemployment (65% of patients were unemployed) and limited social support (10% reported low social support), may exacerbate feelings of isolation and contribute to poorer QOL.[19] The socio-economic context is crucial in understanding QOL in chronic disease patients.[20]

Low income, limited access to healthcare, and poor social support systems often lead to reduced treatment adherence and higher stress levels, negatively impacting both physical and psychological health.

Limitations

This study has some limitations that should be acknowledged. The cross-sectional nature of the study prevents us from making causal inferences regarding the relationship between resilience, QOL, and socio-demographic factors. Longitudinal studies are needed to better understand how resilience and QOL evolve over time in hemodialysis patients. Furthermore, the self-reported nature of the scales used in this study may introduce bias, as patients may have underreported or overreported their experiences due to social desirability or recall bias.

Conclusion

This study highlights the significant psychosocial challenges faced by hemodialysis patients, with low resilience and poor QOL scores being prevalent among the cohort. These findings emphasize the importance of addressing not only the physiological aspects of kidney failure but also the psychological and social dimensions of patient care.

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Conflict of Interest: The authors declare no conflict of interest.

Future Implications

The low resilience and quality of life reported by hemodialysis patients in this study highlight the need for targeted interventions to improve their well-being. Incorporating psychological support services, such as counselling and stress management programs, into routine care could make a meaningful difference. Tools like cognitive-behavioral therapy and mindfulness-based techniques may help patients better cope with the physical and emotional challenges of living with ESRD and its treatment. Future research should include qualitative methods, such as interviews or focus groups, to gain a deeper understanding of the psychosocial challenges faced by hemodialysis patients.

Authors' Contribution: H.Z.: study conception and design, data collection, statistical analysis, manuscript drafting, critical revision; J.I.: data interpretation, manuscript drafting, critical revision.

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Original Article

Role of Metformin in Reducing the Incidence of Gestational Diabetes Mellitus in Obese Women

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Abstract

Objective: To evaluate whether metformin administration reduces the incidence of gestational diabetes mellitus in obese women and to examine its impact on the incidence of preeclampsia, birth weight, and the APGAR scores of newborns.

Methods: This experimental study was done at Shalamar Hospital, affiliated with Shalamar Medical & Dental College, Lahore, Pakistan, from May1st 2022 to June 30, 2024. A total of 150 women with a BMI ≥ 30kg/m2, aged 18-40 years, between 11 to 14 weeks pregnant, were included. Those with contraindications to metformin, pre-existing diabetes, or any co-morbid medical disorder were excluded. The participants were divided into two groups with 75 in each: Group A the control group with only standard care. and Group B receiving metformin 250mg three times daily orally in addition to standard care. The oral glucose tolerance test was performed between 24 to 28 weeks and later at 32 weeks. The participants were followed till delivery to record preeclampsia, neonatal birth weight, and APGAR score.

Results: The mean age, gestational age, and BMI were similar between Group A (32.37 years, 11.37 weeks, 32.37 kg/m²) and Group B (31.35 years, 11.27 weeks, 32.3 kg/m²). The incidence of GDM (10% vs. 42%) and preeclampsia (13% vs. 74%) was significantly lower in the metformin group (p = 0.000). However, no significant differences were observed in birth weights or APGAR scores.

Conclusion: FMetformin reduces the incidence of GDM and preeclampsia in obese women when started at 11 to 14 weeks of gestation, without affecting birth weight and APGAR score of neonates.

Keywords: Gestational Diabetes Mellitus, Pre-eclampsia, Lifestyle changes, Metformin,

Introduction

Gestational Diabetes Mellitus (GDM) is a metabolic condition that arises during pregnancy, affecting approximately 15% of pregnancies. It is linked to numerous adverse maternal and fetal outcomes, including preeclampsia, preterm delivery, cesarean section, macrosomia, stillbirth, low APGAR scores, neonatal hypoglycemia, respiratory distress, and neonatal jaundice.[1,2] Early treatment and good glycemic control have been evidenced to reduce these complications.[3] Similarly, there are many measures to prevent GDM, including lifestyle modification (diet management, exercise) and some pharmacological agents like metformin, myoinositol[4] As obesity is one of major risk factor to develop GDM, the women are at 1.9-2.69-fold increased risk to develop GDM when comparing obese and non-obese women and is associated with maternal and fetal complications.[5] Among the various pharmacological agents, metformin has been studied for its role in the prevention of GDM in pregnant patients with obesity and when it has been used in combination with lifestyle interventions, such as diet and exercise, may help reduce weight gain and prevent GDM in this population.[5] The International Federation of Gynecology and Obstetrics (FIGO) recommends metformin as a first-line medication for GDM patients who do not achieve ideal blood glucose levels through lifestyle interventions alone. Metformin targets insulin resistance and improves insulin action, making it a potential therapeutic option for managing hyperglycemia in pregnancy.[6] Studies have also shown that metformin treatment in early pregnancy may decrease the frequency of preeclampsia, a complication associated with GDM. The function of metformin in this population has been examined in a number of randomized clinical trials. The "Efficacy of Metformin in Pregnant Obese Women" (EMPOWaR) trial, which was conducted from February 3, 2011, to January 16, 2014, compared metformin to a placebo in pregnant women who were obese and did not have diabetes. The results showed that metformin decreased the incidence of preeclampsia but did not lower the frequency of large-for-gestational-age babies.[7] Metformin decreased maternal weight gain but had no effect on neonatal birth weight, according to a another study, the Fetal Medicine Foundation trial (2010–2015), which compared the medication with a placebo in pregnant women who were obese but not diabetic.[8] Metformin should not be advised to prevent unfavorable pregnancy outcomes in obese non-diabetic women, according to a meta-analysis of these trials.

Overall, metformin may have some benefits in reducing the risk of pre-eclampsia and maternal weight gain, its effectiveness in preventing gestational diabetes in obese pregnant patients is still uncertain because literature showed conflicting results.[7,8,9] We took up this study to evaluate the effect of metformin for preventing

GDM in pregnant women with obesity because more research is necessary to completely comprehend the drug's effectiveness in preventing GDM and its impact on maternal and newborn outcomes. So, the objective of this research is to evaluate the preventive role of metformin in obese women for the development of GDM, preeclampsia and its effect on neonatal birth weight and APGAR scores.

Methodology

This experimental study was conducted in the OBGYN Department of Shalamar Hospital, affiliated with Shalamar Medical & Dental College in Lahore, Pakistan, IRB SIHS (IRB-542), between May 1, 2022, and Nov 30, 2024, with two groups by lottery method as Group A: Control group. and Group B Intervention (Metformin) group: With a power of 80% and a 5% threshold of significance, the sample size was determined to be 128 (64 in each group). In obese women, the incidence of GDM was 4% when using metformin versus 20% when not.[7], so 64 women were assigned in each group.. Total of 150 women who were having BMI ≥ 30 kg/m^2 without preexisting diabetes, aged 18-40 years, between 11 to 14 weeks, having singleton pregnancy were included in the study, however women with contraindications to metformin, pre-existing diabetes, renal impairment, or other co-morbid medical disorder, previous history of GDM, history of macrocosmic baby and with multiple gestation or fetus with abnormalities were excluded. Preexisting diabetes was checked by glycosylated (HbA1C) level. The enrolled participants were divided in two groups; Group A (control) who were receiving standard care (Diet & exercise) and the other Group B who were receiving metformin in addition to the standard care (Diet & exercise) only. Gestational diabetes was diagnosed based on standardized criteria as Oral Glucose tolerance test to be done at between 24 to 28 weeks and then 32 weeks. Following WHO Criteria with 75 gm oral glucose, three levels performed with fasting blood glucose < 95 mg/dl, less than 140 mg/dl after 1 & 2 hours are the levels followed to label a patient as case of Gestational Diabetes [10] Whereas pre-eclampsia was labelled when there was more than 140/90 mmHg at 4 hours interval after 20 weeks of gestation and neonatal birth weight and APGAR scores were recorded as per standard criteria.

Data Collection

After getting approval the patients who fulfilled the inclusion criteria from were enrolled in the study. The demographic data (age, gestational age, parity, and BMI) was taken. Pregnant women who were fulfilling the inclusion criteria were enrolled in this research after taking informed consent and divided into two groups as Group A (Control) whereas the other was experimental Group B (metformin treated). In Group B metformin was initiated at a daily dose of 250mg orally three times a day. We followed the patients in antenatal clinic regularly following WHO standards as monthly till 28 weeks followed by fortnight visit till 36 weeks and weekly visit after 36 weeks till the plan of delivery. On all antenatal visit patients were checked for maternal weight gain, blood pressure and glucosuria. Both groups were assessed for the developmental of GDM by OGTT at 24 to 28 weeks and 32 weeks of gestation. The routine followed up by antenatal visits and antenatal ultrasound scans were the same as mentioned for the patients in group A & B. All information was entered into a pre-made proforma in accordance with the operational definition. As OGTT was repeated at between 24 to 28 weeks, 32 weeks, however If the results show positive for gestational diabetes, then no further tests were performed and the study for that patient was concluded and were managed in Maternal Fetal Medicine unit of Shalamar Hospital. All these patients were managed efficiently as per standard protocol. The data were analyzed using the statistical software program IBM SPSS version 23. Mean ±SD was presented for quantitative variables like age, gestational age, BMI. Parity was presented as frequency. Chi-square test was applied to compare efficacy in both groups, taken p ≤0.05 as significant.

Data Analysis

The primary analysis has involved the comparison of the incidence of gestational diabetes between the metformin control groups using appropriate statistical tests (e.g., chi- square test). The proper statistical techniques was applied to the analysis of secondary outcomes.

Results

A total of 200 patients were initially enrolled, with 100 in each group. However, 25 patients from the control group and 23 from the metformin group were lost to follow-up. Furthermore, 2 patients in the metformin group discontinued treatment due to gastric discomfort. The incidence of gestational diabetes mellitus and preeclampsia was significantly lower in the intervention group compared to the control group, as shown in Table 1. Neonatal birth weight and APGAR scores at 1 and 5 minutes did not show any significant difference between the two groups (Table 2). The Chi-square test was used to analyze categorical variables, such as the incidence of gestational diabetes mellitus and preeclampsia, in Table 1. For continuous variables, including neonatal birth weight and APGAR scores, the independent sample t-test was applied in Table 2.

Table 1: Comparison of Gestational Diabetes Mellitus and Preeclampsia Incidence between Control and Intervention Groups

Variable		Control group A	Intervention group B	p-value
GDM	No	37(57.8%)	57 (89.1%)	0.000
	Yes	27(42.2%)	7 (10.9%)	
Preeclampsia	Yes	47(74%)	9 (13%)	0.000
	No	17(24%)	55(87%)	

Table 2: Comparison of Neonatal Birth Weight and APGAR Scores between Control and Intervention Groups

Variables	Group A Mean± SD	Group B Mean± SD	p-value
Birth weight (kg)	3.250 ± 0.50	3.32 ± 0.150	>0.05
APGAR score (1min)	7.12 ± 0.52.	7.35 ± 0.15	>0.05

APGAR score (5min)	7.35 ± 0.15	8.35 ± 0.15	>0.05

Discussion

This experimental study assessed the effectiveness of metformin in lowering the incidence of gestational diabetes among obese women. A total of 150 women with a BMI ≥ 30 kg/m^2 without preexisting diabetes, aged 18-40 years, between 11 to 14 weeks of gestation, and having singleton pregnancy, were included in the study. A Metformin dose of 250 mg was given orally three times a day and showed statistically significant results for reducing the incidence of GDM (Table 1) and preeclampsia but it had no significant effect on neonatal birth weight and APGAR score (Table 2). This study gave a valuable insight about preventive role of metformin in obese women which in turn reduce the consequential complication of gestational diabetes, including polyhydramnios, preterm births, intrauterine death etc. and preeclampsia. Among different interventions to prevent GDM, metformin's role is still under research along with other measures, however the exact mechanism of action by which metformin can reduce weight gain during pregnancy and hence GDM prevention has not been fully understood especially in obese patients with pregnancy, however certain proteins involved in the metabolism of the body may have its role. [11,12,13]. The role of metformin in limiting weight gain has been supported by numerous studies. Additionally, incorporating exercise and nutritional control has proven to be an effective strategy for managing obesity.[14,15,16,17]

It has been reported that starting metformin in early pregnancy, around 12 to 18 weeks, effectively limits weight gain during pregnancy.[15,16,17,18] Previous studies have shown that metformin is not effective in preventing GDM in obese pregnant women, with one study reporting GDM incidence of 15.9% in the metformin group and 19.5% in the control group, showing no significant difference (p = 0.683).[7] Similarly, a meta-analysis of 11 randomized controlled trials reported a comparable risk of GDM between metformin users and controls (risk ratio 1.03).[9] While the study demonstrated limited weight gain with metformin use, it did not support its role in preventing GDM, which contrasts with the findings of our study. In the present study, GDM was observed in 57 (89.1%) patients in Group A compared to 37 (57.8%) patients in Group B (P = 0.000) (Table 1), which is consistent with the findings of previous studies which reported that metformin reduces the risk of GDM by 34%.[11,19]

In this research, metformin was initiated at a daily dose 250mg orally three time a day. This dose is different from Niroomanesh et al. (2010), who reported the use of metformin 500 to 2500 mg of metformin in 104 women and showed the effectiveness of metformin for good blood glucose levels control during pregnancy. They used 500mg twice daily to 2500mg daily and showed the effectiveness of metformin to prevent the GDM in metformin group.[20] Neola et al. (2024) reported the promising effect of metformin to reduce GDM, but the optimal dose is still inconclusive.[21] Another significant point is the level of BMI to be taken as to label as "obese". A multi-center, prospective research was reported from European world in which different strategies were compared to prevent GDM among women with BMI > 29kg/m^2 and the results found the development of GDM in 14% of the patients in their second trimester (24 to 28 weeks), regardless of type of approach or strategy used.[22] However, in this research BMI more than 30 mg kg/m^2 and WHO 2013 criteria was taken to label patient as GDM.[10] In 2022, Seshiah et al. reported that a 2-hour postprandial level of 110 mg/dl in early pregnancy, around 11 to 13 weeks, indicates the need for early intervention, such as metformin, to prevent gestational diabetes.[23] However, in this research WHO recommendation of OGTT at between 24 to 28 weeks and 32 weeks is followed.[10] Since metformin has demonstrated encouraging effects in preventing gestational diabetes in obese patients, this study also highlights the importance of early screening and intervention.

The incidence of preeclampsia as 13% of women in the metformin group compared to 74 % in the control group supports the preventative role of metformin for pre-eclampsia (Table 1). The potential of metformin to reduce the inflammatory response is believed to be the mechanism behind its ability to lower the incidence of pre-eclampsia, as reported by He et al. (2023).[24] However, Feig (2019) presented contradictory findings from randomized trials, with one trial indicating that metformin prevents pre-eclampsia, while another did not show the same result.[25]

The effect of metformin for preterm birth is still under investigations although it does affect the preterm birth by reducing the prevalence of pre-eclampsia as it is one of known etiology for preterm birth. However, this research showed (Table 3) the fetal birth weight, APGAR score at 1 min and 5 minutes are not significantly affected by both groups with and without metformin as evidenced by the EMPOWER trial.[7,11] This research provides insight regarding metformin's preventive role in obese women in the form of metformin in addition to other standard measures like diet control and exercise to be started in early pregnancy, however, metformin solely has not evidenced to prevent GDM in non-diabetic obese pregnant wome.[26]

Limitations

Although, the sample size is small but still have statistical power (80%), which made this study as pilot project to make foundation for future studies and gave insight to the preventive role of metformin. However, the recruitment of participants according to inclusion criteria, like obesity, 11 to 13 weeks' gestation, single fetus with no preexisting diabetes, no fetal abnormalities etc. was challenging. The recruitment constrains, reflect real world challenges, making these results valuable in our clinical practice. However, future studies at large scale research in collaboration with other centers is recommended to overcome recruitment challenges.

