pISSN: 2220-7562
eISSN: 2617-9482
CODEN: JBUMB7
Recognized by HEC & PMDC

JBUMDC

Journal of Bahria University Medical & Dental College

Volume 14 Issue 4, October - December 2024

Bahria University Health Sciences Campus Karachi
Adjacent PNS SHIFA, DHA Phase II, Karachi

JBUMDC
Journal of Bahria University Medical & Dental College
Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482, CODEN: JBUMB7
Recognized by HEC & PMDC
Online edition is available at URL: https://jbumdc.bahria.edu.pk,
Indexed with Index Medicus for the Eastern Mediterranean Region (IMEMR),
https://vlibrary.emro.who.int/journals/jbumdc-journal-of-bahria-university-medical-and-detal-college/
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Published by: Bahria University Health Sciences, Campus Karachi

JBUMDC

Journal of Bahria University Medical & Dental College

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JBUMDC Journal of Bahria University Medical & Dental College
Volume-14, Issue-4. October - December 2024

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Editorial **Open Access**

Dental Decay Dilemma: Addressing Caries in Pakistan's Population

Mehwash Kashif, Farzeen Tanwir, Aman Ashar

How to cite this Article:
Kashif M, Tanwir F, Ashar A. Dental Decay Dilemma: Addressing Caries in Pakistan's Population. J Bahria Uni Med Dental Coll. 2024;14(4):225-6 DOI: https://doi.org/10.51985/JBUMDC2024359

Maintaining good oral health is essential for general well-being since it affects a person's comfort level when speaking, eating, and interacting with others. It affects systemic health as well as the condition of the teeth, gums, and oral tissues. Maintaining good oral hygiene reduces the risk of systemic illnesses like diabetes and cardiovascular disease in addition to common dental problems like cavities and gum disease.[1]

Moreover, dental health has a substantial impact on one's quality of life, influencing both mental and self-worth. Therefore, prioritizing dental health first is essential to reaching the highest level of wellness and health.[2] Oral diseases are considered serious public health issues, due to their high incidence and prevalence around the world.[3] Among those oral disease, dental caries is still a significant issue for practically every nation on the globe, according to the World Health Organization (WHO).[4] Dental caries is the deterioration of teeth caused by acids formed by bacteria also known as tooth decay.[5] Dental cavities are known to have a negative impact on health. Painful and even debilitating functional limitations can result from untreated carious lesions.[6]

There have only been few publications in the last three years regarding the occurrence of dental caries in Pakistani population. Dental caries is still a common oral health problem in Pakistan, accounting for a large portion of the country's oral disease burden. In a study published in 2021, researcher discovered that dental caries was remarkably common among Pakistani schools, with a sizable percentage of students suffering from untreated caries.[7] The high frequency of dental caries in the nation is caused by a number of factors, including intake of sugary foods and beverages, inadequate access to dental care services, and poor oral hygiene habits. An analysis found that dental caries was estimated to be prevalent at 56.62% nationwide. The estimate for the prevalence of dental caries was 55.45% in Punjab, 58.96% in Sindh, and 51.18% in Baluchistan and KPK united. The estimate of tooth decay prevalence in large cities as in Karachi was 61.98%, in Lahore 57.64%, whereas in Rawalpindi and Islamabad collectively was 57.37%. In primary dentition the prevalence figures was 50.44% and in mixed dentition, it was 61.14% whilst in the permanent dentition the prevalence estimate was 57.15%.[8]

Reaching the best possible oral health depends on controlling dental caries, it is essential to first comprehend the prevalence and advancement of dental caries in order to address this issue at the community level. Unfortunately, accurate data about dental caries occurrence at the national or regional level is still elusive in many developing countries, including Pakistan. To elaborate, it is imperative to recognize that dental caries constitute a substantial threat to public health, negatively affecting people's quality of life and taxing healthcare resources. Without thorough understanding of its incidence and patterns, it becomes difficult to develop focused interventions and allocate resources efficiently.

Maintaining good oral health requires preventing dental caries. Good dental hygiene practices, such as using fluoride mouthwash, flossing often, and brushing teeth twice a day with fluoride toothpaste, are effective techniques.[9] In addition, using fluoridated water, eating a balanced diet high in fruits and vegetables, and minimizing sugary food and drinks intake all help prevent cavities. Early caries detection and treatment depend on routine dental examinations and skilled cleanings. Dental sealants and community water fluoridation are two more effective preventive strategies. In general, the key to preventing caries is a holistic strategy that combines personal oral hygiene habits with community-wide initiatives.[10]

It is imperative to report dental caries, also referred to as cavities or tooth decay, for a number of reasons:

Reporting dental caries allows for early detection of the condition. Early cavity detection allows for prompt intervention, which stops future development and possible consequences.

By reporting dental caries, medical personnel are able to determine who is at risk and take appropriate action. These

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Received: 25-04-2024
Accepted: 21-05-2024
1st Revision 21-05-2024

could include fluoride treatments, diet changes, education about oral hygiene, and dental sealants to stop cavities from forming.

Appropriate treatment plans that are suited to the patient's requirements can be developed with the help of accurate dental caries reporting. Treatment options include dental fillings, root canal treatments, or extraction in extreme situations, depending on the type and degree of the decay.

Dental caries reports are useful for tracking changes in oral health within communities or groups. Planning and implementing preventative programs in public health at the local, regional, and national levels benefit greatly from this data. Information about the prevalence and distribution of dental caries aids in studies intended to identify risk factors, patterns, and causes of the disease. The creation of evidence-based preventative and treatment methods is guided by this information. If dental caries is not treated, it may have an impact not only on oral health but also on the body as a whole. For example, it may result in discomfort, infection, trouble eating, and a lower standard of living.

Dental caries can be reported to lower the chance of related health issues and to enable complete healthcare management.

In order to close this knowledge gap, systematic efforts should be made to carry out surveys and epidemiological studies that document the prevalence and patterns of dental caries among Pakistan's various demographics. Governmental agencies, academic institutions, and dentistry groups working together can make data collection simpler and additionally guarantee that the information is accurate and complete. Furthermore, although on a smaller scale, leveraging the healthcare infrastructure and data sources already in place, such as community health initiatives and medical records, might provide insightful information about the incidence of dental caries. These resources can serve as cornerstones for additional study by providing a foundation for future research, guiding new hypotheses, and offering benchmarks for progress. For policymakers, they offer evidence-based information essential for making informed decisions, designing effective public health strategies, allocating resources efficiently, and developing regulations aimed at reducing the incidence and impact of dental caries, thereby enhancing public health outcomes.

In the meantime, it is imperative to increase public knowledge of the significance of proper oral hygiene, dietary practices, and routine dental examinations. Encouraging people to take preventative actions and seek treatment as soon as possible can help lower the incidence of dental caries and improve oral health in general.

To further reduce the prevalence of dental caries at the local level, it is imperative to extend access to dental care facilities and incorporate oral health into primary healthcare services, especially in underprivileged communities. Pakistan can significantly improve oral health outcomes for its populace and manage dental caries by investing in oral health infrastructure and training healthcare providers to provide basic dental care services.

In a nutshell while there is a dearth of information regarding the prevalence of dental caries, coordinated efforts to gather data, raise public awareness, and develop infrastructure can open the door to efficient dental caries management and eventually help Pakistani communities achieve optimal oral health. To sum up, dental caries must be reported in order to support research, early identification, prevention, treatment planning, trend monitoring, and overall health protection. It is essential for fostering oral health and well-being in both the person and the community.

Authors Contribution:
Mehwash Kashif: Conceptualization and wrote the manuscript
Farzeen Tanwir: Literature search and review
Aman Ashar: Collected the data and wrote the manuscript

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Original Article **Open Access**

Immunohistochemical Expression of ROS1 in invasive ductal carcinoma of breast in association with hormonal receptor status and Her2Neu expression

Muhammad Umair, Ahmed Ahson Khan, Nighat Jamal, Akhter Ali Bajwa, Tabish Hassan, Muhammad Umair Khan

ABSTRACT:

Objective: To determine the frequency of immunohistochemical expression of ROS1 in invasive ductal carcinoma of the breast in relation to hormonal receptor status and HER2 expression.

Study Design and Setting: Descriptive cross-sectional study. Department of Histopathology, Armed Forces Institute of Pathology, Rawalpindi from May 2022 to Dec 2022.

Methodology: This study was conducted on a sample size comprising 137 patients diagnosed with invasive breast carcinoma (ductal carcinoma) on histopathological biopsy specimen. Immunohistochemistry was performed using ROS1, estrogen receptor, progesterone receptor and HER2 antibodies on patients' tissue samples. Results were interpreted by two independent histopathologists. Finally data was analyzed using SPSS version 25.

Results: The mean age of sample population was 50.85 ± 12.17 years. 131 patients were women and 6 were men. ROS1 was positive in 54 cases. ROS1 shows weak staining in 41 cases and moderate to strong staining in 13 cases. ER and PR showed no significant statistical correlation with ROS1 expression. HER2 was positive in 37 cases, equivocal in 11 cases and negative in 89 cases. A significant statistical correlation was seen between ROS1 and HER2 as 23 of HER2 positive cases showed ROS1 expression (p=<0.001).

Conclusion: Significant number of ROS1 expressing cases in invasive breast carcinoma can be more revealing in the understanding of pathogenesis of breast carcinoma. In addition, it can also lead to use of certain recent tyrosine kinase inhibitors for treatment of this most common carcinoma in females.

Keywords: Invasive breast carcinoma, ROS1, Estrogen receptor, Progesterone receptor, HER2.

How to cite this Article:
Umair M, Khan AA, Jamal N, Bajwa AA, Hassan T, Khan MU. Immunohistochemical Expression of ROS1 in invasive ductal carcinoma of breast in association with hormonal receptor status and Her2Neu expression. J Bahria Uni Med Dental Coll. 2024;14(4):227-32 DOI: https://doi.org/10.51985/JBUMDC2024354

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Received: 02-04-2024
Accepted: 21-08-2024 1st Revision 20-08-2024

INTRODUCTION:

In 2022, 2.3 million women were diagnosed with breast carcinoma and resulted in 670,000 deaths globally.[1] It is the most common type of cancer in women.[1] Pakistan is at the top of Asian countries with highest incidence of breast cancer where every one in nine women have a lifetime risk of being diagnosed with breast cancer.[2] Invasive breast carcinoma NST (ductal carcinoma) accounts for the majority of breast cancer cases making up-to 75% of all cases.[3] ROS1 protein, a transmembrane receptor protein with a specific tyrosine kinase activity found out to be acting as a growth, differentiation and proliferation factor coded by ROS1 gene (a proto-oncogene, also known as MCF3) on long arm of chromosome 6 (6q22.1) .[4] ROS1 gene genetic rearrangements have been found in numerous malignant tumors most frequently in non-small cell lung carcinoma (NSCLC), gastric adenocarcinomas, ovarian cancers, cholangio-carcinoma, inflammatory myofibroblastic tumor (IMT), angiosarcoma, colorectal malignancies and epitheloid hemangioendothelioma (EHE).[5] The use of tyrosine kinase inhibitors therapy in treating NSCLC have been studied

vastly in modern medical sciences. Many tyrosine kinase inhibitors such as Crizotinib are showing promising results as an effective therapy in patients with NSCLC, showing alteration in *ROS1* gene.[6]

Research and study of ROS1 gene rearrangements has given valuable and significant insight in the pathogenesis of different malignancies which also includes the breast carcinoma as highlighted in current study.

ROS1 can be tested using multiple technologies for positivity. Of these, fluorescence in situ hybridization (FISH) assays utilizing break-apart probe for the ROS1 gene is the most frequently utilized, gold standard and relied upon test for detection of this specific mutation. Recently, Next Generation Sequencing (NGS) is an emerging and accurate test for ROS1 detection. Reverse transcription polymerase chain reaction (RT-PCR) us another molecular technique for detection. Finally, immunohistochemistry is available which utilizes the detection of ROS1 protein by technique of immunohistochemistry instead of genetic alteration detection for ROS1. ROS1 gene rearrangement results in a detached or split of signal in the bulk of cases, or less frequently in absence of 5' probe signal in translocation of FIG1 to ROS1.[7,8]

Fluorescence in situ hybridization (FISH), next generation sequencing (NGS) and reverse transcriptase polymerase chain reaction (RT-PCR) assays are costly and complex laboratory investigations in most modern laboratories requiring specialized equipment and specific technical personnel expertise. Alternate available investigations such as immunohistochemistry may be performed in laboratories where such advanced molecular processes are not available and where financial and expert manpower resource are limiting factors. Immunohistochemistry has the advantage of rapid evaluation and interpretation by surgical pathologists or histopathologists in diagnostic pathology. As such, a ROS1 antibody (EP282 clone) has been developed which is now increasingly utilized to detect ROS1 mutated proteins in carcinomas most frequently NSCLC.[9,10]

Invasive breast carcinoma shows various pathogenetic progression pathways in its tumor progression. The tyrosine kinase progression pathway has been researched in breast cancers most frequently by Epidermal Growth Factor molecules such as, ErbB or HER2. Various HER2 targeted therapies have been used e.g., Trastuzumab, Margetximab, Pertuzumab and fam-trastuzumab. Of these, Trastuzumab was the first HER2 targeted therapy approved in the 1990's. Various TKIs such as Lapatinib, Neratinib, Pyrotinib and Tucatinib are in trial phase and have shown good results when used as monotherapy and in combination with chemotherapy. [11]

In current study we determined the expression of ROS1 protein by immunohistochemical method, in invasive breast carcinoma and studied its correlation (proportion, intensity and expression scores) with status of hormone receptors (ER and PR) and HER2 (another molecule of EGFR family).[12] Correlation between immunohistochemical markers might have an impact on invasive breast carcinoma, both in view of prognosis and treatment.

METHODOLOGY:

This was a cross-sectional study performed in Department of Histopathology at Armed Forces Institute of Pathology (AFIP) Rawalpindi from May to December 2022 after approval from ethics committee [FC-HSP20-17/READ-IRB/21/1279] of Armed Forces Institute of Pathology. A total of 137 formalin fixed paraffin embedded (FFPE) tissue of cases having invasive breast carcinoma of no special type and its subtypes were included. The World Health Organization (WHO) sample size calculator was used to calculate the sample size keeping a confidence level of 95%, margin of error (d) of 0.8 and anticipated population proportion (P) of 0.333, which was the proportion of patients with invasive breast carcinoma from Hameedi *et al*.[13]

All patients diagnosed with invasive breast carcinoma of breast with any histologic grade whether on incisional or excisional biopsy were included in the study. Patients who have received chemotherapy and/or radiation and had extramammary tumor or metastatic tumor were excluded. All patients' demographic data, tumor characteristics were confirmed at the time of sample receipt. Samples taken only as resection/lumpectomy/mastectomy (excisional) and trucut biopsy specimen (incisional) were examined. All cases were initially stained with hematoxylin and eosin stain for confirmation of diagnosis and tumor characteristics by two histopathologists independently. All confirmed cases included in study were then immunostained for ROS1, ER, PR and HER2 using Leica Bond III fully automated IHC staining system. ROS1, EP282, ER 6F11, PR 16 and HER2 antibody clones were used as per manufacturer's instructions. Cytoplasmic, membranous and nuclear staining were assessed for ROS1, HER2 and hormone receptors (estrogen and progesterone receptors), respectively. Allred scoring system was utilized for analysis of immunostained slides for expression of ER and PR by assessing proportion and staining intensity of tumor cells and calculating into scores for final result. HER2 expression was analyzed as per CAP/ASCO guidelines.[14] Immunohistochemical expression of ROS1 was assessed as a percentage of cells stained (proportion) and intensity of staining (cytoplasmic staining) as displayed in Table-I. Cases with >1% cytoplasmic staining with weak, moderate to strong intensity were considered positive while absence of staining or staining in <1% of tumor cells were considered as negative.

IBM Statistical Package for the Social Sciences version 25 is used for analysis of research data. Mean and standard deviation were calculated for quantitative variables. Percentage and frequency were used for qualitative variables

like gender, grade, immunoexpression of ER, PR, HER2 and ROS1 in invasive breast carcinoma. Qualitative variables were compared using the Chi square test and a *p*-value of =0.05 was considered statistically significant.

RESULTS:

This study was conducted on a sample size comprising blocks from 137 patients histologically diagnosed with invasive breast carcinoma (ductal). The mean age of the population was 50.85 ± 12.17 years. 131 (95.6%) patients were women and 6 (4.4%) were men. A total of 20 (14.60%) patients had tumor grade I lesions, while 73 (53.28%) and 44 (32.17%) had grade II and III lesions, respectively. For immunohistochemical expression of estrogen receptors 78 out of 137 cases (56.93%) were positive. Of these ER positive cases, 12/78 (15.38%) were of total Allred core of 8/8, 26/78 (33.33%) were of total Allred score of 7/8, 18/78 (23.08%) were Allred score 5/8, 13/78 (16.67%) were Allred score of 4/8 and 9/78 (11.54%) were of total score of 3/8. For immunohistochemical expression of PR 76 (55.47%) of total 137 cases were positive. Of them 14/76 (18.42%) were of total Allred core of 8/8, 22/76 (28.95%) were of total Allred score of 7/8, 8/76 (10.53%) were Allred score 5/8, 23/76 (30.26%) were Allred score of 4/8 and 9/76 (11.84%) were of score 3/8. 37 (27.01%) of the total 137 cases were positive for HER2 expression, 11 (8.03%) were equivocal and 89 (64.96%) were negative. 54 (39.42%) of all cases showed ROS1 expression (figure 1). Of them, 41/54 (75.92%) cases showed proportion score 1 while 13/54 (24.07%) were of score 2-3. In this study, ROS1 expression evaluated by total stained cell proportion and immunostaining intensity did not show significant statistical correlation with status of ER and PR (evaluated by total stained cell proportion and immunostaining intensity and overall expression calculated by Allred score) as *p* values were greater than 0.05, these cases. This statistical insignificant correlation is explained in Table 2 and 3.

Table I: Immunohistochemical expression of ROS1

Proportion		Intensity		ROS1 Expression
Cells stained	Score	Staining Intensity	Score	
0 %	0	No staining	0	Negative
1-25 %	1	Weak	1	Positive
26-100 %	2	Moderate to strong	2 or 3	

Figure 1: Invasive breast carcinoma, poorly differentiated (A) with immunohistochemical expression of ROS1 (B)

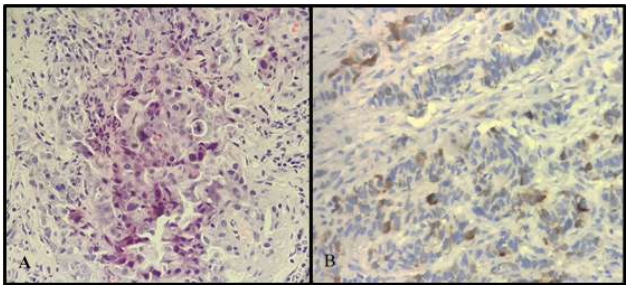

Table 2: Association between immunohistochemical expression of ROS1 expression, ER expression and PR expression (N=137).

Estrogen receptor expression association					
		ER Expression		Total n (%)	p-value
		Negative n (%)	Positive n (%)		
ROS1 Expression	Negative	30 (21.90%)	53 (38.69%)	83 (60.58%)	0.065
	Positive	29 (21.17%)	25 (18.25%)	54 (39.42%)	
Total		59 (43.07%)	78 (56.93%)	137 (100%)	
Progesterone receptor expression association					
		PR Expression		Total n (%)	p-value
		Negative n (%)	Positive n (%)		
ROS1 Expression	Negative	31 (22.63%)	52 (37.96%)	83 (60.58%)	0.064
	Positive	30 (21.90%)	24 (17.52%)	54 (39.42%)	
Total		61 (44.52%)	76 (55.47%)	137 (100%)	

The association between ROS1 expression and HER2 expression was noted to be statistically significant as p-value is <0.05 which is highlighted in Table 4. 23 (42.59%) out of 37 positively expressed cases for HER2 also expressed positive result for ROS1, while 7 (63.64%) equivocal out of 11 and 24 (26.97%) negative out of 89 cases expressed ROS1 immunohistochemically.