Conclusion

Metformin was found to be effective in preventing GDM and pre-eclampsia in obese pregnant women. The study highlights the need for early intervention and emphasizes the importance of lifestyle changes in conjunction with medication. These findings have significant implications for the management and prevention of GDM, and further research in this area is warranted to fully elucidate the safety and efficacy of metformin. **Author Contributions:** SR conceived the idea, designed the study, obtained IRB approval, analyzed, and interpreted the data, and drafted the manuscript; MFM assisted with IRB approval, data collection, analysis, interpretation, and drafting; ST contributed to data interpretation, drafting, and proofreading; and UFA was responsible for data collection and analysis.

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Original Article

Fluoride Levels in Drinking Water across Lahore District Towns and their Link to Dental Fluorosis (2022)

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Abstract

Objective: To measure the concentration of fluoride levels in drinking water and its association with dental fluorosis in various towns of Lahore district, Pakistan in the year 2022.

Methods: This descriptive cross-sectional study was conducted from 27th September to 30th December, 2022 across nine towns in Lahore, where 100 drinking water samples were collected from randomly selected tube wells. The tube wells were chosen using random number tables from a list provided by WASA. Additionally, 400 residents aged 25 years and above (4 residents per area) were interviewed and clinically examined for dental fluorosis in the areas corresponding to the water sample collection sites. Fluoride concentrations in all water samples were analyzed using the spectrophotometric method at the Pakistan Council of Research in Water Resources (PCRWR) laboratory in Lahore.

Results: With 1.5 mg/l as the recommended fluoride level in drinking water, the fluoride concentration ranged from 0.50 to 1.63 mg/l, with a mean of 0.58 ± 0.33 mg/l among individuals with dental fluorosis compared to those without. This difference was statistically significant ($p = 0.013$). Dental fluorosis was observed in 189 participants (47.3%), of whom 48.8% were male and 39.7% were female.

Conclusion: Fluoride levels in drinking water exceeding the recommended limit were significantly associated with a higher frequency of dental fluorosis among residents.

Keywords: Fluoride concentration, Drinking water, Dental fluorosis, Dean's fluorosis index, tube-wells.

Introduction

Pakistan is a developing country where there are limited drinking water sources, and much of the available drinking water comprises of high fluoride concentration, which not only causes dental fluorosis, but also skeletal fluorosis.[1] Fluoride is available to human beings and domestic animals from different sources including drinking fluoridated water, crops and plants grown on the fluorotic soils, certain marine animals that are edible, phosphate supplements that contain fluoride for animal feed, medicines, mineral mixture, cosmetics, industrial fluoride pollution and dust in the air. Concentration of fluoride in the surface water i.e., rivers is usually lower than 0.1 parts per mg/l.[2] However, concentration of fluoride in groundwater undergoes great variations and can be higher considerably, depending upon its composition in host rocks, hydrogeology and climate.[2] The recommended value for fluoride in drinking water is 1.5 mg/l, and there is an increased risk of developing dental fluorosis at concentrations higher than 1.5 mg/l, which may also lead to skeletal fluorosis.[3]

Dental Fluorosis is a mineralization disorder affecting enamel, due to high fluoride intake during the early tooth formation stages.[4] It is most likely to develop from infancy period to eight years of age in children, and might develop aesthetic concerns related to teeth from birth to 6 years of age.[5] Premolars are usually more prone to fluorosis and may sustain greater damage.[5] Characteristics of dental fluorosis include mottled enamel, brownish discoloration of teeth, pitted appearance of enamel and thin, diffuse, horizontal, and bilateral white striations along with plaque.[6] A daily fluoride intake of 0.05–0.07 mg/kg/day is recommended for the primary prevention of dental fluorosis.[6] Fluoride concentrations exceeding 1.5–4 mg/l (above WHO's recommended level) in children can lead to dental fluorosis.[6] As recommended by WHO, optimum fluoride level in drinking water is from 0.5 to 1 parts per million respectively.[3] Excessive consumption of water having high fluoride levels and intake of fluoride containing food products can lead to dental fluorosis.[7] Fluorosis is considered as a globally occurring phenomenon leading to evident aesthetic issues and defective bones and enamel development.[8]

The age range which is critical for dental fluorosis is from 15-30 months.[9] Dental fluorosis occurs due to short-term overexposure to fluoride during tooth formation, leading to disrupted ameloblastic function and resulting in enamel hypomineralization.[10] It is associated with changes in subsurface enamel.[11] It is an important biological marker in indication and identification of fluoride level in teeth.[12] Dental fluorosis has been classified on basis of clinical appearance by using Dean's fluorosis index (presented by Dean, 1934).[10] Scoring in Dean's fluorosis index is

as follows: 1: Questionable, having occasional white spots and flecks on enamel. 2: Mild, having whitish opaque areas that involve more tooth surface. 3: Moderate and the severe forms, having pitted and brown staining on tooth surface. 4: Tooth corrosion.[10]

Skeletal and dental fluorosis are considered as serious public health issues worldwide.[13] In Asia, dental and skeletal fluorosis is prevalent in China, Sri Lanka, India and Pakistan.[13] Pakistan has been listed among countries having greater risk of water crisis.[14] Among various regions of Pakistan, Fluoride toxicity in water has been observed in Balochistan, Lahore and Gujrat, Thar Desert, Nagarparkar, Sindh, and D.I.Khan, respectively.[15] Lahore, the second largest city of Pakistan, depends on groundwater for its drinking needs.[16] Past studies have indicated serious violations in groundwater quality for drinking in Lahore.[16] More significantly, high fluoride and arsenic levels were observed in parts of Lahore in these studies.[16] Water & Sanitation Agency (WASA) Lahore, documents that groundwater levels in Lahore city are dropping every year by roughly 1 ft. of its water Table.[16] It is of significant apprehension on both quality and quantity of groundwater.[16]

In Pakistan, even though several studies have been conducted to assess the concentration of fluoride in drinking water, literature is scarce regarding its association with dental fluorosis, especially in Lahore, Punjab. Moreover, in most of the studies carried out in Lahore, dental fluorosis has been studied and clinically examined in hospital-based settings, whereas in this study, the association between fluoride concentration and dental fluorosis has been addressed at the community level.

Methodology

This descriptive cross-sectional study was conducted across nine Towns of Lahore District from 27th September to 30th December 2022, after obtaining ethical consent from the Institute of Public Health, Lahore (182/ME/IPH). Water samples were collected from Shalimar Town, Aziz Bhatti Town, Wahga Town, Ravi Town, Gunj Baksh Town, Gulberg Town, Iqbal Town, Nishter Town, and Jubilee Town. A list of WASA-operated tube wells in Lahore city was identified, and 100 tube wells were randomly selected using random number Tables. Samples were collected in labeled plastic bottles from running water sources to avoid turbidity. Individuals with missing teeth or undergoing orthodontic treatment were excluded. A total of 400 residents aged 25 years and above (4 individuals per area) were interviewed and clinically examined in the corresponding areas. A self-administered questionnaire was used to gather socio-demographic data, income, educational background, and details on fluoride exposure, including dose, duration, and sources. Clinical examinations were conducted using a dental mirror and probe, and dental fluorosis was scored using Dean's Fluorosis Index. All water samples were transported to the Pakistan Council of Research in Water Resources (PCRWR) to determine fluoride concentration using the SPADNS spectrophotometric method. Each experiment was repeated three times to ensure accuracy, and the average fluoride concentration was calculated. Data were entered, cleaned, and analyzed using SPSS version 26. Frequency Tables were generated for categorical variables, and measures of central tendency were calculated for continuous data. Associations between categorical variables were tested using the Chi-square test, and means were compared using Student's t-test or ANOVA, where applicable. Categorical data were presented using bar and pie charts.

Results

Table 1 summarizes the demographic characteristics of the study participants, including age, gender, BMI, and clinical history. Dental fluorosis was observed in 189 participants (47.3%), with 48.8% being male and 39.7% female (Table 1).

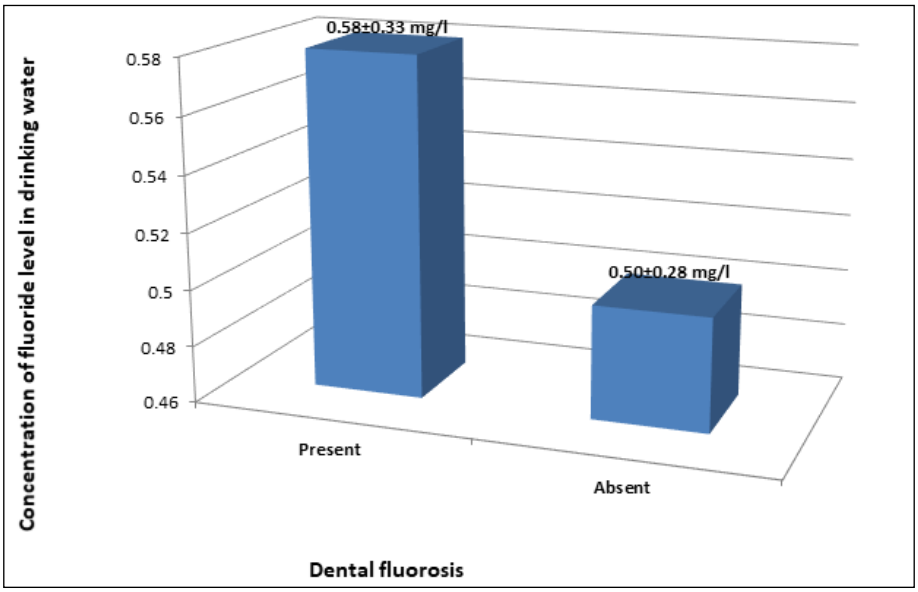
Table 1: Frequency of dental fluorosis among participants across various demographic and lifestyle variables

Variable	Dental Fluorosis				p-value
	Present		Absent		
	n	%	n	%	
Gender					
Male	162	48.8%	170	51.2%	0.171
Female	27	39.7%	41	60.3%	
Age					
25-50 years	161	47.5%	178	52.5%	0.819
Above 50 years	28	45.9%	33	54.1%	
Residence					
Permanent	110	44.9%	135	55.1%	0.24
Temporary	79	51%	76	49%	

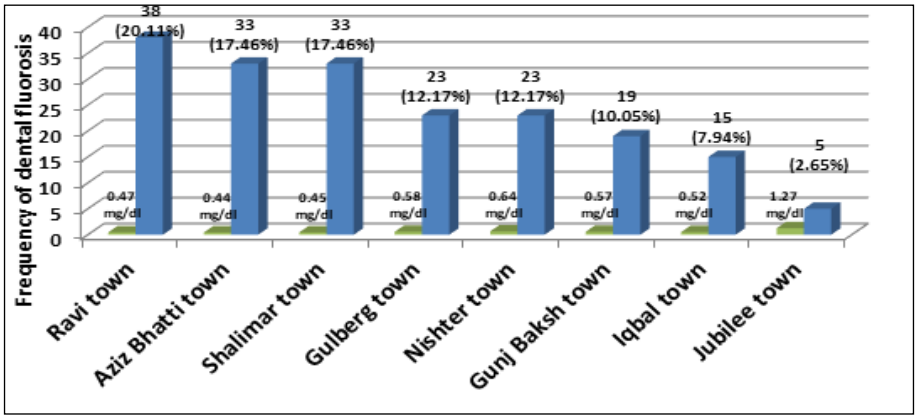
Variable	Dental Fluorosis				p-value
	Present		Absent		
	n	%	n	%	
Economic Status					
Income less than 30,000/ month	168	49.3%	173	50.7%	0.52
More than 30,000 per month	21	35.6%	38	64.4%	
Living in the Area					
More than 10 years	135	51.3%	128	48.7%	0.024
Less than 10 years	54	39.4%	83	60.6%	
Source of Drinking Water					
Tap/ Filtered Water	187	48.7%	197	51.3%	0.004
Bottled Water	2	12.5%	14	87.5%	
Source of Water for Cooking Food					
Tap/ Filtered Water	187	48.4%	199	51.6%	0.013
Bottled Water	2	14.3%	12	85.7%	
Water Consumption per Day					
2 Liters or more	183	49.5%	187	50.5%	0.002
Less than 2 Liters	6	20%	24	80%	
Usage of Fluoride Toothpaste					
Yes	161	44.6%	200	55.4%	0.001
No	28	28.2%	11	71.8%	
Acidic Beverages Consumption					
Yes	164	49.4%	168	50.6%	0.057
No	25	36.8%	43	63.2%	

Table 2: Severity of dental fluorosis among the participants using Dean's Fluorosis Index

Severity	Dean's Fluorosis Index	
	Frequency	Percentage
Normal (0)	211	52.7%
Questionable (0.5)	18	4.5%
Very Mild (1)	44	11%
Mild (2)	72	18%
Moderate (3)	47	11.8%
Severe (4)	8	2%
Total	400	100%



Graph 1: Concentration of fluoride in drinking water and its association with dental fluorosis



Graph 2: Town-wise Distribution of Dental Fluorosis and Mean Fluoride Levels in Drinking Water of these Towns

Discussion

This cross-sectional study evaluated the fluoride concentration in drinking water and its association with dental fluorosis across nine towns in Lahore, Pakistan. Multistage sampling was used to select towns, while convenience sampling was employed to examine 400 individuals and collect 100 water samples. Fluoride levels were measured using the colorimetric method, and dental fluorosis was assessed clinically using Dean's Fluorosis Index. The findings revealed significant fluoride contamination in drinking water, with a high prevalence of dental fluorosis, particularly in areas with elevated fluoride levels. Statistical analysis, including Chi-square and independent t-tests, demonstrated associations between fluoride exposure and socio-demographic factors. The mean fluoride concentration for individuals with dental fluorosis was 0.58 ± 0.33 mg/L, compared to 0.50 ± 0.28 mg/L for those without fluorosis, a difference that was statistically significant ($p = 0.013$) (Graph 1)

Both high fluoride concentration in drinking water and dental fluorosis are serious public health concerns worldwide. A study by Rojanaworarit et al. in 2020 showed that 22% fluoride contamination has been reported in Balochistan, followed by Punjab having 19% contamination.[2] Rana et al. (2020) revealed a shocking 98% prevalence of dental fluorosis in some areas of KPK.[8] In Balochistan, fluoride concentration in drinking water is among the highest reported levels including Quetta.[8] This leads to a possibility that there might be high prevalence of dental fluorosis among people residing in Quetta.[8] Nilchian , Asgary, Mastan (2018) showed that the mean fluoride concentration in drinking water among female students of two towns, Behbahan district was found to be 1.3 ppm.[10]

Rehman et al. (2022) determined the fluoride concentration in groundwater of Isa Khel area of Punjab, ranging between 0.02 mg/l – 5.35 milligram/liter with 58.5% of the water samples having high fluoride concentration.[14] This study also showed that Pakistan has been listed among countries having greater risk of water crisis.[14] Among various regions of Pakistan, fluoride toxicity in water has been observed in Balochistan, Kalallan Wala and Gujarat areas of Punjab, Thar Desert, Nagarparkar in Sindh, and D.I.Khan in KPK respectively.[15] Isa Khel, Mianwali, Punjab is located near Indus river. The Indus River comprises of a range of igneous and metamorphic rocks (i.e. fluoride-bearing rocks). This might be directly contributing to fluorosis in this region. Moreover, In Pakistan fluoride levels in drinking water vary widely; Peshawar had extremely low

levels of fluoride in drinking water while Tharparkar had highest levels of fluoride in drinking water.[20] Habiyakare T et al. in 2021 found that the prevalence of dental fluorosis in children residing in Gihaya Island, Lake Kivu (Rwanda) was 90.7%.[4] The presence of fluoride-bearing rocks in Gihaya Island lead to high fluoride levels in groundwater. Most of the rural population there is dependent on groundwater for drinking and irrigation, causing fluorosis in both human population and livestock. Al Warawreh AM and his team in 2020 determined that the frequency of dental fluorosis was 39.9% in Southern region of Jordan (Karak city).[5]

Rana et al. (2020) conducted a comparative cross-sectional study between inhabitants and non-inhabitants of Quetta on basis of frequency of dental fluorosis. Around 71.4% of the inhabitants and 24% of the non- inhabitants had fluorosis.[8] Quetta valley situated in Balochistan province is surrounded by mountains. These mountains consist of rocks with fluoride-bearing minerals (i.e. granite and gneisses) leading to fluoride contamination of groundwater in this region. This high fluoride concentration in groundwater of Quetta is a leading cause of dental fluorosis in this region. Yasar et al. (2021) determined the toxicity of groundwater caused by fluoride contamination in the southwestern region of Lahore and the fluoride concentration ranged between 0.25 mg/l – 21.3 milligram/liter.[15]

The Southwestern zone of Lahore is occupied by a number of chemical, plastic and food manufacturing industries. These industrial units have improper wastewater management. This wastewater might be polluting the groundwater in southwestern part of the city, thus increasing toxicity of groundwater. Fluoride in drinking water is not the sole cause of dental fluorosis; other sources include certain foods, toothpaste, acidic beverages, and fluoride-containing dental materials. Lahore, as a rapidly industrializing metropolitan city, faces challenges like improper waste management and environmental changes, which contaminate its groundwater. Studies have indicated an increase in fluoride and arsenic levels in Lahore's groundwater, likely caused by pollution and seasonal fluctuations. Furthermore, WASA Lahore reports that the city's groundwater levels decrease by around 1 foot per year, significantly impacting both the quality and availability of groundwater.[16]

However, in this study the fluoride concentration in these towns has increased, ranging from 0.44 to 1.27 milligram/liter. (Graph 2) Several industries are located in the northern and southern zones of Lahore, with the Lokhiodair Landfill site situated in the northern part of the city. The industrialization and improper waste disposal practices may be contributing to the contamination of groundwater, leading to elevated fluoride levels that exceed the WHO's recommended limit of 1.5 mg/L. Ahmed et al. in 2020 conducted a study to determine frequency of dental fluorosis among residents of Thar who were consuming water high in fluoride concentration, and it was found to be 100%.[17]

The Thar dessert of Sindh has high fluoride levels in groundwater. And the groundwater available for drinking purpose is through an open source (i.e. unconfined aquifers), thus leading to higher risk of water contamination. The prevalence of dental fluorosis is relatively lesser in these studies and is aligned with the frequency reported in Lahore among 189 (47.3%) participants. (Table 1) However, in Lahore prevalence of dental fluorosis is 47.3% reported in this study which is much lesser than in Thar and Quetta respectively. This difference is mainly due to geographical variation and changes in climate conditions among these regions. Demelash in 2019 determined the mean fluoride level in groundwater of the Great Rift Valley of Ethiopia to be 6.03 mg/l and frequency of dental fluorosis was 28%.[18] Shyam et al. (2021) studied that the frequency of dental fluorosis in endemic areas of Haryana (India) was 96.6%.[19] Groundwater in many parts of Haryana contain high fluoride concentration and the rural population in these areas is dependent on groundwater for drinking purposes, thus increasing risk of developing fluorosis. While, in this study dental fluorosis was reported to be 47.3% among participants and out of these participants who had dental fluorosis, 48.8% were male while 39.7% were female. (Table 1) The fluoride concentration was above recommended level in only one area of Lahore (1.6 milligram/liter). Lima-Arsati YBO et al. (2018) conducted a study which showed that 19.2 were exposed to a dose equal to or over the limit of 0.07 mg F/kg who were using toothpaste.[9] While in this study, the participants using toothpaste were 44.6% had dental fluorosis. Ahmad et al. (2021) found that 22.7% of students exhibited dental fluorosis, ranging from questionable to severe levels.[12]

Nor et al. (2018) conducted a study that demonstrated a significantly higher prevalence of dental fluorosis (Dean's score ≥ 2) among children residing in areas with high fluoride concentrations in drinking water, compared to those in areas with low fluoride levels ($P < 0.001$).[21] Shruthi and Anil, (2018) reported that among children and adolescents living in high fluoride areas, 16.4% had moderate and 15.6% had very mild dental fluorosis, while in areas with normal fluoride levels, 5.3% and 4.3% had questionable and moderate fluorosis, respectively. Among adults in high fluoride areas, 0.8% and 0.3% had moderate and questionable fluorosis, while in the normal fluoride group, 1.3% and 0.3% had moderate and mild fluorosis.[22]

In this study, dental fluorosis was reported in 189 (47.3%) participants, including 18 (4.5%) with questionable fluorosis, 44 (11%) with very mild, 72 (18%) with mild, 47 (11.8%) with moderate, and 8 (2%) with severe fluorosis according to Dean's Fluorosis Index (DFI). (Table 2) The mean fluoride concentration in drinking water was 0.54 ± 0.31 mg/L, ranging from 0.50 mg/L to 1.63 mg/L (Graph 1). Town-wise fluoride levels were as follows: 0.47 mg/dL in Ravi Town, 0.44 mg/dL in Aziz Bhatti Town, 0.45 mg/dL in Shalimar Town, 0.58 mg/dL in Gulberg Town, 0.64 mg/dL in Nishter Town, 0.57 mg/dL in Gunj Baksh Town, 0.52 mg/dL in Iqbal Town, and 1.27 mg/dL in Jubilee Town. (Graph 2). These findings highlight the urgent need for public health interventions to monitor fluoride levels, raise community awareness, and improve oral health policies, while emphasizing the importance of further research into groundwater quality and its public health implications amidst changing climatic conditions.

Conclusion

Fluoride concentration in ground water of few areas of Lahore was significantly above the recommended value, thus increasing the risk of fluorosis. Dental fluorosis was reported among 47.3% of the participants. In this study fluoride intake through drinking water source was found to be the primary cause of fluorosis.

Limitations

This study did not cover the whole city of Lahore, but a few towns, because of the limited time span. Moreover, this study

was community based and dental fluorosis was clinically examined among participants using oral examination set and by recording its concentration in drinking water, while other sources of dental fluorosis were not addressed.

Recommendations

The groundwater quality must be regularly monitored by government and water sanitation agencies operating in the city. For prevention of dental fluorosis community awareness and education regarding effects of fluoride on dental health and general health must be provided at individual as well as community level. Government should develop policies like Reverse Osmosis plant installation in fluoride endemic areas, screening areas with higher then recommended fluoride limit and monitoring fluoride exposure sources other than water etc. by ensuring water safety and referring people encountering dental fluorosis to dentists to meet their treatment needs. Further research like longitudinal study must be done among children and adults to study their behavior, pattern and effect of dental fluorosis and high fluoride levels in drinking water of those areas with high fluoride concentration.

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Original Article

Role of Preoperative Chlorhexidine Bathing in Prevention of Surgical Site Infections among Women Undergoing Obstetric and Gynecological Procedures

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Abstract

Objective: To evaluate the role of preoperative bathing with chlorhexidine solution in reducing surgical site infections among women undergoing obstetric and gynecological operative procedures.

Methodology: A comparative observational study was conducted at Muhammad Shahbaz Sharif Hospital Campus, Lahore, from 1st of July, 2023 to 28th of February, 2024, where data was collected in the Obstetrics and Gynecology department, after obtaining ethical consent. A total of 1341 patients undergoing either elective or emergency procedures were included, by consecutive non-probability sampling technique and further divided into two groups. In group1 were all patients (963) who took whole body bath with chlorhexidine solution, while in group 2 were patients (423) without bath before the procedure. The collected data was entered and analyzed for clinical characteristics like anemia, diabetes and operative characteristics whether primary or previous surgery and emergency or elective surgery by using SPSS version 21.0.

Results: Surgical site infection rate (SSI) was significantly low in preoperative bathing with chlorhexidine group 1 (0.32%) as compared to non-bathing group 2 (1.89%). The clinical characteristics like diabetes, emergency and previous surgery patients showed statistically significant SSI rate in patients who did not take bath as compared to bath group.

Conclusion: Our study showed that chlorhexidine pre operative bath is safe for SSI prevention. however further research analysis is required for its role in clean surgery before implementing it in health policy especially in developing countries.

Keywords: Chlorhexidine, Surgical site infection, Preoperative bath.

Introduction

Surgical site infection (SSI) is wound infection that occur after performing a surgical procedure within 30 days, and ranked as the third most common type of nosocomial infection acquired in hospitals worldwide.[1] It may present as discharge from wound. The organism may or may not be present in an aseptically obtained culture. SSI may be only superficial at incision site in skin or subcutaneous tissues), while in deep SSI there is soft tissue or organ involvement. There are various strategies for prevention of surgical site infection which includes the bath before surgery, hair removal, intranasal screening for *staphylococcus aureus* and antibiotics prophylaxis.Chlorhexidine bathing is the process of cleaning the body using a solution containing chlorhexidine, an antiseptic that reduces bacteria on the skin.[2] It is commonly used in hospitals to prevent infections, especially in patients at high risk, such as those with surgical wounds or medical devices like catheters.[2] Chlorhexidine bathing can involve either a whole-body bath or targeted cleaning of specific areas, depending on the clinical need. In most hospital settings, especially for infection prevention, a whole-body bath is recommended to reduce bacteria on the entire skin surface.[3] Its use as antiseptic bath prior to surgery has emerged as renewed interest as an additional safety measure for prevention of surgical site infections and hospital stay cost.[3]

Recent clinical studies showed that chlorhexidine use as a standardized protocol demonstrated sufficient skin surface concentrations to inhibit or kill skin colonizing flora.[4] This study focused on one such strategy: the preoperative skin bathing. The safety of chlorhexidine gluconate formulations has been demonstrated in studies involving elective general, orthopedic, cardiothoracic, and obstetrical surgeries.[5] This observational study explores evidence-based literature and contributes additional findings on the role of preoperative bathing with chlorhexidine solution for prevention of surgical site infections in women after surgical procedures at Muhammad Shahbaz Sharif Hospital Campus located in Lahore, Punjab, Pakistan.

Methodology

This comparative observational study was approved by the institutional review committee with reference no IHHN_IRB_2023_03_011. According to hospital policy, all patients undergoing elective or emergency surgery are provided with the facility for preoperative whole body bathing using chlorhexidine solution (CHG) free of cost to every patient. However, in many cases, patients undergoing emergency surgeries do not have sufficient time to undergo CHG bathing before the procedure. The data was collected at the Department of Obstetrics and Gynecology, Muhammad Shahbaz Sharif Hospital Campus of IHHN from 1st July 2023 to 28th Feb 2024. A total of 1341 patients undergoing either elective or emergency

procedures were included, by consecutive non-probability sampling technique and further divided into two groups. In group 1 were all patient (963) who took whole body bath with chlorhexidine solution, while in group 2 were patients (423) without bath before the procedure. Any patients with any evidence of skin disease at surgical site were excluded from study. All data entry and analysis were done on SPSS version 21.0. The descriptive statistics test analysis was done to find the link between different demographic and clinical characteristics clinical like BMI, anemia ,diabetes and operative characteristics whether primary or previous surgery and emergency or elective surgery.

Result

Out of total 1341 patients in this study, 68.5% preoperative bathing with chlorhexidine solution (mostly elective procedures) as compared to 31.5% who did not take bath (majority emergency procedures), as shown in Table 1. Surgical site infection rate (SSI) was significantly low in preoperative bathing with chlorhexidine group (0.32%) as compared to non-bathing group (1.89%). The emergency surgery patients had higher SSI rate in non-bath group as compared to bath group. The Table 2 shows SSI rate with operative characteristics of primary or previous surgery in both groups. In previous surgery patients with pre operative bath group the less SSI rate was observed as compare to non-bath group (Table 2). Chlorhexidine preoperative bath was statistically more effective than non-bath group for prevention of SSI. The associated clinical observational characteristics like anemia and diabetes were analyzed in both groups and showed statistically significant SSI rate in patients who did not took bath as compared to the bath group, as shown in Table 3.

Table 1: Impact of Chlorhexidine Bath on Surgical Site Infection Rates in Total, Emergency, and Elective Procedures

Descriptive Analysis	Patient take chlorhexidine bath n=918	Surgical site rate n=3	Patient did not take chlor-hexidine bath n=423	Surgical site rate n=8	Odds Ratio, Confidence Interval, P Value
Total Procedures n =1341	68.5%	3(0.32%)	31.5%	8(1.89%)	Odds ratio 0.172895 % CI:0.0456 to 0.6546 P value= 0.0098
Emergency Procedure n=569	13.3%	1	29.1%	7	Odds ratio 0.142995 % CI:0.0175 to 1.1649 P value = 0.0691
Elective Procedure n=779	55.1%	1	2.4%	2	Odds ratio 0.276495 % CI:0.0730 to 1.0465 P value = 0.0583

Table 2: Inter-Group Comparison of Surgical Site Infections (SSI) in Primary and Previous Surgeries

Variable	Group 1 (n=918)	SSI	Group 2 (n=423)	SSI	Odds Ratio (OR), Confidence Interval, P value
Primary surgery n=439	334	1	105	2	OR 0.3267 95% CI:0.0776 to 1.3760 P = 0.1273
Previous surgery n=902	584	2	318	6	OR 0.1815 95 % CI:0.0364 to 0.9046 P = 0.0373

Table 3: Effect of Chlorhexidine Bath on Surgical Site Infections (SSI) in Patients with Diabetes Mellitus and Anemia

Variables	Group 1 (n=918)	SSI	Group 2 (n=423)	SSI	Statistical significance
Associated DM	209	3	117	8	OR 0.209995 % CI:0.0546 to 0.8066 P = 0.0230
Anemia	194	4	148	7	OR 1.111595 % CI:0.3167 to 3.9005 P = 0.8689

Discussion

Surgical site infections can be prevented through various strategies, one of which is preoperative skin bathing. This study focused on evaluating the effectiveness of preoperative chlorhexidine bathing in reducing SSIs. In our comparative analysis, the SSI rate was significantly lower (Table 1) in the chlorhexidine bath group (0.32%) compared to the non-bath group (1.89%). Additionally, the study examined the role of preoperative chlorhexidine bathing across various demographic, clinical characteristics. Our study findings showed significant reduction in SSI rates in patients with anemia, diabetes, elevated BMI, previous surgeries, and those undergoing emergency procedures in the bath group (Table 3).

A 2023 study published in JAMA demonstrated that using 4% CHG after showering resulted in significantly higher concentrations of CHG at different sites of skin as compare to immediately rinsing off the antiseptic agent.[6] In a meta-analysis of four clinical trials found that chlorhexidine significantly reduced the total infection incidence to 1.69%.The reduction was particularly noTable in moderate and high-risk patients.[7] These findings align with our study, where the SSI rate decreased to 0.32% following preoperative chlorhexidine bathing. In our study, the reduction in SSI rates was particularly evident in the high-risk category within the chlorhexidine group compared to the non-bath group. A review by Edmiston showed compliance for preoperative showering with chlorhexidine and impregnated wipes as low-cost intervention.[8] The study on compliance of SSI prevention standards showed that nursing staff with five years of experience, only 43.7% compliance to protocols.[9] In a Military Medical-Surgical Unit, the implementation of a 4-day preoperative bathing protocol using 4% CHG for surgical patients led to a reduction in surgical site infection (SSI) rates, decreasing from 7.2 to 3.5 infections per 1,000 surgeries over the following year,[10] which are similar to our study where SSI rate was reduced to 0.32% as compare to 1.89% in non-bath group.