DISCUSSION

In this modern age of targeted therapy for carcinomas there is a need to look for most precise and specific therapies for effective treatment in these lethal conditions. ROS1, a receptor tyrosine kinase is usually associated with non-small cell lung carcinoma and in a large variety of other tumors.[15] Anti ROS1 drugs such as entrectinib, crizotinib and repotrectinib have been developed and used to target ROS1 gene translocation pathway in NSCLC.[16]

The important role of ROS1 targeted therapy in NSCLC inspired to study its role in many other human cancers such as spitzoid neoplasms, thyroid cancer, colorectal adenocarcinoma, glioblastoma multiforme, inflammatory myofibroblastic tumor, vascular tumors, angiosarcoma, atypical meningioma and other tumors.[17]

ROS1 mutation was first characterized by FISH assay and Tissue Microarray assays (TMA) both of which are expensive and technical procedures requiring specialized equipment and technical expertise. Recently antibodies against mutated ROS1 protein assessed by immunohistochemistry proved to be valuable, in NSCLC.[18]

Molecular classification of breast cancer based on expression or loss of hormonal receptor expression (ER & PR) and EGFR most commonly HER2 expression is one of the most significant aspects of decision making in treatment of invasive breast carcinoma. Immunohistochemical evaluation of ER, PR and HER2 in invasive breast cancer represent a critical

part in molecular classification and is a critical factor to be correlated with other tumor facets.[19, 20] In this research, we compared the immunohistochemical occurrence of ER, PR and HER2 (molecular classification markers) with immunohistochemical expression of ROS1 in invasive breast carcinoma (ductal). By this assessment the prognostic and predictive value of ROS1 in invasive breast carcinoma can be found.

In our research, statistically significant correlation was not found between immunoexpression of ROS1 and hormonal receptor status of estrogen receptor and progesterone receptor. Hormone receptor status was assessed by Allred scoring system as recommended by international guidelines. As per Allred score neither proportion score nor staining intensity correlated significantly with ROS1 histochemical expression (comprising tumor cells-stained proportion score and staining intensity score).

Eom M, *et al* in his study of occurrence of ROS1 protein expression in invasive breast carcinoma with histologic grade, ER status and HER2 status. In their study, ROS1 was expressed in 70% of ER positive cases and 30% of ER negative cases, thus ROS1 expression was significantly enhanced in ER positive cases. In their study ER expression and staining intensity were not correlated with ROS1 expression. ROS1 was positive in 70.9% HER2 negative and 29.1% of HER2 positive cases, which was not statistically significant.[21] In our study, 25 out of 54 positive ROS1 cases (46.30%) were also positive for ER, while 29 out of 54 (53.70 %) were negative for ER, while for PR expression 24 out of 54 ROS1 positive cases (44.44%) were positive for PR and 30 out of 54 (55.56%) were negative.

In our study, ROS1 was expressed in 23 of 37 (62.16%) HER2 positive cases while it was negative in 14 of 37 (37.84%) HER2 positive cases. Hence, ROS1 immunohistochemical expression was significantly correlated with HER2 expression (*p* value of <0.001).

In a somewhat similar study conducted by Hameedi *et al* immunohistochemical expression of ROS1 was correlated with ER, PR and HER2 expression. It was found that a statistically significant correlation was found among ROS1 expression and HER2 expression as 70 % of ROS1 expressive cases were also positive for HER2, while no significant correlation was found with ER and PR expression.[13]

Raut A *et al* concluded that ROS1 immunohistochemistry is not a true diagnostic and predictive screening test in breast carcinoma as none of the 631 patients with breast carcinomas demonstrated positive immunohistochemical staining for ROS1. However, it was significantly expressed in our study population. [22]

Li K *et al* studied genetic mutation profile of Chinese HER2

Table 3: Association between ROS1 proportion score, Estrogen receptor proportion score and Progesterone receptor proportion score (N=137)

Estrogen receptor proportion score association						
		ER Proportion Score			Total n (%)	p-value
		Negative n (%)	Score 1 to 3 n (%)	Score 4 to 5 n (%)		
ROS1 Proportion Score	Score 0	23 (16.79%)	31 (22.63%)	29 (21.17%)	83 (60.58%)	0.133
	Score 1	15 (10.95%)	18 (13.14%)	8 (5.84%)	41(29.93%)	
	Score 2-3	10 (7.30%)	1 (0.73%)	2 (1.46%)	13 (9.49%)	
Total		48 (35.04%)	50 (36.50%)	39 (28.47%)	137 (100%)	
Progesterone receptor proportion score association						
		PR Proportion Score			Total n (%)	p-value
		Negative n (%)	Score 1 to 3 n (%)	Score 4 to 5 n (%)		
ROS1 Proportion Score	Score 0	26 (18.98%)	30 (21.90%)	27 (19.71%)	83 (60.58%)	0.145
	Score 1	17 (12.41%)	19 (13.87%)	5 (3.65%)	41 (29.93%)	
	Score 2-3	10 (7.30%)	1 (0.73%)	2 (1.46%)	13 (9.49%)	
Total		53 (38.69%)	50 (36.50%)	34 (24.82%)	137 (100%)	

Table 4: Association between ROS1 expression and HER2 expression (N=137)

		HER2 Expression			Total n (%)	*p*-value
		Negative n (%)	Equivocal n (%)	Positive n (%)		
ROS1 Expression	Negative	65 (47.44%)	4 (2.92%)	14 (10.22%)	83 (60.58%)	<0.001
	Positive	24 (17.52%)	7 (5.11%)	23 (16.79%)	54 (39.42%)	
		89 (64.96%)	11 (8.03%)	37 (27.01%)	137 (100)	

positive patients in order to evaluate response of anti HER2 responses. In their study ROS1 mutation by NGS was found in 5 patients out of 40 belonging to HER2 positive group with a *p* value of 0.049.[23]

Eggmann H *et al* in his research established that HER2 overexpression is a poor prognostic indicator in breast cancer.[24] Hence, based on our study results of significant relation between HER2 and ROS1 expression, we can indicate that ROS1 immunohistochemical expression could represent a factor of poor prognosis in addition to HER2. Also supportive of this statement is the result of Force J *et al* establishing that ROS1 alterations were strongly associated with metastatic disease of the breast to CNS and lymphoid organs.[25]

Based on discoveries there is a need to study ROS1 expression in breast carcinoma in relation to prognostic significance and to follow up the patients for a significant period. Also ROS1 expression could be adopted for targeted therapy in invasive breast carcinoma by inducing growth inhibition and cell growth as highlighted by O'Neil SR. et al. [26] ROS1 immunohistochemical expressions need to be studied more in invasive breast carcinoma especially if there is an increased consideration of use of targeted therapy for TKIs in cases of breast carcinoma showing alteration of ROS1.

CONCLUSION

The study finding of significant number of ROS1 expressing cases in HER2 positive invasive breast carcinoma can be more revealing in the understanding of pathogenesis of breast carcinoma. In addition, it can also lead to use of certain recent tyrosine kinase inhibitors for treatment of this most common carcinoma in females.

Authors Contribution:
Muhammad Umair: Data collection, analysis, abstract writing and references
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Original Article **Open Access**

Long Term Outcomes of Pain, Disability and Quality of Life in Open vs Minimally Invasive Surgery of Transforaminal Lumbar Interbody Fusion

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ABSTRACT

Objective: This study aims to evaluate the short- and long-term outcomes—specifically in terms of pain, disability, and quality of life—between minimally invasive surgery (MIS) and open transforaminal lumbar interbody fusion (TLIF) for treating lumbar spondylolisthesis.

Study Design and Setting: A prospective cohort study was carried out at Liaquat National Hospital & Medical College, Karachi, and a teaching institution in South Asia. The study included patients with chronic back pain for over three months, unresponsive to medical treatment or accompanied by radicular symptoms, with MRI-confirmed grade I and II degenerative lumbar spondylolisthesis, lateral recess stenosis, and unilateral disc herniation. Patients with spinal metastasis, previous surgeries, inflammatory arthritis, or metabolic bone diseases were excluded.

Methodology: The outcomes of MIS-TLIF and open-TLIF were assessed using the Visual Analog Scale (VAS), Oswestry Disability Index (ODI), and SF-36 quality of life scores at 1, 6, and 24 months postoperatively.

Results: Among 93 patients, 35 underwent open-TLIF and 58 received MIS-TLIF. MIS-TLIF resulted in significantly less blood loss and faster recovery. At four weeks, the MIS group had lower VAS and ODI scores, and higher SF-36 scores. Similar trends continued at six months, with improvements in ODI and SF-36. By 24 months, the MIS group maintained lower ODI scores, though VAS and SF-36 scores were comparable.

Conclusion: MIS-TLIF shows superior outcomes, especially in the early postoperative phase, with reduced morbidity and improved quality of life, making it a preferable option in resource-limited settings.

Keywords: MISTLIF; Open-TLIF; Transforaminal lumbar interbody fusion; short and long-term outcomes.

How to cite this Article:
Khan AU, Afsar A, Sharif S, Ali FA. MIS TLIF vs. Open TLIF- Long Term Outcomes of Pain, Disability and Quality of Life: A South-Asian Perspective. J Bahria Uni Med Dental Coll. 2024;14(4):233-9 DOI: https://doi.org/10.51985/JBUMDC2024365

INTRODUCTION:

Lumbar interbody fusion can address multiple spinal pathologies, including the degenerative spine, trauma, tumors, and infections[1]. Lumbar interbody fusion techniques tend to improve back pain, fusion rate and help maintain vertebral alignment. Also it can be performed via minimally invasive approach[2].