Cruz-López et al. (2022) demonstrated that carbapenem-resistant *Acinetobacter baumannii* can persist on healthcare surfaces, highlighting its role in infection transmission and the need for effective disinfection protocols.[11] Fan et al. (2019) in a systematic meta-analysis demonstrating that chlorhexidine bathing significantly reduces colonization and infection rates of Acinetobacter baumannii in healthcare settings.[12] Prayugo et al. (2022) evaluated the effectiveness of a chlorhexidine pre-operative bath for surgical site infections prevention, their finding showed that the intervention significantly reduced the infection rate. This study supports the use of chlorhexidine bathing as an effective measure to improve surgical outcomes.[13] Mezemir et al. (2020) conducted a cross-sectional study for identifying the associated risk factors in surgical site infections, cases which were largely attributed to inadequate infection control practices and patient-related factors. The findings emphasize the need for improved preventive measures and healthcare protocols to reduce SSI rates in similar settings.[14]

Curcio et al. (2019) studied SSIs in elective surgeries in developing countries, finding higher infection rates in clean-contaminated procedures. The study highlights the need for better infection prevention in these settings.[15]

Among a study on 145 patients in Jinnah Post graduate medical center, Karachi, in 2020 showed 35 (24.1%) surgical site infection in emergency cesarean section cases.[16] In our study SSI rate was 0.32% in emergency surgeries who took chlorhexidine bath as compare to 2.9% in non-bath group. In another study a significant association of surgical site infection was found with anemia , diabetes mellitus , and prolonged hospital stay .[16] Their results correlate with our study associated factors like diabetes, previous elective and emergency surgery (Table 2, 3). A cross-sectional study on 143 cases showed that diabetes, smoking and obesity as independent associated factors for SSI. A significant result was noted on analysis for the presence of risk factors, and SSI occurrence.[17] Our study showed a reduction in SSI in these diabetics who take chlorhexidine bath as compared to non-bath group (Table3).

Dégbey et al. (2021) examined the prevalence and factors associated with surgical site infections by identifying key factors contributing to infection rates.[18] They evaluated errors in patient care , medical errors and financial hinderance as factors which may leads to surgical site infections and suggested low-cost implementation in health care facility.[18] In Pakistan different sub specialties of surgery showed 9.3% to 33.6% range of SSI .[19] Sattar et al.(2019) evaluated with a finding of a noTable incidence of SSIs. The study highlights the need for improved infection prevention strategies in post-operative care within the region.[20] Different associated factors also contribute SSI occurence.[21] Our study showed association among clinical risk factors in patients and SSI. Nursing care of patient play a vital role in prevention of SSI. One study reported a poor knowledge and practices among nurses for SSI compliance safety checklist.[22] Martin et al.(2016) in a meta-analysis to assess the relationship between diabetes and the surgical site infections, concluded that diabetes significantly increases the likelihood of SSIs. The study emphasizes the importance of managing diabetes effectively to reduce infection risks in surgical patients.[23] In a study on 1471 patients in teaching hospital in Peshawar the prevalence was 12.5% in elective surgeries and 17.7% in emergency cases, which are similar to our study.[24] The chlorhexidine pre-operative bath seems to have role in surgical site infection prevention, contributing to improved management of surgery by shortening hospital duration and helps reduce the financial cost of surgery, especially in developing countries.

Limitations

There are a few limitations in the study like different behaviors for hand hygiene and bath compliance. As the follow-up period was relatively short, and the infection rate may have been thus underestimated.

Conclusion

The study showed that pre-operative chlorhexidine bath is safe for SSI prevention. however further research analysis is required for its role in clean surgery before implementing it in health policy especially in developing countries.

Conflict of interest: All authors declared no conflict of interest while conducting study.

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Authors' Contribution: RB: Data analysis, interpretation with clinical significance, critical revision, and final approval of the manuscript; study design. RA & SS: Drafting, data editing, refer-

ence collection, and revision for intellectual content; NB & AH: Data collection and acquisition of research work. SA: Data analysis with clinical significance.

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Review Article

Short vs Standard Duration Dual Antiplatelet Therapy after Percutaneous Coronary Intervention with New-Generation Drug-Eluting Stents: A Meta-Analysis

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Abstract

Objective: In patients with coronary artery disease, dual antiplatelet therapy (DAPT) is recommended after percutaneous coronary intervention, but the duration is still debated. This meta-analysis compared short-duration (1 to 3 months) to standard-time (twelve months) double antiplatelet treatment in patients who received coronary intervention with new generation drug eluting Stent.

Methodology: To conduct this examination, we methodically looked at PubMed, Cochrane CENTRAL, Embase, and Web of Science databases for randomized controlled trials, evaluating varying durations of double antiplatelet treatment following new generation stents implantation from July to September 2023. Seven randomized controlled trials were included with a total of 22,945 patients. The primary efficacy endpoint was the incidence of Major adverse cardiovascular events, such as cardiac mortality, heart attack, stent coagulation, and target vessel revascularization; while the safety endpoint was the incidence major bleeding. Secondary endpoints were major adverse cardiovascular and cerebro-vascular complications, any bleeding, and net adverse cardiovascular incidence for a year after stent implantation.

Results: Short-time DAPT was linked to a significantly less incidence of major bleeding (0.8% vs 1.5%), any bleeding (2.5% vs 4.2%) and NACE (2.5% vs 4.2%) compared to standard duration of DAPT. No significant variation was noticed among the two groups regarding major adverse cardiovascular events (4.1% vs. 4.2%) and acute cardiovascular and cerebrovascular incidents (4.7% vs. 4.8%). Short-duration DAPT in patients with acute coronary syndrome was linked with decreased risk of bleeding and net adverse cardiovascular events.

Conclusion: Short-duration (1- or 3-month) DAPT significantly lowers bleeding risk and reduces net clinical adverse events without increasing ischemic risk, making it a reasonable choice for people with new-generation drug eluting stents, particularly those with high bleeding risk or recent surgery.

Keywords: Acute coronary syndrome, Coronary artery disease, New generation drug eluting stents, Dual antiplatelet therapy.

Introduction

To reduce the likelihood of stent clots and restenosis in patients with coronary artery disorders, double anti-platelet therapy (DAPT), which consists of aspirin and a P2Y12 channel antagonist, is a crucial intervention.[1,2] Based on evidence from studies using bare-metal and initial-generation pharmaceutical stents, the latest suggestions indicate a DAPT time of 12 months after percutaneous coronary intervention (PCI) for people with coronary artery disease.[3] Nowadays, many new-generations drug eluting stents (DES) contain a better biocompatible polymer or does not contain a polymer, which tends to cause a lower stent thrombosis rate and has a lower tendency to DAPT.[4,5] Therefore, the 12-month duration of DAPT may no longer be appropriate in the arrival of the latest generations DES.[6] Previous studies demonstrated that prolonged DAPT increased the likelihood of blood loss despite reducing ischemic events.[6,7] The appropriate length of DAPT following the placement of a new-generation DES stent is still unknown. To determine the proper period of DAPT, a careful balance of bleeding and ischemia risk should be measured.

Due to the 2017 policies of the European Society of Cardiology, after the placing of the latest version of pharmaceutical stents, persons with sTable coronary artery disorder should have a 6-month DAPT, and individual at elevated hazards of bleeding should have a 1- to 3-month DAPT.[8] It is unknown whether short-duration DAPT will decrease blood loss without raising the probability of major adverse cardiovascular conditions in contrast to standard-period DAPT in peoples with coronary arteries disorder and acute coronary syndrome. Several RCTs have examined the protection and effectiveness of short-term DAPT (e.g., 1-3 months) compared to the usual 12-month DAPT for patients with unique pharmaceutical stents.[9,10] This meta-analysis sought to assess the protection and effectiveness of short-time DAPT (one to three months) towards standard-period DAPT (12 months) in person undergoing coronary intervention with new generation drug eluting stents.

Methodology

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

Database Search

To conduct this research, we extensively searched the PubMed, Cochrane CENTRAL, Embase, and Web of Science databases for RCTs evaluating various periods of DAPT following new-generation drug-eluting stent placement from July to September 2023. Trials relevant to this topic were also searched at https://clinicaltrials.gov/. Language restrictions were not imposed on the search. The search was limited to RCTs that compared short-duration DAPT (one to three months) and long duration DAPT (12 months) following drug-eluting stent implantation. Search terms included: "percutaneous coronary therapy" OR "coronary stent installation" OR "drug-eluting stent" AND "time of DAPT" OR "period of double anti-platelet treatment". An overview of the choice of eligible studies screened by titles, abstracts, and a full-text review for final determination is illustrated in Figure 1a.

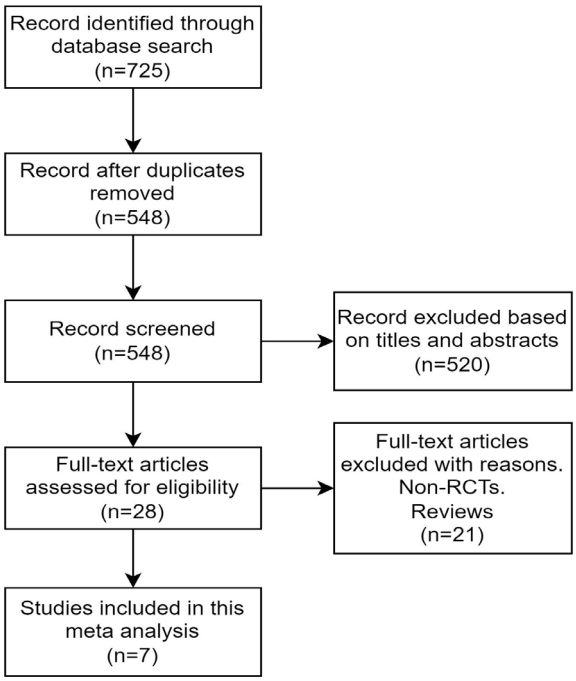


Figure 1a. Prisma flow chart for the articles selection process

Inclusion and exclusion criteria

All randomized controlled trials for comparison of three-month DAPT to twelve-month DAPT after the installment of new-generation drug-eluting stents were systematically reviewed. All potentially relevant randomized trials were independently reviewed by two investigators (I.U, M.A) to identify studies that met the following criteria: enrolled coronary artery disease patients were ≥18 years and underwent novel drug-eluting stents implantation; participants were allocated at random to get a DAPT of aspirin coupled with a P2Y12 channel blocker (clopidogrel, prasugrel or ticagrelor) for short duration (3 months) or a standard duration (twelve months) following coronary implantation by percutaneous; at least 12-month monitoring; outcomes, including cardio-cerebro-vascular events and bleeding events. The exclusion criteria were non-randomized controlled designs, editorial comments, reviews, conference abstracts, reports on the same population or duplicated data.

Outcomes measured

The main safety outcome was significant adverse cardiovascular events, which included mortality, heart attack, stent thrombosis, and target vessel regeneration after 12 months of treatment. The key protection result was substantial blood loss at 12 months, as defined by BARC or TIMI criteria.[12] The 2nd outcome was significant harmful cardiovascular and cerebro-vascular conditions, any bleeding, and gross unfavorable cardiovascular problems at twelve months.

Data collection

The data was gathered, and the manuscripts of the listed publications were examined irrespectively by two investigators (IU and MA). The principal effectiveness outcome, key safety measurement, and secondary outcomes were examined above.

Bias assessment

Cochrane Collaboration's tool was used by two investigators (IU, MA) to independently assess bias risk for the following items: sequencing, concealing allocations (selection bias), blinded people and respondents (performance bias), hiding result evaluation (detection bias), ensuring that result data are full (attrition bias), and selectively disclosing outcomes (reporting bias) (Figure 1b).

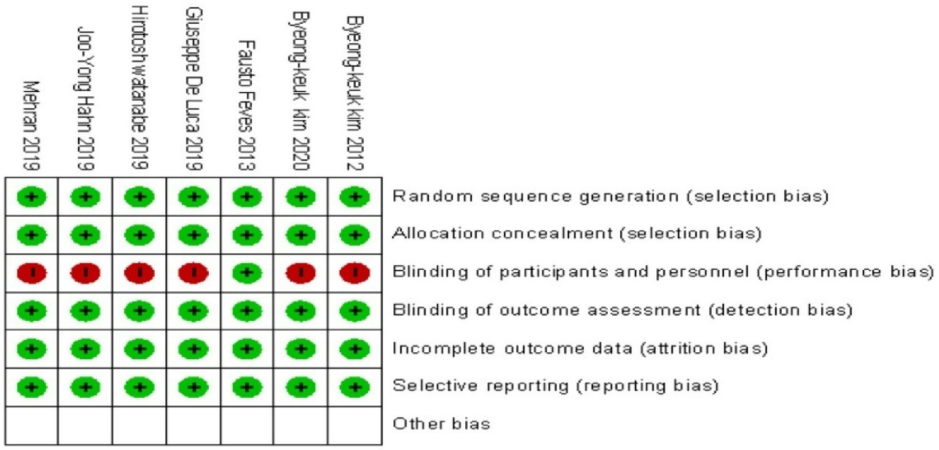


Figure 1b. Bias assessment using the risk of bias assessment tool (RoB) developed by the Cochran Collaboration, evaluate bias risk.

Statistical Analysis

Using Review Manager Version 5.4.1, the statistical analysis was conducted following the Cochrane Collaboration recommendations. The Mantel-Haenszel Fixed Effects method was used to calculate odds ratios and confidence intervals at 95% to quantify the effects of different DAPT durations. The research variation was determined using Cochrane's Q test and the I2 statistic, which calculates the percentage of the overall variance among trials caused by variation rather than chance. Additionally, I2 statistics with values of <50% and ≥50% indicated low and high variability, correspondingly. A sensitivity analysis was conducted in cases of high heterogeneity to identify any study that might be considered outliers. If no data for a specific outcome was available, the trial was excluded from the pooled analysis corresponding to that endpoint. Forest plots were utilized to assess the entire effectiveness of the investigations. All tests were two-tailed, with a p-value of < 0.05 indicating significance. A prespecified analysis of people with acute coronary disorder was also conducted to assess the relative benefits and risks of short-duration DAPT. Publication bias was visually evaluated based on the asymmetry of the funnel plot.

Results

A total of 7 RCTs, which enrolled 22,945 patients, were included in our meta-analysis [9,10,13-17] to compare short-duration (1- to 3-month) with standard-duration (12-month) DAPT. Among them, 11,473 (50.00%) were randomized to short-term DAPT, and 11,472 (50.00%) were randomized to standard-duration DAPT. According to the study plan, the period of DAPT in the experimental arm was 1 month in STOPDAPT-2[15] and 3 months in the remaining 6 trials.[9,10,13,14,16,17] The main characteristics of the listed trials are presented in Table 1.

REDUCE [13] and TICO [17] trials recruited people with acute coronary disorder (n = 4,552), while the other five trials, [9,10,14-16] recruited patients with sTable coronary artery disease (n = 11,409) and ACS (n = 6,984). The following latest version stents that encapsulate drugs were utilized: everolimus-eluting stents, zotarolimus-eluting stents, sirolimus-eluting stents, and COMBO bioabsorbable polymer stents in these seven trials. The DAPT of aspirin with a $P2Y_{12}$ inhibitor was used as follows: clopidogrel was used in RESET[9] and OPTIMIZE[10] trials, while ticagrelor was administered in TWILIGHT[16] and TICO[17] trials, respectively. The $P2Y_{12}$ inhibitor was not confined to clopidogrel, prasugrel or ticagrelor in REDUCE[13] and SMART-CHOICE[14] trials. Clopidogrel or prasugrel was given on the physician's prescription in STOP DAPT-2 trial.[15] Figure 1b displays the potential evaluation of bias for every randomized controlled trial that was a part of the investigation. Other biases were low in all trials except that blinding was only performed in the OPTIMIZE trial[10]. The publication bias was accepTable in all enrolled trials shown in the funnel plot. Heterogeneity among the trials was low in all endpoints among the 7 trials (Figure 2).