Open transforaminal interbody fusion was first described by Harms and Rollinger in 1982. Circumferential fusion by posterolateral approach may result in a good outcome[3], but excessive retraction, muscle dissection, prolonged hospital stay, and high treatment cost were the downsides of open TLIF[4, 5, 6]. Therefore, minimally invasive technique (MIS) was introduced by Foley to decrease tissue trauma using a smaller wound leading to quicker recovery[7]. Extensive soft tissue dissection is essential to expose the anatomic landmarks for pedicle screw insertion, to identify a proper screw trajectory, and to resect the facet complex. The degree of iatrogenic muscle and soft tissue injury that occurs during the surgical approach can result in increased postoperative pain, lengthened recovery time, and impaired spinal function.

Recently, MIS techniques have been introduced and preferred over open TLIF. The advantages of MIS TLIF include, small wounds, reduced muscular dissection, early post op recovery and minimal hospital stay.

Outcomes of MIS, when compared with open TLIF assessed at 6 months and 2 years also showed the superiority of MIS in terms of reduced length of hospitalization and cost, although the effectiveness for other outcomes was equivocal[8].

In a developing country like ours, it is important to evaluate the impact of a surgical procedure on the short and long-

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Received: 06-05-2024
Accepted: 23-07-2024 1st Revision 17-06-2024

term outcome of a disease, which is an indirect measure of its cost-effectiveness. Long-term usage of narcotics and delayed return to work translates to a loss of early functionality and productivity. Persistent or recurrent back pain increases morbidity leading to poor quality of life. This intends to delineate the comparison of immediate, short, and long-term outcomes of pain and quality of life through three different tools. The scales utilized are Visual analogue scale (VAS) for the evaluation of pain. Oswestry disability index (ODI) for assessing the disability in functionality due to back pain and 36 item Short Form health survey (SF-36) as a general measure of the patient's overall health. Quality of life was also assessed via a QOL score investigating the three parameters, pain, activity limitation, and depression. We also analysed the preoperative metabolic parameters in the two groups including Vitamin D3, Vitamin B12 and Uric acid. These parameter have shown to have effects on the degeneration of spine.

To the best of our knowledge, this is the only prospective study in the English language from the South Asian region, comparing outcomes (pain, disability, and quality of life) of open versus MIS -TLIF, with a 2-year follow-up. A similar prospective study from India evaluating the outcomes of the two procedures was performed half a decade back with 6 months follow-up[9].We also compared the complications and adverse effects, duration of analgesia, duration of surgery, blood loss, hospital stay, and need for re-do surgery as other variables.

METHODOLOGY

This was a prospective cohort study in which all patients were followed for a post-operative period of 2 years. An institutional review board approved the study. Written informed consent was taken from participants (20-75 years) who were advised open TLIF or MIS for the following indications:

Patients with intractable chronic backache unresponsive to medical management or backache with radicular symptoms for more than 3 months, with Magnetic Resonance Imaging (MRI) showing grade I and II degenerative lumbar spondylolisthesis, lateral recess stenosis, and unilateral postero-lateral disc.

Patients were excluded if they had metastasis, pre-existing spinal pathology, redo surgery, patients with inflammatory arthritis, or metabolic bone disease.

Patients were reviewed for eligibility by the principal investigator. Socio-demographics were determined through a questionnaire. Neurosurgical trainees filled up the Visual Analogue Scale (VAS) to assess for pain, ODI to assess for disability, and SF-36 to determine the quality of life for all participants at baseline and on their follow-up visit 1, 6, and 24 months.

Quality of Life (QOL) was also assessed in these patients separately. Its questionnaire (QOL)had three categories (mild, moderate, and severe) to estimate pain, depression, and activity limitation. For analysis of variables, scores of mild, moderate, and severe symptoms of pain, depression, and activity limitation were scored as 1 point for mild symptoms, 2 for moderate, and 3 points for severe symptoms. The average was then compared among TLIF and MIS groups at baseline,1,6, and 24 months.

Both the procedures were performed by a single surgeon for standardization. Postoperatively, all the patients were encouraged discharge from the hospital the next day. Postoperative analgesics were tapered according to the patient's symptoms after both surgical procedures. Both groups were encouraged to return to work once given fitness.

Surgical Technique MIS-TLIF

The procedure was performed on the most symptomatic side and with obvious pathology. Pedicles were marked with fluoroscopy, and small incisions are given 3-4 cm from the midline on each pedicle. Jamshidi needle is passed into the pedicle under the c arm, and K wire is passed through the Jamshidi needle into the pedicle and vertebral body, which is confirmed with the C arm. Bone tap is done and followed by the passing of cannulated screws over the guidewire. The guidewire is removed after the passing of screws. Rod is applied on the non-pathological side, and distraction is done to open the disc space.

An incision is given on the symptomatic side 3 to 4 cm from the midline using an Image intensifier, subcutaneous tissue dissected, dorsolumbar fascia opened, and sequential dilators inserted down the facet joint until the desired diameter is obtained.

Facetectomy is done using a high-speed drill and chisel, and bone is saved for grafting, ligamentum flavum excised. Kambin's triangle was identified, discectomy performed, disc space prepared with different instruments. An appropriate size cage is placed in disc space, keeping in mind the contralateral indirect decompression. In cases where a contralateral decompression of traversing or exiting nerve root is required, extensive decompression was done through the same side by drilling through the base of the spinous process and opposite lamina. The rod is then applied percutaneously to connect the screws. Compression is done before ?nal tightening to compress disc space and maintain lumbar lordosis.

Open-TLIF

The incision is marked in the prone position, with C arm over the appropriate level using the midline. Incision is given, fascia is incised, and subperiosteal dissection is done. Entry points for the screws are exposed and confirmed with the help of fluoroscopy. Screws are passed on the non-pathological side, rod connected with screws, and distraction is done. The lower third of the lamina and facet joint taken

on the pathological side, and ligamentum flavum was excised. Traversing and exiting roots identified in Kambin's triangle, after discectomy and disc preparation, appropriate size cage is placed, screws are inserted and connected with the rod, and compression done.

Data were entered and analyzed on SPSS Version 21. Means and SD for quantitative variables like age, duration of pain, duration of surgery, and metabolic parameters were reported and compared between the two groups by unpaired t-test. Mann Whitney U test was applied if data was not normally distributed. Percentages and proportions were calculated for categorical variables like co-morbid diseases and compared between groups by Chi-square. To compare VAS, ODI, SF-36, and Qol scores between the two groups at baseline, 1, 6, and 24 months unpaired t-test or Mann Whitney U test was applied. A paired t-test or Wilcoxin signed-rank test (for data not normally distributed) was used to compare the scores within groups. Comparison of scores at baseline, 1, 6, and 24 months was done between and within-group through ANOVA statistics. P <0.05 was considered statistically significant, and 95% Confidence intervals (CI) were reported.

RESULTS:

A total of 58 patients underwent single level MIS, while 35 patients were operated on through open TLIF. table 1 shows the comparison of the baseline characteristics of participants. There were no differences in gender, presenting symptoms, duration of pain, duration of surgery, co-morbids, and metabolic parameters in both groups. Age was significantly lower in MIS than open TLIF group (p 0.004).

Table 2 shows postoperative parameters and complications in both groups. Blood loss was almost four times more in the open TLIF group (p <0.001). Return to work was delayed by 3 days in the open TLIF group compared to the MIS (p<0.001). The probability of mobility on the same postoperative day was significantly higher in the MIS group (p<0.001). The rate of postoperative complications and infections was more in the open TLIF but the difference was not significant compared to the MIS group (p 0.058 and 0.08, respectively).

Table 3 and figure 1 show a comparison of MIS with open TLIF. VAS, ODI, SF-36, and Qol scores at baseline, 1, 6, and 24 months. There was no significant difference between the baseline scores of MIS and TLIF groups. At 1 month, the VAS and ODI scores were significantly lower in the MIS group, whereas the SF-36 score was significantly higher (p < 0.001). At 6 months, ODI was significantly lower (p <0.001), whereas SF-36 was higher in the MIS group (p0.002). There was no difference in VAS between the two groups at 6 months. At 24 months, the ODI was significantly lower in the MIS group (0.007), whereas the VAS and SF-36 were not different at 24 months between the two groups. VAS, ODI, and SF-36 scores of both the groups were significantly different at baseline, 1, 6, and 24 months. It shows that the QoL score for pain and depression was significantly higher at baseline in the TLIF group than MIS. However, postoperatively, the pain, depression, and activity limitation scores were significantly more among TLIF than the MIS group at week 4, 6 months, and 2 years.

Table 4 and figure 1 show a comparison of VAS, ODI, and SF-36 scores at baseline, 1, 6, and 24 months among patients undergoing MIS TLIF with open TLIF. In the MIS TLIF group, the VAS was significantly lower at 1,6 and 24 months (p <0.001), however it remained static at 6 and 24 months. The ODI was significantly lower at 1,6 and 24 months from baseline (p <0.001). The SF-36 score was significantly higher at 1, 6, and 24 months from baseline (p <0.001). hence, this brings us to the conclusion, that among MIS, the scores were significantly low at 1,6 and 24 months for pain, depression, and activity limitation compared to baseline.

The VAS and ODI was significantly lower within the open TLIF group at 1, 6 and 24 months (p <0.001). The SF-36 score was significantly higher at 6 and 24 months from baseline (p <0.001).