Primary efficacy composite endpoint: MACE

All 7 trials, including 22,873 participants, reported the end point of MACE. There were 475 events among 11, 432 patients in the short-duration DAPT group versus 472 events among 11,441 patients receiving the standard-duration DAPT. The pooled analysis revealed no statistically significant variations among the two classes (4.2% *vs.* 4.1%, OR 1.01, 95% CI 0.88-1.15, p=0.93, Figure 2a).

Primary safety endpoint: Major bleeding

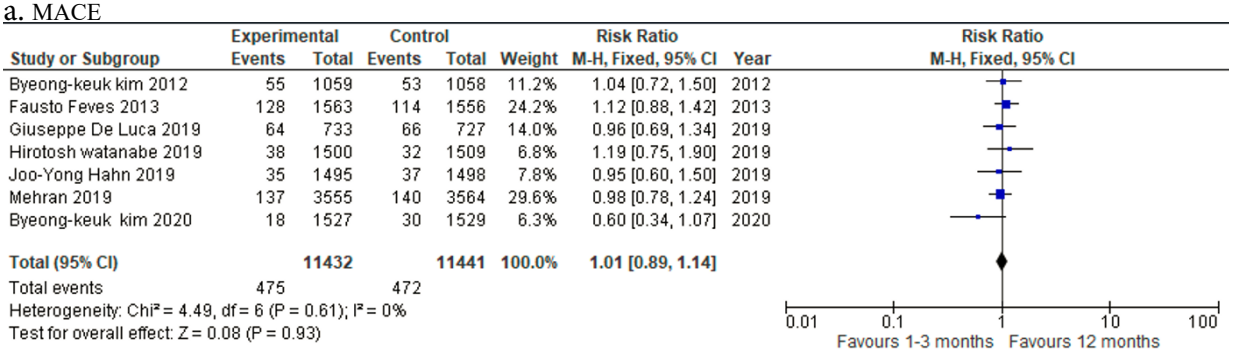
The principal safety endpoint of significant blood loss was reported by all the trials (21,413 participants) except the RECUCE trial.[13] Major bleeding in patients receiving DAPT for a short duration occurred in 86 out of 10,699 patients, and in patients receiving DAPT for a standard duration occurred in 164 out of 10,714 patients. A statistically significant reduction of 48.1% in major bleeding risk was observed for the short DAPT group, as shown in Figure 2b (0.8% vs. 1.5%, OR 0.52, 95% CI 0.40-0.68, p=0.00001).

Table 1. Characteristics of the Included Trials

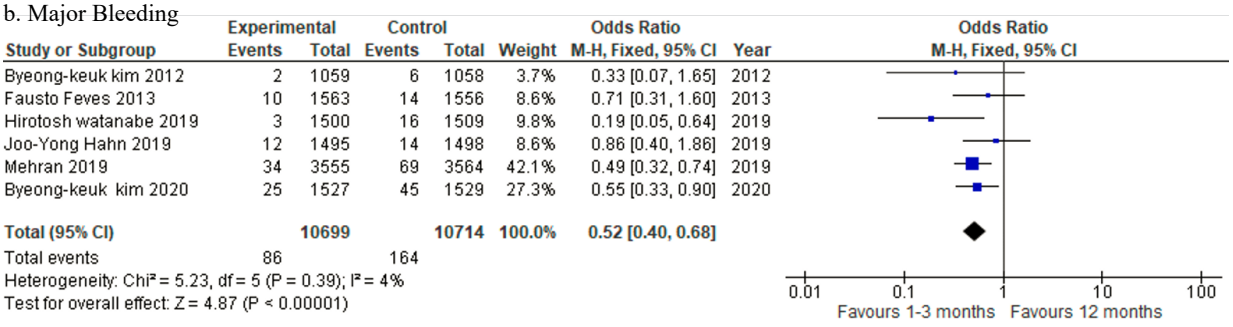
No	Trial (year)	Country	Journal	Sample size	DAPT Duration	Stents	CAD diagnosis	Follow-up
1	RESET 2012	Korea	JACC	2117	Three-month *vs.* twelve-month	ZES/EES/SES	ACS, sTable CAD	12-months
2	OPTIMIZE 2013	Brazil	JAMA	3119	Three-month *vs.* twelve-month	ZES	ACS, sTable CAD	12-months
3	REDUCE 2019	Italy	Euro Intervention	1496	Three-month *vs.* twelve-month	COMBO	ACS	12-months
4	SMART CHOICE 2019	Korea	JAMA	2993	Three-month *vs.* twelve-month	EES/ZES/BES	ACS, sTable CAD	12-months
5	STOP DAPT-2 2019	Japan	JAMA	3045	Three-month *vs.* twelve-month	EES	ACS, sTable CAD	12-months
6	TWILIGHT 2019	US	NEJM	7119	Three-month *vs.* twelve-month	ZES/EES/SES	ACS, sTable CAD	12-months
7	TICO 2020	Korea	JAMA	3056	Three-month *vs.* twelve-month	SES/AG	ACS	12-months

ZES: zotarolimus-eluting stent; EES: everolimus-eluting stent; SES: sirolimus-eluting stent; COMBO: SES; bioabsorbable polymer (Orbus Neich, Hong Kong, China), BES: biolimus-eluting stents; ACS: Acute coronary syndrome, CAD: coronary artery disease, DAPT: dual antiplatelet therapy.

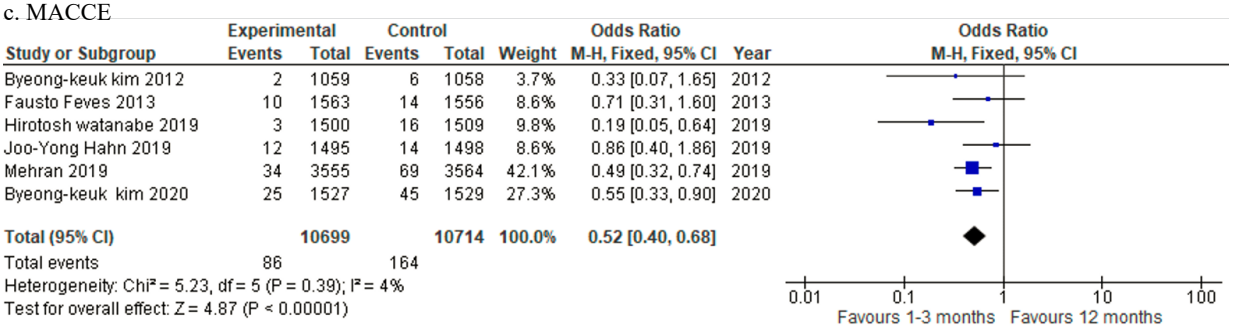
a. MACE



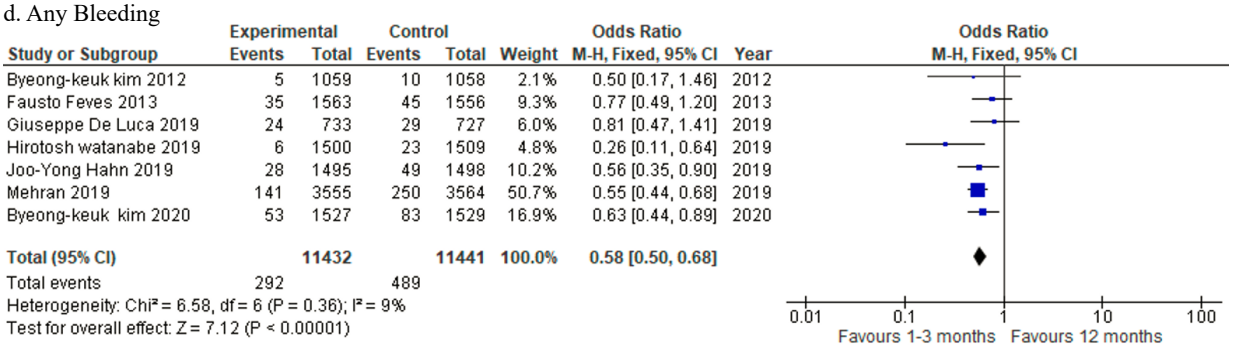
b. Major Bleeding



c. MACCE



d. Any Bleeding



e. NACE

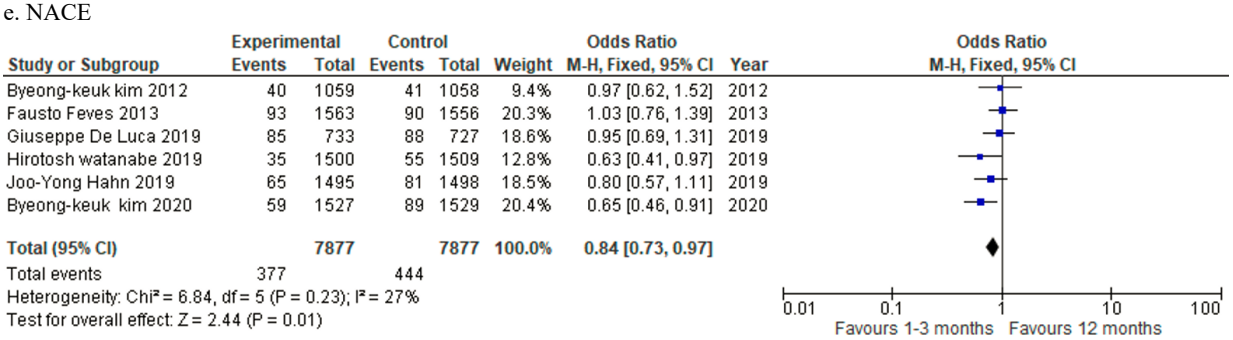


Figure 2. Forest plot for efficacy and safety endpoints.

Comparison of efficacy and safety outcomes among short-duration and standard-duration DAPT classes (a) MACE: major adverse cardio-vascular events, (b) Major blood loss, (c) any bleeding, (d) MACCE: major adverse cardio-cerebrovascular events, (d) NACE: net adverse cardiovascular events.

Supplementary Figure 2. Forest plots for ACS patients analysis (click here)

Secondary endpoint: MACCE

The endpoint of MACCE was presented in 6 trials. MACCE events were recorded in 370 out of 7,877 patients medicated with one to three months of DAPT and 378 out of 7,877 patients receiving twelve-month DAPT. Moreover, the pooled analysis revealed no statistically significant variation among the two classes (4.7% *vs.* 4.8%, OR 0.98, 95% CI 0.84-1.13, *p*=0.74, Figure 2c).

Secondary endpoint: any bleeding

The endpoint of any bleeding was reported by all the 7 trials (22,873 patients). The incidence of bleeding was found in 292 patients among 11,432 patients treated with short-duration DAPT. In contrast, 489 out of 11,441 patients in the standard-duration DAPT presented with any bleeding. In comparison to the standard DAPT, there was a statistically significant 42% decrease in the likelihood of blood loss among the individuals undergoing the short DAPT (25.0% vs 4.5%, OR 0.58, 95% CI 0.50-0.86, p=0.00001, Figure 2d).

Secondary endpoint: NACE

NACE was demonstrated in 6 trials. NACE was observed in 377 and 444 patients in the little-duration and standard-time DAPT groups, respectively. NACE chances were reduced by 16% in the short DAPT class (2.5% vs 4.2%, OR 0.84, 95% CI 0.73-0.97, p=0.01, Figure 2e). The ischemic risk in acute coronary syndrome patients would be higher than in sTable CAD patients under short-term DAPT, so the benefits and risks were

analyzed for acute coronary syndrome patients under different durations of DAPT.

The findings showed no statistically significant difference in the frequency of MACE (3.6% *vs.* 3.8%, OR 0.94, 95% CI 0.70-1.26, *p*=0.68, Supplementary Figure 2a) and MACCE (4.0% vs. 4.7%, OR 0.84, 95% CI 0.66-1.07, p=0.16, Supplementary Figure 2b) among short-time and standard-time DAPT in individuals with acute coronary disorder. However, the risk of any bleeding (2.7% vs. 4.0%, OR 0.66, 95% CI 0.51-0.86, p=0.002, Supplementary Figure 2c) and NACE (5.52% vs. 6.51%, OR 0.83, 95% CI 0.70-0.99, p=0.04, Supplementary Figure 2d) was significantly reduced by 34% and 17%, respectively, in the short duration DAPT group.

Discussion

This meta-analysis included seven RCTs that evaluated short-time (one to three months) and standard-time (twelve months) DAPT in individuals who had coronary intervention through percutaneous with the latest generation DES and received standard medical treatment.[9,10,13-17] Our study found that short-duration DAPT reduced the risk of principal blood loss, any kind of bleeds, and NACE (Figure 2b, d, e). Short-duration DAPT significantly reduced major bleeding risk by 48.1% as compared to standard-duration DAPT (0.8% vs 1.5%, OR 0.52, 95% CI 0.40-0.68, p=0.00001) without raising the chance of MACE (4.1% vs. 4.2%) and MACCE (4.7% vs. 4.8%) when compared with standard-duration DAPT (Figure 2).

Regarding the efficacy endpoints, we did not find that a 12-month DAPT could decrease the risk of MACE or MACCE (Figure 2a, c) compared to a 3- or 1-month DAPT, consistent with the findings of the published meta-analysis.[18] Regarding safety endpoints, our results demonstrate that short-duration (1-3 months) DAPT significantly reduced major bleeding risks by 48.1% and any bleeding risks by 42% compared with standard-duration DAPT (Figure 2b, d).

The latest RCT, such as the TICO trial, has been included, and the heterogeneity in our meta-analysis is low for all endpoints. The incidence of the secondary endpoint of NACE was significantly reduced by 16% for short-duration (1-3 months) DAPTs relative to standard-duration DAPTs (2.5% vs 4.2%, OR 0.84, 95% CI 0.73-0.97, p=0.001). A meta-analysis by *Khan et al.* reported similar findings.[19] Our results added a new advantage of a remarkable decrease in net unfavourable medical conditions for short-duration DAPT.

Besides, major and total bleeding risks are significantly reduced with comparable risks of MACE and MACCE in short-duration DAPT, which concur with the present evidence.[18] DAPT is a combination of aspirin and P2Y12 receptor inhibitors (clopidogrel, ticagrelor, and prasugrel), mainly employed to decrease the chance of ischemia in persons receiving transdermal coronary implantation.

According to the European Society of Cardiology's 2017 and the Canadian Cardiovascular Association's 2018 recommendations, individuals with acute coronary disease getting coronary implantation through percutaneous method ought to be on the DAPT for twelve months, while people with sTable coronary artery disorder through PCI must remain on the DAPT for six months.[8,20] However, our meta-analysis revealed that one to three months of DAPT was better than the twelve-month DAPT at safety endpoints, and NACE differs from the current guidelines, which recommend a 6- or 12-month DAPT duration.

It's vital to remember that the recommendation for DAPT is based mainly on evidence from first-generation DES. In contrast, RCTs using new-generation DES only were enrolled in this meta-analysis. Improving the stent's texture and using potent P2Y12 inhibitors makes it feasible to minimize the time of DAPT. DES has reduced the incidence of restenosis by creating metal frames, polymer coverings, and antiproliferative chemicals.[21] In the LEADERS FREE trial,[22] Polymer-free umirolimus-coated stents were linked with a substantially decreased incidence of cardiac mortality, heart attack, and coagulation of the stent than stents with bare metal in individuals under one month of DAPT following coronary intervention through percutaneous.

The latest P2Y12 enemy, ticagrelor and prasugrel, have a stronger inhibitory impact on the accumulation of platelets than clopidogrel and are more useful in individuals who do not respond well to the medication.[23,24] The DAPT time may theoretically be reduced due to using powerful antiplatelet medications and new-generation stents in clinical settings. However, there is no generally accepted optimal period of

DAPT after new-generation DES installation; short DAPT must be further explored for its efficacy and safety.

Clinical implication

According to our meta-analysis, the short-duration (1 or 3 months) DAPT following an innovative pharmacutical stent placement greatly decreased the probability of blood loss and improved net medicinal value without raising the chance of likelihood cardiovascular and cerebrovascular events compared with 12-month DAPT.

Notably, the results imply that a short duration of DAPT is suiTable for individuals with high blood loss chance or those who need non-cardiac surgery or invasive procedures within 3 months. Besides, the short-duration DAPT alleviates the medical burden. Our results align with the 2019 and 2020 ESC guidelines that suggest that DAPT duration be shortened in particular clinical scenarios.[25]

Limitations

Several limitations exist in this study. Firstly, the baseline characteristics, drug-eluting stents and P2Y12 inhibitors, and randomization method were not the same among the 7 RCTs in this meta-analysis. However, the heterogeneity across the trials was low in all endpoints. Secondly, the ischemic and bleeding risks may differ individually, confounding the results. Thus, the acute coronary disorder persons were analyzed, and the endpoint results were consistent with the study. Anyhow, the conclusions need to be interpreted cautiously, and the duration of DAPT is suggested based on specific clinical conditions.

Conclusion

Compared to standard-duration (≥12-month) DAPT, short-duration (1- or 3-month) DAPT substantially decrease the bleeding likelihood (main blood loss and any blood loss) by more than 40% without increasing the ischemic risk for patients after new-generation DES implantation. Besides, a significant reduction of up to 16% in net clinical adverse events was found in the short-duration DAPT arm, including the acute coronary syndrome subgroup. It is reasonable to reduce DAPT time to 1- or 3 months in individuals implanted with new-generation drug-eluting stents, especially those with high bleeding risk or scheduled to receive surgery recently.

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Authors' contributions: IU and MA did the original draft preparation, study design, validation and analysis; MU and HZ did the writing—review and editing; IU, MA did data extraction and quality assessment; HZ did supervision. All authors listed have made a substantial, direct and intellectual contribution to the manuscript, All authors have read and agreed to the published version of the manuscript.

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Review Article

The Role of Multidisciplinary Rehabilitation in Enhancing Comprehensive Cancer Care: A Descriptive Review

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Abstract

Objective: To highlight the effectiveness of cancer rehabilitation in improving physical, emotional, and social outcomes for patients with various forms of cancer. It evaluates the impact of cancer rehabilitation on physical function, psychological health, and social reintegration while identifying barriers and facilitators in the implementation of cancer rehabilitation programs.

Methodology: A literature search was conducted from December 2023 to February 2024, using two electronic databases: MEDLINE (via PubMed) and Google Scholar. After screening the titles and abstracts, the study selected 34 articles, including RCTs, clinical trials, observational studies, and systematic reviews. The study did not include letters to the editor, editorials, special and short communications, animal-based research, and non-English language publications. There were no restrictions on geographical distribution, age of the sample population, type, severity, duration, and outcome of cancer, or the year range from which the studies were selected.

Results: Rehabilitation interventions were effective in different cancer types, including breast, prostate, lung, and colorectal cancers. These interventions addressed common treatment-related challenges such as fatigue, pain, lymphedema, incontinence, and psychological issues, improving patients' quality of life and physical functioning. However, challenges such as physical limitations, emotional distress, access to care, financial barriers, and coordination of services were frequently noted. This highlights the need for tailored, accessible, and well-coordinated cancer rehabilitation programs.

Conclusion: Multidisciplinary and coordinated cancer rehabilitation has the potential to improve mobility, quality of life and physical functioning across various cancer types, but challenges in accessibility and coordination must be addressed.

Keywords: Cancer Rehabilitation, Multidisciplinary rehabilitation, Quality of life, Rehabilitation Medicine.

Introduction

Cancer rehabilitation is a multidisciplinary approach to helping people with cancer maintain and restore physical, emotional, and social function.[1] It can be started before, during, or after cancer treatment.[2,3] Rehabilitation professionals examine and devise customized rehabilitation plans for the cancer patient or survivor that address individual's problem list and rehabilitation goals. Cancer rehabilitation is a multifaceted approach ng including physical therapy, occupational therapy, psychological help, provision of orthotics and prosthetics (where required), and nutritional support .

It is designed to improve quality of life and help individuals return to their normal daily activities. There is strong evidence to support the role of cancer rehabilitation in improving physical function, reducing fatigue, and increasing overall well-being. It can also help individuals maintain their independence and reduce the need for additional medical care or institutionalization.[4] In addition to the benefits to individuals, cancer rehabilitation can also have a positive impact on the healthcare system as a whole. By helping cancer survivors return to their normal daily activities and reducing the need for additional medical care, cancer rehabilitation can potentially lower healthcare costs and reduce the burden on the healthcare system.[5]

Cancer rehabilitation can be an important part of the cancer journey for many individuals and can help improve physical, emotional, and psycho-social well-being. There is a need for increasing the knowledge of physicians about cancer rehabilitation. A study conducted in 2019, in Puerto Rico on physiatrists, reports that 66.7% of the Rehabilitation Medicine Physicians reported receiving no or minimal formal education on cancer rehabilitation.[6] Lack of education may result in sub optimal services the oncologists and rehabilitation medicine physicians may provide to the patients. We conducted this descriptive review to highlight the need for early, coordinated and comprehensive multidisciplinary cancer rehabilitation, explaining its types and summarizing the effectiveness of various forms of cancer rehabilitation in improving physical, emotional, and social outcomes for patients with cancer. The review evaluates the impact of cancer rehabilitation on physical function, psychological health, and social reintegration while identifying

barriers and facilitators in the implementation of cancer rehabilitation programs.

Methodology

Search Strategy

We conducted a comprehensive online literature search from December 2023 to February 2024 using two electronic databases: MEDLINE (via PubMed) and Google Scholar. The search strategy utilized a combination of the following keywords with Boolean operators (AND, OR, NOT): Oncology, Cancer Rehabilitation, Physical Therapy, Rehabilitation, Occupational Therapy, Pain Management, Breast Cancer, Colon Cancer, Prostate Cancer, Brain Tumor, Bone Cancer, Rehabilitation Interventions, Lymphedema, Quality of Life, Complication, Cancer Survivors, Outcomes, Exercise Therapy, and Exercise.

Inclusion/ Exclusion Criteria

We included the following; Original research articles, Randomized controlled trials, Quasi-experimental studies, Clinical trials, Review Articles (narrative and systematic reviews), Studies conducted in humans, Publications in English language, Articles focusing on cancer rehabilitation services worldwide, Studies reporting on effective interventions for cancer survivors. There were no restrictions on geographical distribution, age of the sample population, type, severity, duration, and outcome of cancer, or the year range from which the studies were selected.The following articles were excluded; Letters to the editor, Editorials, Special communications, short communications, Animal-based research, Non-English language publications. Some articles were excluded as they were behind pay walls, and the authors were unable to access them.

Study Selection

Two authors (FA and SA) independently performed the literature search and screening process. The initial screening was based on titles and abstracts, followed by full-text review of potentially eligible articles. Any disagreements were resolved through discussion and consensus.

Data Extraction

We extracted relevant data from the included studies, focusing on; Types of cancer rehabilitation services, Geographical distribution of services, Effectiveness of interventions, Outcomes in cancer survivors. The extracted data were synthesized narratively to provide a comprehensive overview of cancer rehabilitation services globally and to highlight effective interventions for cancer survivors.

Results

After screening the titles and abstracts, authors selected 34 articles, including RCTs, clinical trials, observational studies, and systematic reviews for data extraction. From the results of the studies included, there is evidence that cancer rehabilitation is effective in various forms of cancers in different stages (Table 1). Rehabilitation not only addresses the disability associated with the cancer but also

Table I: Summary of the Multidisciplinary Team Interventions in Cancer Rehabilitation.

Authors	Type of Manuscript	Cancer Type	Summary Points
van Weert E et al. (2005)[3]	Clinical Trial	Various Types	A 15-week rehabilitation program was developed for cancer survivors to improve QOL, and overcome physical and psychosocial problems. It showed statistically significant improvements in health-related QOL (0.38-0.99), exercise capacity, and muscle force. 80% of patients initially preferred the multidimensional program, as it had beneficial effects on QOL, exercise capacity, and muscle force.
Silver et al. (2011)[4]	Review	Various types	This review highlights the role of cancer rehabilitation in survivorship, improving pain, musculoskeletal issues, fatigue, balance, lymphedema, and psychosocial problems through physical and occupational therapy.
Brown et al. (2018)[7]	Randomized Controlled Trial	Colon Cancer	Aerobic exercise significantly improved physical functioning, sleep quality, and reduced fatigue in colon cancer survivors, with greater benefits at 300 minutes per week.
Möller et al. (2019)[8]	Systematic Review	Breast Cancer	This review identified exercise/PA, yoga, and tailored programs as effective for improving mobility, lymphoedema, pain, fatigue, QOL, and mental health in breast cancer rehabilitation.

Authors	Type of Manuscript	Cancer Type	Summary Points
Messaggi-Sartor et al. (2019)[9]	Randomized Controlled Trial	Lung Cancer	An 8-week aerobic and high-intensity respiratory muscle training program improved exercise capacity, respiratory strength, and IGFBP-3 levels post-lung cancer surgery, but did not enhance QOL.
Houben et al. (2023)[10]	Randomized Controlled Trial	Prostate Cancer	A 20-week resistance exercise program improved body composition, muscle mass, strength, and aerobic capacity in prostate cancer patients on ADT, with no additional benefit from protein supplements.
Molenaar et al. (2023)[11]	Randomized Controlled Trial	Colon Cancer	A 4-week multimodal prehabilitation program before colorectal cancer surgery reduced severe complications and improved recovery compared to standard care.

ADT: Androgen Deprivation Therapy; QOL: Quality of Life; PA: Physical Activity.

alleviates complications associated with the treatment of cancer, including chemotherapy and radiation. A summary of selected studies is presented in Table 1 below.

Based on our review of various manuscripts, we found that cancer rehabilitation was effective for individuals with different types of cancer at various stages of their journey. This included breast cancer,[9] prostate cancer,[11] lung cancer,[10] and colorectal cancer.[8,12] Breast cancer treatment often led to challenges such as fatigue, pain, and lymphedema, and cancer rehabilitation helped manage these issues, enhancing patients' quality of life.[9] Prostate cancer treatment can sometimes result in physical and emotional challenges, such as incontinence (inability to control urine) and sexual dysfunction.[12] Cancer rehabilitation can help individuals manage these challenges and improve their quality of life.[13] Lung cancer patients benefited from a multifaceted rehabilitation approach that improved fatigue, pain, and breathing difficulties.[10] Colorectal cancer treatment often resulted in fatigue, pain, and bowel and bladder dysfunction, with rehabilitation interventions playing a crucial role in optimizing physical and psychological well-being.[12] The findings from the review suggest that cancer rehabilitation is beneficial for a variety of cancer types. It is important for the cancer patients and cancer survivors to discuss their rehabilitation needs and goals with their healthcare team to determine the most suiTable interventions. The oncologists and other cancer team members should proactively offer guidance about cancer rehabilitation and make appropriate and timely referrals to Rehabilitation Medicine physicians.

The literature also highlighted several challenges patients faced during cancer rehabilitation. Physical limitations such as weakness, fatigue, and mobility issues were common, making participation in rehabilitation activities difficult.[13] Emotional challenges for cancer patients included fear, anxiety, depression, and grief.[14] This could potentially hinder active participation in rehabilitation and require additional psychological support. Access to rehabilitation services posed a significant challenge, especially for those in remote or rural areas, who often faced long travel distances to reach specialized care facilities.[15,16] Financial barriers were another issue identified. Rehabilitation services are frequently excluded from standard cancer treatment insurance policies, leading to decreased access.[17] This is particularly true for developing countries like Pakistan, where patients frequently pay out of pocket for rehabilitation services.[18] Coordination of care was identified as crucial but challenging, particularly when services were spread across different locations. Effective coordination, including the use of cancer patient navigators and interdisciplinary collaboration, was highlighted as essential for ensuring timely referrals and comprehensive support for diverse patient needs.[12]

Discussion

This review, based on an online literature search of 2 major databases provides evidence for the effectiveness of various forms of cancer rehabilitation in improving physical, emotional, and social outcomes for cancer survivors. It evaluated the impact on physical function, psychological health, and social reintegration, emphasizing that rehabilitation helps with the disabilities associated with both the disease and its treatment.

A cancer patient goes through psychological, physiological, or functional dysfunction or defects in anatomical structures before during or after cancer treatment. Some of the impairments are muscle mass loss, osteopenia/osteoporosis, plexopathy, radiation fibrosis syndrome, radiculopathy, scar adhesion, sensory deficits, sexual dysfunction , shoulder pain, speech impairment, urinary dysfunction, visuospatial and/or proprioception dysfunction, difficulty with activities of daily living, difficulty with instrumental activities of daily living (chores/shopping, etc.), fatigue, joint pain, musculoskeletal pain (e.g., myalgias, myofascial pain), neuropathic pain, somatic pain, visceral pain, deconditioning, backache, imbalance, bowel dysfunction, chest pain, cognitive impairment , abnormal gait , and joint range-of-motion limitations.[1-3] Associated disabilities include Physical, cognitive, psychological, social, and emotional disabilities and activities of daily living/ functional disabilities.[19] The analysis of the included studies highlights the benefits of cancer rehabilitation across various types and stages of

cancer (Table 1). Rehabilitation interventions have proven effective not only in addressing the disabilities directly associated with cancer but also in alleviating complications related to treatments such as chemotherapy and radiation therapy. For breast cancer survivors, Multidisciplinary Team (MDT) cancer rehabilitation programs have shown particular success in addressing post-treatment complications such as lymphedema, shoulder dysfunction, and cancer-related fatigue. This improvement in physical symptoms consequently enhanced the overall quality of life for these patients. Similarly, in prostate cancer, rehabilitation programs focusing on pelvic floor exercises, coupled with psychological support, were proven effective in managing post-treatment complications such as incontinence and sexual dysfunction, which are common issues.[13,14] Lung cancer treatment can sometimes result in physical and emotional challenges, such as fatigue, pain, and difficulty breathing.[20] Integrating respiratory therapy, exercise physiology, and nutritional support resulted in significant improvements in exercise capacity, respiratory strength, and helped manage treatment-related fatigue and pain and improved the quality of life for lung cancer survivors.[9,15] In colorectal and prostate cancer, rehabilitation in addressed fatigue, pain, and bowel and bladder dysfunction resulted in both physical and psychological well-being.[16,17]

These findings highlight the critical role of personalized rehabilitation programs that cater to the specific needs of patients based on their cancer type and individual health conditions. Despite the clear benefits of cancer rehabilitation, several challenges were identified. For cancer patients and survivors, physical limitations such as weakness, fatigue, and mobility issues often restrict the patients' ability to adequately participate and engage in rehabilitation activities. In addition to that, emotional challenges, including fear, anxiety, depression, and grief, were significant barriers in providing adequate cancer rehabilitation, Therefore, it is necessary to integrate psychological support into rehabilitation services.