Figure 1a Comparison of VAS at baseline, 4 weeks, 6 months, and 2 years among patients who underwent minimally invasive surgery (MIS) and open Transforaminal Lumbar Interbody Fusion (TLIF)

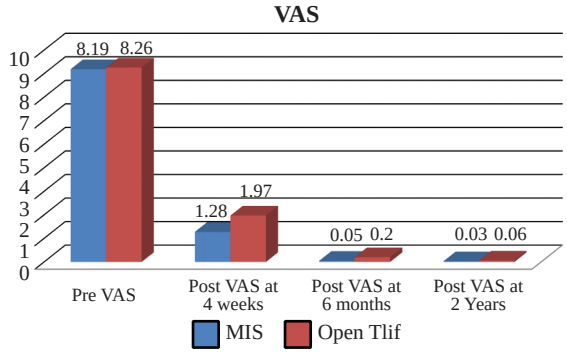

Figure 1b Comparison of ODI at baseline, 4 weeks, 6 months, and 2 years among patients who underwent minimally invasive surgery (MIS) and open Transforaminal Lumbar Interbody Fusion (TLIF)

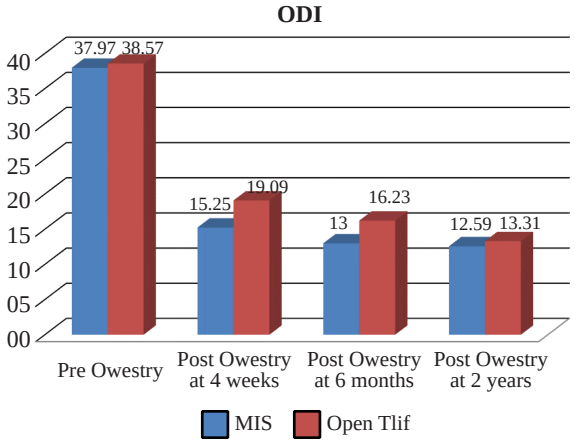

Figure 1c Comparison of SF-36 at baseline, 4 weeks, 6 months, and 2 years among patients who underwent minimally invasive surgery (MIS) and open Transforaminal Lumbar Interbody Fusion (TLIF)

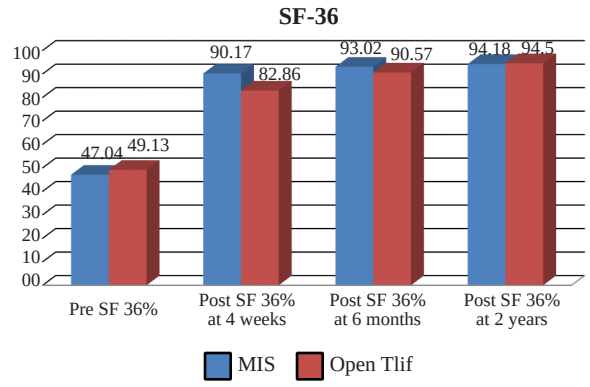

Table 2: Comparison of postoperative parameters of patients undergoing Minimally Invasive surgery (MIS) and open Transforaminal Lumbar Interbody Fusion (TLIF)

	MIS n= 58	Open TLIF n=35	p-value
Blood loss in ml	86.34±18.47	315.71±54.7	<0.001***
Return to work	4.00±0.00	7.06±2.36	<0.001***
Mobilization Day			
Next Morning	17(29.3)	27(77.1)	<0.001***
Same Day	40(69)	0(0)	
Next Day	1(1.7)	4(11.4)	
Complications			
Yes	4(6.9)	7(20)	0.058
No	54(93.1)	28(80)	
Infections			
Yes	1(1.7)	5(14.3)	0.080
No	57(98.3)	30(85.7)	

(VAS, ODI, SF-36 at baseline, 4 weeks, 6 months, and 2 years)

DISCUSSION:

Conventional lumbar fusion is generally associated with extensive soft tissue dissection and increased morbidity.[4,5,10,11] Inter and supraspinous ligaments along with paraspinal muscles on the opposite sides are preserved in MIS-TLIF. Hence, the posterior natural tension band remains intact. Ipsilateral paraspinous muscle injury is limited in the muscle splitting tubular retractor system used in MIS-TLIF, contributing to decreased postoperative pain and facilitating earlier mobilization**.** This approach preserves the contralateral facet instead of the open-TLIF approach in which facet joint may be taken. The ipsilateral facetectomy helps complete intervertebral disc space exposure far laterally, and minimal retraction is applied on thecal sac or nerve roots while placing the interbody graft. Intraoperative retraction contributes to postoperative pain and dysesthesia. In MIS-TLIF, retractors are merely placed to protect the neural structures during the graft placement. Soft tissues at adjacent levels are minimally affected by percutaneous pedicle screw fixation.

Table 1: Baseline characteristics of patients undergoing Minimally Invasive surgery (MIS) and open Transforaminal Lumbar Interbody Fusion (TLIF)

	MIS n= 58	Open Tlif n=35	p-value
Age	45.49±16.31	54.61±12.32	0.004**
Pain duration in months	36.44±41.90	30.53±51.34	0.565
Duration of surgery in hours	2.99±0.91	3.21±0.56	0.165
Gender			
Male	17(29.3)	16(45.7)	0.109
Female	41(70.7)	19(54.3)	
Presenting complains		0.31	
BP/LP	56(96.5)	32(91.4)	
BP	1(1.7)	0(0)	
Numbness in leg	1(1.7)	0(0)	
Metabolic parameters			
Uric acid level	5.06±1.78	5.02±1.34	0.909
Vitamin B 12 level	461.3±330.7	486.2±539.3	0.806
Vitamin D level	25.34±15.04	25.95±13.08	0.839

Table 3: Comparison of Minimally Invasive Surgery (MIS) with open Transforaminal Lumbar Interbody Fusion (TLIF) (VAS, ODI, SF-36 at baseline, 4 weeks, 6 months, and 2 years)

	MIS	Open TLIF	P-value[1]	P-value[2]
VAS				
Baseline	8.19±1.27	8.26±1.19	0.801	<0.001***
4 weeks	1.28±0.48	1.97±0.74	<0.001***	
6 months	0.05±0.22	0.20±0.47	0.089	
24 months	0.03±0.18	0.06±0.23	0.606	
ODI				
Baseline	37.97±4.77	38.57±3.78	0.524	<0.001***
4 weeks	15.25±1.66	19.09±1.86	<0.001***	
6 months	13.00±0.97	16.23±1.92	<0.001***	
24 months	12.59±0.77	13.31±1.38	0.007**	
SF-36				
Baseline	47.04±6.39	49.13±4.10	0.058	<0.001***
4 weeks	90.17±5.98	82.86±3.47	<0.001***	
6 months	93.02±3.46	90.57±3.85	0.002**	
24 months	94.18±2.78	94.50±2.74	0.590	

1 Independent t-test is applied to obtain a p-value between MIS and TLIF groups
2 ANOVA applied to calculate p-value between more than two unpaired groups

*Significant at p 0.05 -0.01
** Significant at p 0.01-0.001
*** Significant at p<0.001

We prospectively compared MIS TLIF with open TLIF for 2 years and also observed the quality of life in these patients. It was seen, there was a significant decrease in VAS at 1 month post-operatively, which was maintained at 6 and 24 months. VAS is a subjective analysis, so immediate post-operative pain improvement is to be expected. SF-36, a general health questionnaire, revealed improvement at 1 and 6 months, but it showed no difference at 24 months.

Table 4: Comparison of VAS, ODI, SF-36 scores at baseline, 4 weeks, 6 months, and 2 years among patients undergoing Minimally Invasive surgery (MIS) with open Transforaminal Lumbar Interbody Fusion (TLIF)

	Baseline	4 weeks	6 months	24 months	P value[1]	Baseline	4 weeks	6 months	24 months	P value
Baseline	-	<0.001***	<0.001***	<0.001***	<0.001***	-	<0.001***	<0.001***	<0.001***	<0.001***
4 weeks	<0.001***	-	<0.001***	<0.001***		0.001***	-	0.001***	0.001***	
6 months	<0.001***	<0.001***	-	0.322		<0.001***	<0.001***	-	0.058	
24 months	<0.001***	<0.001***	0.322	-		<0.001***	<0.001***	0.058	-	
ODI										
Baseline	-	<0.001***	<0.001***	<0.001***	<0.001***	-	<0.001***	<0.001***	<0.001***	<0.001***
4 weeks	<0.001***	-	<0.001***	<0.001***		<0.001***	-	<0.001***	<0.001***	
6 months	<0.001***	<0.001***	-	<0.001***		<0.001***	<0.001***	-	<0.001***	
24 months	<0.001***	<0.001***	<0.001***	-		<0.001***	<0.001***	<0.001***	-	
SF-36										
Baseline	-	<0.001***	<0.001***	<0.001***	<0.001***	-	<0.001***	<0.001***	<0.001***	<0.001***
4 weeks	<0.001***	-	<0.001***	<0.001***		<0.001***	-	<0.001***	<0.001***	
6 months	<0.001***	<0.001***	-	0.002**		<0.001***	<0.001***	-	<0.001***	
24 months	<0.001***	<0.001***	0.002**	-		<0.001***	<0.001***	<0.001***	-	

Paired t-test is applied to obtain a p-value within each paired group
[1] ANOVA applied to calculate p-value between more than two paired groups
*Significant at p 0.05 -0.01
** Significant at p 0.01-0.001
*** Significant at p<0.001

Similarly, ODI was less with the MIS group at 1 and 6 months, and it continued to show improvement at 24 months. ODI Disability Index, compared to SF 36, is more specific for better functionality. The Quality of life (QOL) scores were also lower postoperatively in the MIS TLIF group when compared with open. It was seen that baseline scores in both groups were significantly different, with higher scores in open TLIF and lower scores in the MIS group. However, like all other parameters assessed in this study, QOL scores also converged at the 2-year follow-up.