There is a growing interest in implementing cancer prehabilitation and rehabilitation programs before cancer treatment begins. Proponents argue that prehabilitation can improve treatment tolerance and post-treatment outcomes. Zamora et al. (2023) evaluated the impact of prehabilitation on treatment costs in patients undergoing gastrointestinal cancer surgery.[18] The model estimated that prehabilitation resulted in significant cost savings, with a patient-weighted average of £785, excluding ICU costs. ICU cost savings were £1,620. For the NHS, this translated to £186.1 million in cost savings from reduced complications and hospital days, and £52.8 million from ICU stay.[18]

Despite its potential to improve function and QOL in the cancer survivors, MDT cancer rehabilitation faces several challenges.[19] Accessibility to cancer rehabilitation services is a significant challenge, especially for individuals residing in remote or rural areas. These individuals often have to travel long distances to reach specialized cancer care facilities, which can be a considerable burden.[20] Onega et al. (2008) found that while 91.8% of the U.S. population had access to specialized cancer care within an hour, nonurban residents and Native Americans faced significantly longer travel times.[21] Similarly, Liu et al. (2023) from the USA reported that pediatric cancer care also faces geographical accessibility issues, impacting timely treatment.[22] Lin et al. (2015) highlighted the extreme travel times patients endure, and the geographical distribution of oncologists.[23] He observed that increased travel burden was associated with a decreased likelihood of receiving adjuvant chemotherapy, regardless of insurance status. Another similar study emphasized the low utilization of cancer rehabilitation services, attributing this to logistical demands and travel challenges.[24]

Cancer rehabilitation can be expensive, and individuals may not have insurance coverage for certain rehabilitation services.[25] In developing countries like Pakistan where patients have to pay out of pocket for the medical treatment, it becomes very difficult to manage the cost of rehabilitation once the medical or surgical management of cancer is completed. This can be addressed by exploring hub and spoke care models and mobile rehabilitation units. Coordination of care in cancer rehabilitation is crucial for improving patient outcomes, but it presents significant challenges when services are spread across different locations. Nicole et al. highlight the importance of proactive functional screening and assessment in bridging oncology and rehabilitation systems. They advocate for cancer patient navigators to coordinate care, ensuring timely referrals to rehabilitation services. This model involves interdisciplinary collaboration to address diverse patient needs through a coordinated effort. Overall, cancer rehabilitation can be a challenging process. It is important for individuals to work closely with their healthcare team and to seek support from family, friends, and support groups as needed. Early and seamless integration of rehabilitation services with standard oncology care remains a challenge around the globe and particularly in the Low- and Middle-Income Countries (LMIC).[25] Patients are usually discharged home without a referral to the rehabilitation medicine physician or addressing their needs to improve their functioning and mobility. This is often complicated by the fact that the patients based in the LMIC have usually exhausted their out-of-pocket finances by the time curative cancer care is completed.

Cancer rehabilitation encompasses various management options tailored to individual needs, including physical therapy, occupational therapy, psychological support, speech therapy, lymphedema therapy, prosthetics and orthotics, and nutritional support. Physical therapy focuses on enhancing strength, mobility, and managing side effects like fatigue and lymphedema, especially in breast cancer survivors. Occupational therapy aids in resuming daily activities and adapting home environments, while psychological support addresses emotional challenges such as anxiety and depression. Speech therapy is crucial for addressing swallowing difficulties, particularly in head and neck cancers. Lymphedema therapy involves managing swelling through exercises, compression, and manual lymphatic drainage.[26]

Prosthetics and orthotics assist in regaining functionality after the loss of body parts, and nutritional support ensures adequate health and strength maintenance. The choice of interventions depends on the individual's specific needs and rehabilitation goals. It is important to work closely with a cancer rehabilitation team to determine the most appropriate interventions for an individual's unique situation. The specific steps of cancer rehabilitation will depend on the individual's needs and goals and may be modified as their condition changes.

To summarize, we may say that cancer rehabilitation is a collaborative process and may involve a range of healthcare professionals, including rehabilitation medicine physicians, nurses, physical therapists, occupational therapists, psychologists and other rehabilitation professionals, to provide comprehensive and tailored support for each patient's recovery journey.

Limitations

This review has several limitations that should be considered when interpreting its findings. First, the literature search was limited to only two databases, potentially missing relevant studies indexed elsewhere. Second, no formal quality assessment of the included articles was conducted, which may introduce bias in the interpretation and synthesis of the findings. Third, some potentially relevant articles were excluded due to being behind paywalls, limiting the comprehensiveness of the review. Additionally, this review only included articles published in English, which may have led to language bias and the omission of research published in other languages. As a descriptive review, it lacks the systematic and comprehensive approach of a systematic review or meta-analysis, potentially introducing subjectivity in the selection and interpretation of studies. The absence of a formal assessment of the quality of included articles further limits the ability to weigh the strength of evidence presented in the review. These limitations highlight the need for caution when generalizing the findings and underscore the importance of conducting more comprehensive, systematic reviews on this topic in the future.

Conclusion

While cancer rehabilitation offers considerable benefits in enhancing the quality of life and functional outcomes for cancer patients, addressing the identified challenges is essential for its widespread implementation and effectiveness. This includes improving accessibility to services, integrating psychological support, and ensuring effective coordination of care. Future research and policy efforts should focus on overcoming these barriers to make cancer rehabilitation services more universally accessible and effective, ultimately supporting better patient outcomes across various cancer types and stages.

Conflict of Interest: The authors declare no conflict of interest.

Author contributions: FAR contributed in conception, design, literature search and writing the initial draft; SA did literature search and writing the final draft HMM did literature search and writing the final draft. All authors approve the final draft of the manuscript and take responsibility for the contents of the article.

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Case Report

Intracardiac Ectopic Thyroid Tissue: A Case Report

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Abstract

We present the case of a 36-year-old female who visited the OPD of a local hospital in Lahore, Pakistan, with history of chest pain, shortness of breath and palpitations. Echocardiogram and transesophageal echocardiography revealed right ventricular outflow tract mass, dilated coronary sinus and atrial septal defect. Surgery was advised, and successful excision of the mass was done and the specimen later sent to Chughtai Institute of Pathology for histopathological evaluation and diagnosis. The results revealed benign thyroid tissue with no evidence of malignancy. The patient was symptom-free on follow up after 6 months.

Keywords: Ectopic thyroid, echocardiography, intra-cardiac ectopic thyroid tissue, right ventricular outflow tract.

Introduction

Ectopic thyroid is an unusual developmental anomaly that in majority of the cases presents at the base of tongue.[1] Thyroid gland is the first endocrine gland to develop at 24th day of intrauterine life near base of tongue between first and second pharyngeal pouches from where it descends to its final location in front of trachea between 2nd to 5th tracheal rings.[1] Therefore, 90% of the cases of ectopic thyroid are reported at the base of the tongue. Various other sites including heart have been described.[2,3]

Case Presentation

A 36-year-old female presented in February, 2023, at the OPD of a local hospital in Lahore, Punjab, with complaints of shortness of breath, chest pain and palpitations for a couple of months. The chest pain was gradual in onset and constant. However, it was not associated with fever, weight loss and cough. She had no significant past medical, surgical, drug or family history. Her physical examination was unremarkable. Her laboratory parameters were normal. She underwent echocardiogram that showed an organized mass in right ventricular outflow tract causing obstruction. In addition, dilated coronary sinus and small atrial septal defect causing left to right shunt was also found. She was advised transesophageal echocardiography which was performed after two days followed by Gated cardiac CT and thoracic aortogram which showed a broad-based spherical contrast enhancing mass (29.2x29.9x31.2 mm) in right ventricular outflow tract attached to interventricular septum. Based on these findings, she was diagnosed to have a large right ventricular outflow tract mass, in addition to atrial septal defect. Closure of atrial septal defect and excision of right ventricular outflow tract mass was planned and successfully executed in March, 2023. Her specimen was received and processed in Chughtai institute of Pathology for subsequent histopathological evaluation and diagnosis. On gross inspection, it was an intact nodular piece of tissue measuring 3.0 x 2.5 x 1.5 cm and weighing 11 grams. Surface was smooth and shiny (Figure 1).

Serial slicing revealed myxoid cut surface with small cystic spaces (Figure 2). A total of 3 sections were submitted for microscopic examination. Microscopic examination revealed benign thyroid tissue composed of variably sized follicles. Atypical features or evidence of malignancy was not seen. At periphery, thick muscle bundles were present, but cardiac myocytes were not identified. The final diagnosis was concluded as an intra-cardiac ectopic thyroid tissue. The patient had an unremarkable postsurgical course and was asymptomatic on 6 months follow up.

Discussion

We reported a case of 36-year-old female diagnosed with ectopic thyroid tissue in the right ventricular outflow tract. This case is interesting and fascinating for pathologists, because intra-cardiac ectopic thyroid is a quite unusual and rare phenomenon. It was first reported in 1941 by Dosch during an autopsy examination and was successfully operated in 1984 for the first time. Most of the cases were reported after 1985 with approximately 10 cases every decade. Four Studies have shown that ectopic thyroid tissue is more frequent in middle to advanced aged females as compared to males, with a female to male ratio of 3:1 to 8:1, as in our case. Thyroid profile might also be normal, that makes diagnosis even complicated. Symptomatic patients usually

present with dyspnea and palpitation due to outflow tract obstruction. In our case, the patient had a complaint of chest pain, shortness of breath and palpitations for a couple of months with normal laboratory parameters. It is fascinating to mention that most of the reported cases of intracardiac ectopic thyroid presented as interventricular septal mass lesion which gradually increased in size causing ventricular outflow tract obstruction.[5] The proposed theory behind this phenomenon is an anatomical linkage of developing thyroid primordium with bulbus cordis of developing heart. Hence, during normal decent of heart and great vessels into the chest, ectopic thyroid may happen in the right ventricle. In our case too, an organized mass was identified in right ventricular outflow tract causing outflow obstruction. But there was an association with ostium secundum defect.[2,3] Rare cases of intra-cardiac ectopic thyroid at other sites such as ascending aorta and right side of atrial septum approaching the superior vena cava and aortic root have been described.[6] The patients with ectopic thyroid may be either completely asymptomatic or symptomatic depending on the site.[7] In our case, perioperative clinical suspicion was of myxoma but it surprisingly came out to be ectopic thyroid giving valuable information to the clinicians for patient management.

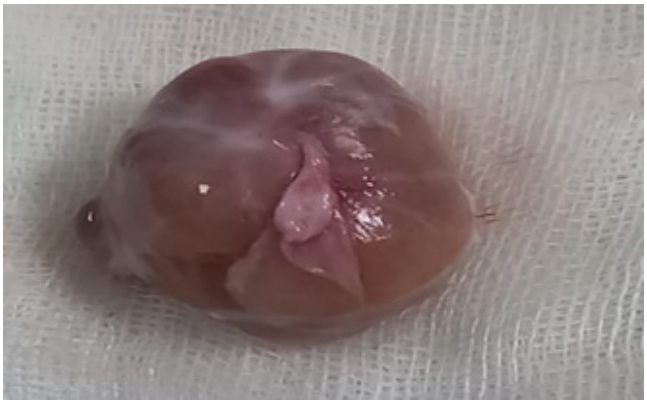

Figure 1: A single intact and nodular tissue fragment (3.0x2.5x1.5cm, 11 grams) with smooth and shiny surface.

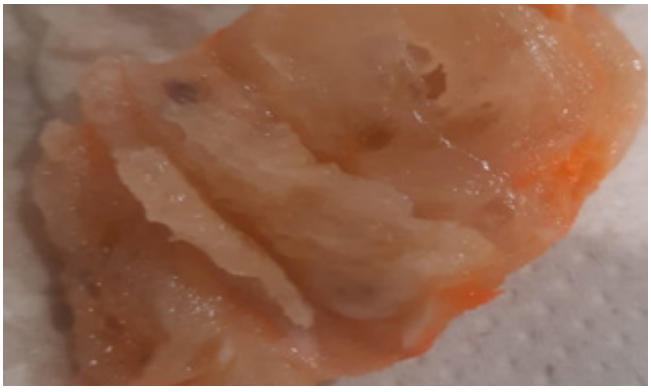

Figure 2: Gross Appearance: On serial slicing, cut surface is homogenous and myxoid.

Conclusion

Ectopic thyroid tissue should always be kept in differentials while diagnosing a mass present at any site other than its usual anatomical location, including the heart.

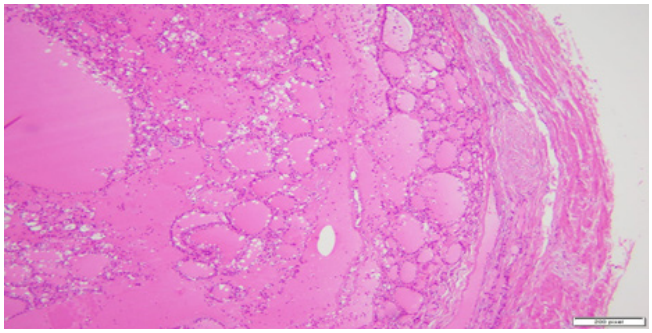

Figure 3: Low power (10x magnification): Ectopic Thyroid; A thyroid nodule showing variably sized follicles and abundant colloid. No thick capsule seen. No cardiac myocytes appreciated.

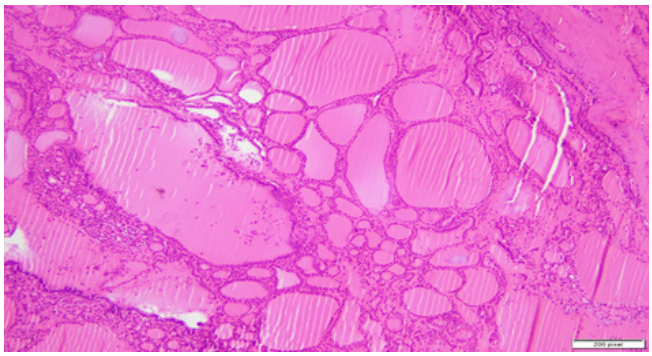

Figure 4: High power (40x magnification): Ectopic Thyroid; Variable sized dilated follicles with flattened to hyperplastic epithelium and abundant colloid. No cardiac myocytes appreciated.

Conflict of Interest: The authors have no conflicts of interest.

Informed Consent: An informed consent was taken from the patient for the purpose of this case report, without revealing her identity.

Authors' Contribution: The authors hereby validate their participation in the preparation of the manuscript in the following manner: The inception, formulation of the study and collection of information was done by HN; the analysis and interpretation of results was carried out by AB, FW & AA; overall supervision and final approval of the manuscript was done by ASC.

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Case Report

Post COVID-Vaccine Cerebritis: A Case Report

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Abstract

We are reporting here a case of a 33-year-old male who presented to the Emergency Department at Lahore General Hospital in June, 2021, with a short history of fever and generalised tonic-clonic seizures. The symptoms started one day after getting the first dose of Sinopharm vaccine. He was managed initially on the line of refractory status epilepticus in the ICU and was given empirical cover for meningoencephalitis. CSF analysis report came out normal. MRI of the brain showed left frontal lobe cerebritis. Fits and fever settled and the patient fully recovered on the third day of admission. There are very few reported neurological complications of Covid-19 vaccination. One of the rare complications which we have seen with the sinopharm vaccine is cerebritis. This case raises awareness among physicians and contributes to the existing literature so that more vigilance is done while administrating COVID-19 vaccines.

Keywords: COVID-19, Cerebritis, Sinopharm Vaccine

Introduction

Sinopharm vaccine is a deactivated vaccine that carries SARS-CoV-2 antigens to the body. Its efficacy is around 9.8%. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2Adverse events following immunization are a critical area of study, particularly in the context of the widespread administration of COVID-19 vaccines.[2]onset of COVID-19-like symptoms, and 7 days later, confirming COVID-19 using Nucleic Acid Amplification Test (NAAT). Many vaccines have been shown to trigger autoimmune reactions in body which might be a reason for cerebritis by this vaccine.[3] Neurological complications, although rare, can pose significant challenges in both diagnosis and management.[4,5] This case report discusses a 33-year-old, previously healthy male who developed severe neurological symptoms following the administration of the Sinopharm COVID-19 vaccine. The patient presented to the Emergency Department of Lahore General Hospital with high-grade fever, vomiting, and generalized tonic-clonic seizures. Despite an initial management regimen that included anti-seizure medications and ICU admission, his condition required further intervention and diagnostic evaluation. Imaging later revealed left frontal lobe cerebritis, an unexpected finding that emerged only after the patient had been discharged. This case reflects the importance of thorough post-vaccination monitoring and the need for healthcare professionals to be vigilant about potential severe adverse events. By sharing this case, we aim to contribute to the broader understanding of vaccine-related complications and highlight the need for comprehensive patient follow-up in the post-vaccination period.