Both cohorts showed improvement in the pain score at 2 years (VAS) and disability (ODI), consistent with earlier studies[12]. Advantages of the MIS technique are evident in the early recovery phase, as is shown by a meta-analysis that reviewed 12 studies from 2009-2017.These 6 studies showed an improvement in VAS-B (Visual Analogue Scale-Back) with MIS-TLIF at 6 months follow-up. They reflected no difference in outcome at 2 years except for the study by Wong, which showed no difference in outcome at 24 and 36 months postoperatively, but at 4 years, the ODI and VAS-B showed improvement compared with baseline open-TLIF.[12]

The surgery duration while comparing open versus minimally invasive approaches depends upon the surgeon's learning curve. Initially, MIS might be associated with increased operative time. Interestingly, the duration of surgery was less in our study, which may be due to our surgeons reaching their learning curve prior to this study. Kulkarni et al.[13] conducted a prospective study examining 61 patients and showed a longer operative time for MISTLIF, which was secondary to the learning curve. Hey and Peng also showed a longer operative time for MISTLIF, which was explained by the technically demanding MISTLIF due to the limited visibility of the surgical field.[14] Once the learning curve of 15 cases is achieved, it results in a significant decrease in the operative time (1.8 to 3.2 hours).[15]

The preoperative mental health of the patient undergoing spine surgery also plays an important role in his outcome. SF-36 is a commonly used instrument to ensure generic health-related quality of life. A systematic review noted that one of the most frequently investigated predictor variables was depression (5 times), followed by the SF-36 (3 times).[16]

Return to work was earlier in the MIS group, suggesting occupational benefits. The postoperative narcotic use for MIS-TLIF patients was only half, despite similar preoperative pain and disability scores. Economic and social productivity is markedly associated with earlier return to work in the MIS-TLIF group. However, both groups had similar long-term improvement.[17, 18, 19]

Also, while assessing the quality of life in such patients, the parameters analyzed in our manuscript include pain, depression, and limitation of activity. On various occasions, it has been documented that minimally invasive procedures do shorten the length of stay by an average of 1 or 2 days and thus results in early ambulation when compared with its open counterparts.[20]

Smaller incisions decreased muscle retraction, and early mobilization are the major advantages of MIS TLIF. It leads to early discharge and hence is cost-effective. It has a lesser risk of reoperation and infections. Wong found a significantly lower rate of infections with MISTLIF, attributed to patients' overall earlier mobilization and ambulation.[21]

MIS TLIF is associated with significant improvement in the

overall mental health of patients with psychological distress, especially in the early post operative phase. Despite poorer patient-related outcome measures preoperatively, patients with depressed mood or increased stress levels undergoing MIS-TLIF still achieved comparable outcomes from 3 months onward. A greater proportion of these patients experienced a clinically meaningful improvement in pain, function, function, and quality of life.[22]

Another significant observation in the MIS TLIF group was decreased intraoperative blood loss. Mobilization on the same day encourages early discharge from the hospital, resulting in decreased exposure to nosocomial pathogens, ultimately minimizing hospital costs and medical resources. We observed that only one patient in the MIS group and five patients in the open-TLIF developed an infection. It is speculated that the major contributing factors to these complications are the longer duration of surgery, late mobilization, increased blood loss, excessive dissection, and delayed discharge of the patient. The reoperation rate of open compared to MIS-TLIF is higher and is reported to be approximately 20% compared to 8%.

Both MIS-TLIF and open-TLIF were associated with marked improvements in long-term pain, disability, and function. Only one other prospective cohort study has compared 2-year outcomes between MIS-TLIF and open-TLIF.[6] As compared to our observation, Peng[6] reported VAS (2.2 vs. 2.0) and ODI (18.2 vs. 19.7) scores at both 6 months and 2 years (VAS: 1.0 vs. 1.2; ODI: 16.2 vs. 17.5) after MIS-TLIF versus open- TLIF. Wong et al. [21] showed better ODI, VAS-B, and VAS-L outcomes with MIS-TLIF at 6 months postoperatively. Those clinical outcomes were not different at 24 and 36 months postoperatively, but ODI and VAS-B were better with MIS-TLIF than with open-TLIF at 4 years postoperatively.[21] Therefore, it is inferred that mental health improvement in distressed patients post MIS TLIF could be due to improved pain and functional mobility. In contrast, poorer preoperative mental status could be due to chronic low back pain, limited functionality and spinal instability.

We also evaluated certain metabolic parameters between the two groups, Vitamin D3 levels, Vitamin B12 and uric acid, which have a proven role in degenerative spine. However, our results did not show any significant difference between the two groups. It has been observed, that Vitamin D3 has a protective role in disc degeneration because of its effect on inhibition on NF-KB signaling pathway which is a major contributor in the activation of inflammatory pathways.[23] Also, of note is the role of hyperuricemina, it is observed that it plays a significant role in accentuating the narrowing of disc spaces in lumbosacral spine and degenerative spondylolisthesis resulting in chronic low back pain.[24] These are the reasons, that our patients were worked up in this domain and their deficiencies were corrected prior to procedure.

The results of our study suggest that both techniques are equally useful for long-term pain relief, thus reducing disability and improving quality of life. However, the advantage of MISTLIF is more in the early period.

CONCLUSION:

Minimally invasive TLIF manifests its advantages in the immediate postoperative phase with a shorter hospital stay, early mobilization, return to work, decreased risk of reoperation and infections. These factors result in reduced morbidity and hence may be cost-effective in the long term. Compared with open-TLIF, it reflects similar pain, disability, and quality of life at long-term follow-up.

Authors Contribution:
Aman Ullah Khan: Drafting the article, Data Collection
Afifa Afsar: Data Analysis
Salman Sharif: Conception and Design
Faridah Amir Ali: Analysis and Interpretation/ Revision of the Article

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Original Article **Open Access**

Association of pre-op TSH levels with Thyroid Carcinoma in a Tertiary Care Setup in Karachi, Pakistan

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ABSTRACT

Objectives: This study aimed to explore the relationship between pre-operative TSH levels and the presence of thyroid cancer in patients with nodular thyroid disease in the Pakistani population, using data gathered from patients treated at Dr. Ruth K. M. Pfau Civil Hospital Karachi.

Study Design & Setting: A cross-sectional study was conducted at the Dow University of Health Sciences and Dr. Ruth K. M. Pfau Civil Hospital Karachi from January 2022 to December 2022.

Methodology: Patients with thyroid swellings (presenting with either solitary nodules or with multinodular goiter), both benign as well as suspected/confirmed malignancy based on FNAC results were recruited in the study. Preoperative TSH levels, along with other clinical data, were collected. Thyroidectomy was carried out in patients fulfilling the criteria for surgery, with specimens sent for histopathology. An independent t-test was used to compare TSH levels between malignant and benign nodules.

Results: A total of 82 patients were enrolled. Malignancy was confirmed in 41.5% (25 papillary carcinoma, 9 follicular carcinoma). Significantly higher mean TSH levels were observed in patients with malignant nodules (4.76 IU/mL) compared to those with benign nodules (2.48 IU/mL) ($p < 0.001$).

Conclusion: This study suggests a potential association between elevated pre-operative TSH levels and thyroid cancer in the Pakistani population. These findings warrant further investigation to explore causality and potential underlying mechanisms. The study highlights the value of TSH monitoring, particularly in resource-constrained settings.

Keywords: Thyroid carcinoma, TSH, Pakistan, South Asia.

How to cite this Article:
Junaid T, Siddiqui AFI, Khan TZ, Ahmed Z, Arif B, Kazmi S, Tahseen MU. Association of pre-op TSH levels with Thyroid Carcinoma in a Tertiary Care Setup in Karachi, Pak J Bahria Uni Med Dental Coll. 2024;14(4):240-245 DOI: https://doi.org/10.51985/JBUMDC2024366

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Received: 29-04-2024
Accepted: 11-09-2024
1st Revision 04-06-2024
2nd Revision 05-07-2024
3rd Revision 21-08-2024

INTRODUCTION:

Thyroid carcinoma stands as the most prevalent type of endocrine malignancy, potentially compromising thyroid hormone production and causing health problems. This malignant tumor can arise from different cell types in the thyroid, requiring specific tests and treatments depending on its origin and severity. It ranks as the seventh most prevalent cancer in women globally, an estimated 586,202 individuals were diagnosed with thyroid cancer in 2020. In 2023, approximately 43,720 adults in the United States are expected to receive a thyroid cancer diagnosis, with 12,540 cases among men and 31,180 among women. In Pakistan, thyroid carcinoma remains a health burden with being in twenty most prevalent cancers in the country.

Until recently, thyroid cancer experienced a notable surge in diagnoses in the United States, attributed in part to the enhanced sensitivity of diagnostic tests leading to the detection of smaller cancers. However, since 2014, there has been an annual decrease of around 2% in the incidence rate, coinciding with the adoption of newer diagnostic criteria.

Thyroid cancer often manifests at a younger age compared to other adult cancers, with white individuals being 70% more likely to be diagnosed than their Black counterparts, who exhibit the lowest incidence rates. The projected toll

for 2023 includes an estimated 2,120 deaths in the United States, with 970 among men and 1,150 among women. Despite a stable death rate between 2011 and 2020, women are three times more likely to be diagnosed with thyroid cancer than men. Interestingly, while men and women face similar mortality rates, men tend to have a less favorable prognosis than women upon receiving a thyroid cancer diagnosis, highlighting gender-specific differences in outcomes. In 2020, an estimated 43,646 people worldwide succumbed to thyroid cancer .

Recent studies suggest a potential link between TSH and thyroid carcinoma progression.[1] It has been reported that higher pre-operative TSH levels might be associated with worse overall and disease-free survival in papillary thyroid carcinoma patients after surgery.[2] This adds to the evidence suggesting a link between TSH and disease aggressiveness. It has also been reported that high pre-operative TSH levels can predict disease progression in patients with papillary thyroid carcinoma undergoing active surveillance. This highlights the potential role of TSH monitoring in managing this group of patients.[3] While several studies have linked higher TSH levels in thyroid nodules to a higher risk of malignancy, even within the normal range, this hasn't been thoroughly investigated in South Asian populations. To address this gap, we set out to explore the relationship between pre-operative TSH levels and thyroid cancer in this specific population.

METHODOLOGY:

This study, conducted at the Dow University of Health Sciences and Dr Ruth K. M. Pfau Civil Hospital Karachi over a one-year period, from January 2022 to December 2022, employed a cross-sectional observational design within the department of ENT and Head and Neck Surgery. Ethical approval was secured through the Institutional Review Board.

Participants were recruited from patients presenting to the ENT OPD of Dr. Ruth K. M. Pfau, Civil Hospital Karachi, with thyroid swellings (presenting as either solitary nodules or multinodular goiter), which included both benign cases as well as suspected/confirmed malignancy based on FNAC results. All the individuals exhibiting thyroid swellings underwent pre-operative evaluation, including T-3, T-4, and TSH level measurement, neck ultrasonography, and FNAC. Those meeting surgical criteria underwent thyroidectomy, with subsequent histopathological examination of the excised tissue.

Inclusion criteria for the study stipulated informed consent, age between 15 and 65 years, and those patients who presented with benign thyroid swellings, and were planned to undergo thyroidectomy, as well as patients with suspected thyroid malignancy based on FNAC results. Conversely, exclusion criteria encompassed pregnancy, Bethesda 1/Thy 1 cytology on FNAC, and prior use of thyroxine or anti-thyroid medications.

This approach ensured the recruitment of a representative sample while minimizing potential confounding factors, thereby strengthening the study's internal validity and generalizability. The sample size of 61 was calculated using web based sample size calculator. The confidence interval was kept at 95%, and the margin of error was kept 7% with a population proportion of 8.4%. However, a total of 82 patients with thyroid swellings were enrolled.

Data Analysis was performed using SPSS version 24.0. An independent t-test was used to find out if there is any relationship between the presence of malignant and benign nodules with the TSH value.

RESULTS:

This study investigated the characteristics and outcomes of 82 patients undergoing evaluation for thyroid nodules. The average age of participants was 40.2 ±7.56 Standard Deviation (SD), with a predominance of females (72%) compared to males (28%).

A total of 41.5% (25 patients with papillary carcinoma + 9 patients with follicular carcinoma) of the 82 patients were diagnosed with malignant nodules. Papillary carcinoma was the most prevalent type of cancer, affecting 30.5% (25 out of 82 patients) of the study population. Follicular carcinoma was identified in 11% (9 out of 82 patients) of the participants.

58.5% (10 patients with solitary nodules + 38 with multinodular goiter) of the patients had benign nodules. Solitary nodules were found in 12.2% (10 out of 82 patients). Multinodular goiter was the most common benign condition, affecting 46.3% (38 out of 82 patients) of the participants.

Importantly, a significant association emerged between TSH levels and the presence of malignant nodules. In patients with thyroid malignancy, the mean TSH level was 4.76 IU/mL ± 2.43 SD, while it was 2.48 IU/mL ± 1.65 SD in patients with benign disease (P = 0.001). Results are shown in Figure 1. Patients diagnosed with papillary carcinoma (30.5%) or follicular carcinoma (11%) had higher average TSH levels compared to those with benign nodules (solitary nodule: 12.2% and multinodular goiter: 46.3%). The majority of patients who underwent surgery received total thyroid-ectomy (87.8%).

a: The chi-square test was used to compare the relationship between the gender, FNAC, and ultrasound findings with the TSH value

b: An independent t-test was used to find out if there is any relationship between the presence of malignant and benign nodules with the pre-operative TSH value. P-value <0.001 is significant

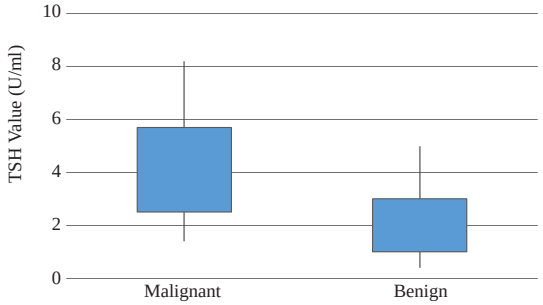
DISCUSSION:

Our cross-sectional study in the Pakistani population of Karachi, Sindh using data gathered from patients treated at Dr. Ruth K. M. Pfau Civil Hospital Karachi, adds another

Table 1: Number and Percentage of patients according to sample size, ultrasound findings, FNAC, Diagnosis of carcinoma type and surgical procedure performed.

N	82	%	P-value
Age	40.2±7.56 (26-59)		
Gender			0.348[a]
Male	23	28	
Female	59	72	
TSH (IU/mL)	3.05±1.74		
Ultrasound Findings (TIRADS Classification)			0.346[a]
1	0	0	
2	2	2.4	
3	26	31.7	
4	25	30.5	
5	21	25.6	
6	5	6.1	
7	3	3.7	
FNAC (Bethesda Classification)			0.561[a]
I	1	1.2	
II	4	4.9	
III	48	58.5	
IV	15	18.3	
V	11	13.4	
Diagnosis			<0.001[b]
Solitary Nodule	10	12.2	
Multinodular Goitre	38	46.3	
Papillary Carcinoma	25	30.5	
Follicular Carcinoma	9	11	
Surgery Performed			
Hemithyroidectomy	10	12.2	
Total Thyroidectomy	72	87.8	

Graph 1: Number and Percentage of patients according to sample size, ultrasound findings, FNAC, Diagnosis of carcinoma type and surgical procedure performed.



crucial piece to the puzzle of understanding the relationship between TSH levels and thyroid carcinoma. Our findings suggest intriguing trends that warrant further exploration. The observed difference in mean age between malignant (42.35 years +/- 8.29 SD) and benign (38.75 years) cases aligns with existing literature. Studies report a higher incidence of thyroid cancer in individuals aged 40-55 years.[4,5] Interestingly, the gender distribution in both groups (approximately 70% female, 30% male) reflects the well-established higher prevalence of thyroid cancer in women.[6]

Our study found a significantly higher prevalence of multinodular goiter (MNG) compared to solitary nodules within the benign nodule group. This aligns with previous research suggesting MNG is the most common thyroid disorder.[8,9,10]

Our investigation revealed a malignancy rate of 41.46%, consistent with previous research indicating a diverse range of malignancy prevalence in thyroid nodules, spanning from 5% to 44% across various study cohorts. Nonetheless, it is crucial to acknowledge that this figure may not accurately depict the actual prevalence of malignancy within the broader population.

While our findings align with existing literature on the variability of malignancy rates in thyroid nodules, several factors merit consideration when interpreting these results. Firstly, the heterogeneity of study populations and methodologies employed in previous research can contribute to discrepancies in reported malignancy rates. Variations in patient demographics, geographic locations, and diagnostic criteria may influence the observed prevalence of thyroid cancer across different studies.

Furthermore, the inherent limitations of our study design, such as the reliance on a specific patient cohort and diagnostic modalities, may impact the generalizability of our findings to the broader population. Our inclusion criteria, which targeted patients with suspected thyroid malignancy based on fine-needle aspiration cytology (FNAC), inherently skewed our sample towards individuals with a higher likelihood of cancer, potentially inflating the observed malignancy rate.

Additionally, referral biases within the healthcare system, particularly within the ear, nose, and throat (ENT) specialty, may influence the composition of our study population and contribute to the observed malignancy rate. Patients referred to specialized centers for further evaluation and management of thyroid nodules may exhibit different clinical characteristics and disease profiles compared to individuals in the general population, leading to potential overestimation of malignancy prevalence.

Population-based studies suggest a lower true prevalence, typically between 5% and 10%.[16,17] This disparity from the existing population-based malignancy rate can be attributed to the fact that the inclusion criterion of our study inherently followed patients with suspected thyroid malignancy based on FNAC, a population with a higher pre-test probability of cancer. FNAs are not routinely performed on all thyroid nodules, and those deemed suspicious enough to warrant an FNA are more likely to harbor malignancy compared to the general population with thyroid nodules.[18] Additionally, referral patterns within the ENT ward might have introduced

patients with more concerning features, contributing to the observed high cancer rate.

Of the malignant cases in our study (34), 73.5% (25) were cases of papillary carcinoma, and 26.4% (9) cases of follicular carcinoma. This finding aligns with papillary carcinoma being reported as the most prevalent thyroid carcinoma.[19,20]

The most striking finding is the significant difference in mean TSH levels between the two groups, with malignant cases exhibiting a considerably higher average TSH (4.17) compared to benign cases (2.27). This observation aligns with prior research suggesting an association between subclinical hypothyroidism (elevated TSH with normal thyroid hormone levels) and an increased risk of thyroid cancer.[9,21]

A study investigating the potential role of TSH in the development of thyroid carcinoma suggested that TSH stimulation might promote the development of undetectable thyroid microcarcinomas into larger, identifiable tumors.[7] It has also been reported that activating mutations in the TSH receptor gene are detected within certain differentiated thyroid carcinomas. These cancers are characterized by a twofold abnormality: elevated basal adenyl cyclase activity and diminished responsiveness to TSH stimulation.[22]

Several noteworthy studies bolster our observations. A large-scale meta-analysis by Hu et al (2019)[23] encompassing over 14 million individuals identified a clear dose-response relationship between elevated TSH and thyroid cancer risk, particularly for papillary thyroid carcinoma, the most common type. Similarly, another study investigated the relationship between TSH serum concentrations and thyroid malignancy. Their analysis suggests a link between higher TSH levels and an increased risk of thyroid carcinoma.[24] Additionally, a separate study involving over 11,000 patients observed an approximate 11% rise in the likelihood of papillary thyroid carcinoma (PTC) for every milliunit per liter (mIU/L) increase in TSH levels.[25]

Although age, gender, and the existence of thyroid nodules are acknowledged as established risk factors for thyroid cancer, the intricate interplay among these factors, cancer onset, and TSH levels continues to be subject to ongoing scrutiny. Our results reaffirm this stance, emphasizing the viability of TSH as an accessible and economical screening tool, particularly in resource-limited contexts such as Pakistan.

Understanding the precise relationship between demographic variables, thyroid nodules, TSH levels, and cancer development presents a multifaceted challenge that necessitates comprehensive investigation. While age and gender have been consistently identified as significant risk factors for thyroid cancer, the mechanistic links between these factors and TSH dynamics remain elusive. Unraveling these complexities requires interdisciplinary approaches that integrate clinical, epidemiological, and molecular perspectives to elucidate the underlying pathophysiological mechanisms driving thyroid carcinogenesis.

Moreover, our findings underscore the pivotal role of TSH assessment in early detection and risk stratification for thyroid cancer, particularly in resource-constrained settings where access to advanced diagnostic modalities may be limited. By leveraging TSH as a screening biomarker, healthcare providers can identify individuals at heightened risk of thyroid malignancy and implement timely interventions to mitigate disease progression and improve clinical outcomes.

Furthermore, the cost-effectiveness and simplicity of TSH testing render it an attractive option for population-based screening programs aimed at reducing the burden of thyroid cancer in high-risk populations such as Pakistan. Integrating TSH assessment into routine healthcare protocols can facilitate early diagnosis, enhance patient prognosis, and optimize healthcare resource allocation, ultimately alleviating the socioeconomic burden associated with advanced-stage thyroid cancer.