Case Presentation

A 33-year-old male with no previous comorbidities, businessman by occupation presented to the Emergency Department of Lahore General Hospital (LGH) in June 2021 with a history of fever, vomiting and fits after getting the Sinopharm vaccine. Fever and vomiting developed on the first day after the vaccine and fits developed on the second day. Fever was high grade with chills and rigours relieved on taking the Tablet paracetamol, and associated with vomiting in 3 episodes. The following day, he developed seizures which were generalized tonic-clonic variety with tongue biting, urinary incontinence and loss of consciousness. He had 6 to 7 episodes of fits without gain of consciousness in between. On examination, he had Blood Pressure = 130/90, Heart Rate = 90/min, Temp. = 101 F, Respiratory rate= 20/min. Systemic examination was unremarkable. He had no previous history of any such illness or epilepsy. He had no known allergies and his vaccination status was not known other than intake of this particular vaccine. On CNS examination, there were no signs of focal deficits, raised intracranial pressure or loss of motor power.

White Blood Cell count was 13000/mm^3. X-ray chest showed bilateral lower zone infiltrate. The rest of the baseline labs including BSR, RFTs, LFTs, Serum Electrolytes, PT, aPTT, and INR were normal. Malaria parasite (MP slide) and PCR for COVID-19 were also negative. CT brain showed diffuse cerebral oedema and CSF analysis was normal. HRCT Chest showed a small area of air space opacification in the left lower zone indicatinga mild infective process. The patient had to be shifted to ICU becausethe fits were not being controlled by inj. diazepam and the maximum dose of valproic acid. The patient remained on ventilator support in ICU for one day. Afterwards, he was extubated. The patient gained consciousness and he was

shifted to the medical ward. During his stay in the hospital, he was given IV fluids, InjecTable antibiotics before LP report, which included triple cover with ceftriaxone (2 g), vancomycin (1 g), acyclovir (500 mg) and anti-malarial (Artemether 80 mg) along with iv steroids (Dexamethasone 2 cc). He remained afebrile and seizure-free. EEG couldn't be performed during fitsand afterwards, it came out normal.MRI brain was performed in the medical ward when the patient was sTable. Treatment was continued for ten days. The patient had an uneventful recovery and was discharged from the hospital. Here, it is interesting to mention that MRI was done during his hospital stay but its report by an expert radiologist came 2 days after he was discharged because of the high patient load on the radiology department. One of the relatives of the patient brought the report and surprisingly it showed left frontal lobe cerebritis (Figure 1a, 1b)

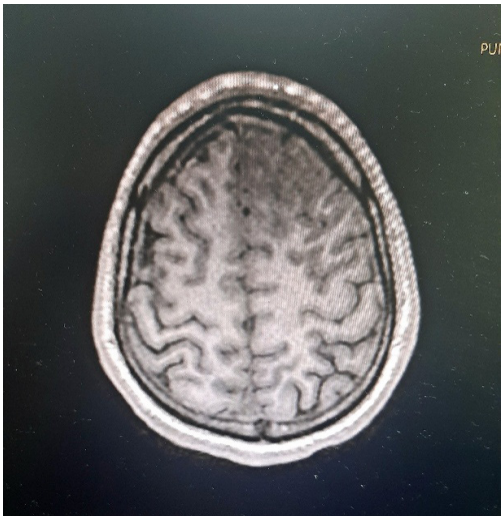

Figure 1a

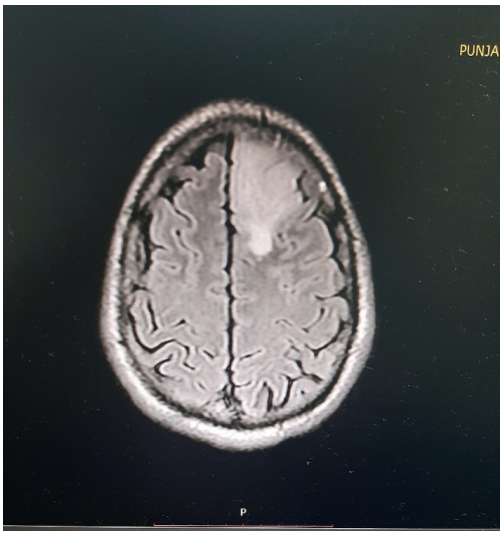

Figure 1b

Figure 1a and 1b MRI Brain showing hypo and hyper-intense areas in the left frontal region respectively which is suggestive of ongoing inflammation i.e. cerebritis When he enquired about the health of the patient he said that the patient had got sickagain, having high-grade fever along with vomiting. He was advised to bring him back but he never showed up neither we were able to contact him.

Discussion

We reported a case of a 33-year-old male diagnosed with post-vaccine-induced cerebritis. This case is fascinating for neurologists as well as physicians because this side effect has not been reported before in Pakistan. Although stroke-like symptoms and autoimmune phenomenon have been reported previously all over the world.[4],[2]onset of COVID-19-like symptoms, and 7 days later, confirming COVID-19 using nucleic amplification test (NAAT testSinopharm vaccine contains dead mRNA of coronavirus. It induces high levels of neutralizing antibodies.[6]the first half of 2021 has seen vaccine rollout in many countries. In this Progress article, we provide a snapshot of ongoing vaccine efficacy studies, as well as real-world data on vaccine effectiveness and the impact of virus variants of concern.

Where they have been deployed in a high proportion of the adult population, the currently approved vaccines have been extremely effective in preventing COVID-19, particularly severe disease. Nonetheless, there are still significant challenges in ensuring equiTable vaccine access around the globe and lessons that can be learned for controlling this pandemic and for the next pandemic.Apparently, it should not produce any serious side effects. However, there are reports of lethal side effects from all over the world. The common side effects recorded so far are local pain, redness, tenderness at the injection site, headache and fever.[7] Serious side effects like acute disseminated encephalomyelitis are also reported.

According to WHO, lethal side effects, although rare, are also seen, like some vaccines are reported to produce blood clots, myocarditis and severe anaphylactic reactions. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2,[8] In our case we had a differential diagnosis of Meningoencephalitis, cerebral malaria and other systemic infection. Cerebritis can have many causes, like bacterial, fungal, viral, penetrating trauma to the head or haematogenous spread that can be from any systemic infection. It may also follow meningitis.Britt and Enzamen described the spectrum of this process into four stages, earlycerebritis, latecerebritis, early capsule formation and late capsule formation.[9]and the findings correlated with the appearance on computerized to mography. Through all relative tests mentioned above, we were able to conclude that the patient was completely healthy and these symptoms were due to side effect of Sinopharm vaccine which might have acted as an autoimmune trigger. The unavailability of patients might limit the study but this opens the door for further research on Vaccine-induced autoimmune reactions.

Conclusion

This case highlights the potential for severe neurological complications following COVID-19 vaccination, emphasizing the need for vigilant post-vaccination monitoring and timely diagnostic intervention. It also emphasizes vaccination history in any case where the diagnosis doesn't fit into any category. Comprehensive follow-up is essential to promptly identify and manage unexpected adverse events, ensuring patient safety and effective healthcare outcomes.

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Informed Consent: An informed consent was taken from the patient for the purpose of this case report, without revealing her identity.

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Short Communication

Infodemic and its Impact on the Mental Health of Researchers and Health Professionals: The COVID-19 Pandemic Aftermath

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Abstract

Before the pandemic, research focused on measuring stress and workload in the workplace. However, during the pandemic, the mental health of researchers, clinicians, policy makers, and the public, became a significant topic. The COVID-19 pandemic not only triggered a global health crisis but also unleashed an "infodemic"—an overwhelming flood of information significantly impacting the mental health of researchers and health professionals. This short communication is an attempt to explore how mental health issues were often overlooked during the global pandemic. Addressing mental health issues for researchers and health workers globally is crucial. As we continue to deal with COVID-19 challenges, understanding the large amount of existing information and the future impact on mental health will be important and interesting to track in the coming years.

Keywords: COVID-19, Health Professionals, Mental Health, Researchers, Pandemic.

Introduction

The mental health and well-being of researchers, clinicians, health professionals, policymakers and the public during the pandemic and afterwards was a significant concern and will continue to be in the future. The COVID-19 pandemic also triggered a global health crisis.[1] This led to an "infodemic"—an overwhelming surge of scientific information.[2] Unlike previous infectious disease outbreaks, such as the Spanish flu, where information was scarce, the COVID-19 pandemic has been marked by a vast and rapidly expanding body of scientific literature, policy documents, and media reports.[3] The unprecedented volume of publications, guidelines, and research outputs during the COVID-19 pandemic has placed an extraordinary burden on those responsible for synthesizing and applying this knowledge, and hence as a result has the potential to have detrimental effects on one's mental health. In addition to the rise in information, there was also misleading information.[4]

The Infodemic

The rapid dissemination of information during the COVID-19 pandemic had positive and negative effects. On one hand, the swift exchange of scientific findings and public health guidelines was crucial in managing the spread of the virus.[2] Not only did the sheer volume of information increase but a misinformation proliferation occurred including conflicting or inaccurate information.[4] Health professionals were faced with ever changing protocols, guidelines, and treatment recommendations, often based on preliminary data. There was the need to stay informed and there was the necessity to provide accurate patient information. This was leading to stress and possibly even burnout. Researchers, on the other hand, faced an avalanche of scientific literature, some of which was released without rigorous peer review due to the situation's urgency. The need to rapidly produce and disseminate research findings contributed to a culture of "publish or perish", further exacerbating mental health challenges. In fact, Suart and colleagues reported increased publication pressure across academic researchers in Canada following the pandemic.[5]

Impact of the Pandemic on Mental Health

This phenomenon significantly impacted the mental health of the community, researchers and healthcare professionals, and there was immense pressure due to the demands of the pandemic. The infodemic's impact on mental health was profound, particularly among those on the frontlines of the pandemic response. Health professionals were inundated with ever-changing protocols and guidelines, adding to their workload and stress. There were wide and diverse gaps in the knowledge of COVID-19 and there was no linkage globally between studies, authors and institutions.[2] Medical assistants in Germany reported increased levels of symptoms and signs related to anxiety, depression, stress and burnout that could relate to workload requirements and time burdens leading to worse psychosocial conditions occurred during the COVID pandemic.[6] The uncertain situation and the responsibility of providing accurate and up-to-date care created a perfect storm of stress. Vindegaard and Benros reported on

the need for social support of health professionals in relation to the potential for mental disorder outbreaks.[7]

Researchers were not immune to these pressures with concerns related to insufficient personal protective equipment and the need for support.[8] Challenges included delayed ethical clearance, disrupted funding and grant applications, obstacles related to participant availability and the need to pivot towards pandemic-related priorities.[9] There was a rapid pace of scientific discovery, combined with the need to sift through vast amounts of data. This potentially led to feelings of overwork or being underequipped. The pressure to contribute to the science relating to the virus, with time pressures and under-resourcing compounded difficulties. Additionally, the competitive nature of academic publication pressure, with pandemic intensification, could be related to misconduct and burnout.[5]

Impact of Misinformation on Mental Health

Misinformation significantly impacted mental health and healthcare decision making. The spread of false or misleading information undermined public trust in science and medicine, resulting in misunderstandings and decreased compliance to guidelines.[10] Health professionals were often left to correct misconceptions and combat misinformation. This added to an already heavy workload. For researchers, the proliferation of misinformation created an additional layer of complexity and burden on those working in these disciplines aside from purely the infodemic. The need to navigate and refute false claims while simultaneously advancing legitimate scientific inquiry created exhaustion. The need to produce reliable research where misinformation was prevalent resulted in frustration and powerlessness. Recommended solutions and strategies for minimising misinformation for the future have been documented.[11]

Coping Strategies and Support Systems

Several strategies emerge as crucial for both immediate and future crises in addressing the psychological impact of infodemics on health professionals. Communication strategies are the most important. Accurate information that is checked, enhances communication and is vital for minimizing anxiety that can arise from misinformation. Utilising fact checking, reviewing regular reliable updates and adherence to evidence-based guidelines is crucial.[10] Mental health resources including counselling services, forums for discussion and peer support, are crucial to manage the stress associated with pandemics that maybe related to information overload or other factors.[12] Other therapies may also be beneficial such as art or creative activities to help individuals express emotions, manage stress, and improve mental well-being.

Goal setting and prioritisation of necessary tasks, facilitates time management and workload distribution and hence may combat burnout. Micro-breaks have been reported as beneficial for improving overall performance and vigour and decreasing fatigue.[13] Promoting a collaborative environment, rather than fostering competition, can reduce the pressures of "publish or perish" and enhance research quality. Finally, educational campaigns to counter misinformation can alleviate the strain on professionals by ensuring the public receives accurate information. These strategies address current challenges and provide a framework for managing the psychological impact of information overload in future pandemics. It must be remembered that while researchers and health professionals are working or adjusting to the COVID-19 pandemic and the impact afterwards, they are also community members, may have families and have a life outside of their work in that they may be involved in social, sport or religious organizations. Research on coping or resilience strategies related to stress, anxiety, burnout and depression that have been conducted in patients or employees also provides useful coping or alleviation information relevant to professionals. A randomized controlled multicentre trial provided evidence that digital home exercise during lockdowns had beneficial effects on mental health when parameters such as sleep quality, anxiety or mental well-being were assessed.[14] E-mental health solutions were also discussed regarding social media platforms, e-learning content, online resources and mobile applications and the usage of mHealth apps.[15]

Lessons to be Learned

Any global catastrophe, with its disruptive societal changes, necessitates protective and resilience mechanisms to safeguard mental health. Reflections on and consideration of the experiences of health professionals and researchers are crucial. We must reflect on past experiences in terms of research and lockdowns while looking to the future. Medway and Micik aimed to review the experiences of South Australian COVID-19 quarantine medihotel nurses using van Manen's phenomenology of practice method. They identified four themes and two of these related to unity on the frontline and feeling disappointed by organizational systems.[16]

Despite the challenges faced, valuable lessons were learnt, and key takeaways for the future identified. Future studies will explore the long-term effects and outcomes, including a 2024 publication by Reutter and colleagues titled mental health improvement after the COVID-19 pandemic in individuals with psychological distress.[17] In the future, there is also a requirement to objectively measure suicide rates, self-harm, and other mental disorders.[18] During the pandemic, many people turned to religion for comfort and explanation. Bentzen's rough estimate suggests that by April 1, 2020, over half of the world's population had prayed for an end to the coronavirus, indicating a rise in global religiosity.[19] While this isn't the main topic, it's worth noting that there needs to be more research on the effectiveness of religious practices in coping with crises given the dearth of scientific justification for religion. If over 50% of the world's population prayed, as mentioned, securing funding and conducting studies to evaluate the potential beneficial outcomes or harms maybe

warranted to justify religiosity, but also would be highly challenging, incredibly complex and financially unviable due to the sheer number of people involved.

Conclusion

The infodemic during the COVID-19 pandemic has had a lasting impact on the mental health of researchers and health professionals. The overwhelming influx of information and the spread of misinformation created significant challenges for those working in these fields. The most critical takeaway to address these challenges incorporates a multi-faceted approach, including clear communication, mental health support, and promoting collaboration as opposed to competition. As a result of implementing these strategies, we can better support the mental well-being of those who are critical in responding to global health crises in the future. This paper calls for further research to develop and validate coping strategies that can mitigate the mental health consequences of information overload in future public health crisis. It will be interesting to see the results of follow-up studies conducted over the next decade.

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