Furthermore, our study sheds light on the specific context of the Pakistani population. Previous research suggests that the prevalence of thyroid disorders, including thyroid cancer, might be higher in South Asia compared to Western countries. A study by Bukhari et al. (2009) reported a higher incidence of thyroid cancer in Pakistan compared to the United States, potentially due to factors like iodine deficiency and genetic susceptibility. Considering this context, our findings become even more compelling, emphasizing the importance of vigilant TSH monitoring and early intervention for the Pakistani population.

The distribution of FNAC categories aligns with expectations in our study, with the majority of benign diagnoses (62.9%) falling under the Bethesda III (indeterminate) category, as shown in the table. This is consistent with the known limitations of FNAC in definitively diagnosing thyroid nodules.[8]

The prevalence of TIRADS 3 and 4 ultrasound findings in both malignant and benign groups (53.9% and 46.1%, respectively) is unsurprising, as these categories encompass nodules with uncertain malignant potential . However, the increased prevalence of TIRADS 5 in malignant cases (25.6%) compared to benign cases (6.1%) as seen in the image, further reinforces the opinion that ultrasound is a valuable tool in risk stratification for thyroid nodules.

Our study reveals that the link between serum TSH levels and thyroid malignancy is complex and multifaceted. Recent researches on this topic have provided valuable insight but still further research is required to understand the mechanism of TSH induced carcinogenesis as well as the link between serum TSH levels and thyroid carcinoma progression.

However, it is crucial to acknowledge the limitations of our study. The cross-sectional design precludes establishing

causal relationships, and further research is warranted to explore the underlying mechanisms linking TSH and thyroid carcinogenesis. Additionally, our study population might not be entirely representative of the broader Pakistani population, necessitating further investigations in diverse geographical and socioeconomic groups.

Despite these limitations, our research contributes significantly to the growing body of evidence on the TSH-thyroid cancer association. By illuminating this crucial link in the Pakistani context, we pave the way for more targeted screening strategies and potentially life-saving interventions for this population. Future research should delve deeper into the underlying mechanisms, explore potential genetic and environmental risk factors, and assess the efficacy of TSH-based screening programs in Pakistani healthcare settings. Ultimately, our collective efforts can lead to a future where early detection and effective treatment minimize the burden of thyroid carcinoma in Pakistan and beyond.

CONCLUSION:

The implications of our study extend beyond the realms of clinical research to encompass public health initiatives and healthcare policy formulation. The potential association between elevated TSH levels and thyroid carcinoma diagnosis underscores the imperative of integrating TSH assessment into routine screening protocols for thyroid disorders, particularly in regions with a high burden of thyroid cancer such as Pakistan.

Furthermore, our study underscores the importance of addressing modifiable risk factors contributing to TSH dysregulation and thyroid cancer susceptibility. Public health initiatives aimed at promoting iodine sufficiency, mitigating environmental pollutants, and fostering healthy lifestyle behaviors can potentially attenuate the incidence of thyroid disorders and alleviate the burden of thyroid cancer within the Pakistani populace.

Authors Contribution:
Tehmina Junaid: Conceived and designed the study
Areej Fatimah Iqrar Siddiqui: Conceived and designed the study, wrote the paper
Tariq Zahid Khan: Supervised the study
Zeba Ahmed: Supervised the study
Basit Arif: Data collection
Sana Kazmi: Wrote the paper
Muhammad Umair Tahseen: Data Analysis

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Original Article **Open Access**

Efficacy of Laparoscopic-Assisted Subcostal Transversus Abdominis Plane (TAP) Block: A Double-Blind, Randomized Controlled Trial

Sadaf Ishaque, Sarmad Masud, Rizwan Ahmed Khan, Nauman Ismat Butt

ABSTRACT

Objective: To analyze efficacy of laparoscopic administered Transversus Abdominis Plane (TAP) block on pain scores and opioid consumption in the first 24 hours in patients undergoing laparoscopic cholecystectomy.

Study design and setting: The randomized, double-blinded trial was conducted in surgical unit, Shalamar Medical & Dental College Lahore from September 2019 to March 2020.

Methodology: 100 patients of either gender scheduled for elective laparoscopic cholecystectomy were included using consecutive probability sampling method. After informed consent, patients were randomized into Intervention TAP Group-A and Control Group-B. Intervention TAP Group-A received laparoscopic aided TAP block with 20ml 0.5% Ropivacaine in subcostal region while Control Group-B received 20ml saline solution which was used as placebo. Both groups received paracetamol 1gm intravenous eight-hourly and Ketorolac 30mg intravenous 12-hourly. Nalbuphine 5mg intravenous was administered as "rescue analgesic" in patients having pain score of four or above. Postoperative pain scores at rest and on coughing were documented using numerical rating scores (VAS) at 2, 4, 6, 12, and 24 hours.

Results: There was a significant difference (p-value=0.038, 0.000, 0.025, 0.000, 0.000) in pain scores over the first 24 hours postoperatively in laparoscopically assisted Intervention TAP Group-A. The total nalbuphine consumption was significantly reduced in Intervention TAP Group-A as compared to Control Group-B.

Conclusions: Laparoscopic administered TAP block significantly reduced postoperative pain and total opioid consumption following laparoscopic cholecystectomy.

KEYWORDS: Analgesia, VAS, Laparoscopic Cholecystectomy, Transversus Abdominis Plane Block

How to cite this Article:
Ishauqe S, Masud S, Khan RA, Butt NI. Efficacy of Laparoscopic-Assisted Subcostal Transversus Abdominis Plane (TAP) Block: A Double-Blind, Randomized Controlled Trial. J Bahria Uni Med Dental Coll. 2024;14(4):246-50 DOI: https://doi.org/10.51985/JBUMDC2024375

INTRODUCTION:

One of the vital issues following abdominal and other major surgeries is effective postoperative pain control. Even though laparoscopic surgeries help to reduce invasiveness and pain severity postoperatively, pain may still lead to significant delay in recovery and patient distress. Patients who suffer complications require more postoperative pain relief and the occurrence of postoperative complications leads to reduced overall health, poor mental health, fatigue and lower physical activity affecting the patient's quality of life.[1] Furthermore, other psychological factors such as depression can also contribute in marked postoperative pain, slow recovery and prolongation of hospital stay.[2,3] Therefore it is important to target these factors to reduce the incidence of postoperative pain and complications so that patient outcomes may be optimized. The use of opioids in pain management is usually standard practice of care worldwide but excessive use may result in various drawbacks such as opiate dependence, abuse and subsequently overdose.[4,5] Patients with comorbid conditions, pre-existing mental health illness and those who develop complications are at highest risk to develop postoperative opioid analgesic dependence.[6] Various preoperative techniques including Shapley additive explanations (SHAP) technique help detect risk factors for severe pain which aid in tailoring the pain management plan thereby providing more effective pain control and mitigating the risk of opioid overuse and dependence.[7]

Laparoscopic cholecystectomy is presently considered the gold standard treatment for gallstone diseases. With significantly less postoperative pain, early mobilization, and enhanced postoperative recovery, this minimally invasive technique has become an appropriate option for day case

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Received: 16-05-2024 1st Revision 12-06-2024
Accepted: 11-09-2024 2nd Revision 12-08-2024

surgeries.[8,9] Despite reduced pain incidence for laparoscopic cholecystectomy, the incision site, trocar insertion site, pneumo-peritoneum, and abdominal muscle stretching may still lead to high levels of discomfort and pain in some patients. Therefore, a multimodal analgesia strategy is adopted in the perioperative period for effective postoperative pain control.[10] Components of multimodal analgesia include non-steroidal anti-inflammatory drugs, paracetamol, local anesthetic infiltration, regional nerve blocks, and non-opioid adjuncts.[10,11] For breakthrough pain, opioids and opioid-related analgesics are used. Initially described in 2001, TAP block used a new approach via the lumbar triangle for effective pain relief.[12] Since then, implications of TAP block in abdominal, urological, and gynecological surgeries have been explored.[13]

Laparoscopic-assisted TAP block involves the injection of the local anesthetic agent between the transversus abdominis and the internal oblique muscles and provides analgesia to the skin, anterior abdominal muscles, and parietal peritoneum.[14] Though ultrasound-guided administration makes the TAP block much easier, the identification of the muscle planes can be difficult in a few cases. A new technique of TAP block directly under observation in open surgery has been advocated and inferences that the conventional approach risks could be avoided with this easy approach.[15] Considering TAP block under direct vision in a laparoscopic procedure, a similar laparoscopic-guided TAP block approach during laparoscopic bariatric surgery and nephrectomy has also been explained.[16] The transabdominal plane (TAP) block is a regional anesthesia technique used for postoperative pain management in abdominal wall procedures, providing somatic analgesia to the anterior and lateral abdominal walls. . Ultrasound-guided transversus abdominis plane (TAP) block involves the injection of LA in between the transversus abdominis (TA) and internal oblique (IO) muscles. The TAP block can also be targeted using anatomical landmarks at the level of the Petit triangle. This interfascial plane contains the intercostal, subcostal, iliohypogastric, and ilioinguinal nerves. These nerves give sensation to the anterior and lateral abdominal wall and the parietal peritoneum, providing only somatic and not visceral analgesia. The TAP block can be used for postoperative analgesia management in open and laparoscopic abdominal surgeries and inpatient and outpatient surgical procedures. However, the efficacy of TAP block administration under direct vision in laparoscopic cholecystectomy remains to be studied in the local population in Pakistan. Thus, our study aims to establish the TAP block efficacy by analyzing the mean pain scores and opioid consumption in patients undertaking laparoscopic cholecystectomy at a tertiary care hospital in Lahore Pakistan.

METHODOLOGY

The study design was a randomized, double-blinded trial was conducted in the surgical unit of Shalamar Hospital, Shalamar Medical & Dental College Lahore Pakistan from September 2019 to March 2020. This clinical trial has been approved by the Institutional Review Board at Shalamar Medical and Dental College (Ref No: SMDC/IRB/21-8/046). The RCT has been registered with Australian New Zealand Clinical Trials Registry (Trial Reg No: ACTRN12621001432808) and the International Clinical Trials Registry Platform (Universal Trial No: u1111-1263-0186). Using postoperative pain as the primary endpoint expressed as mean ± SD pain VAS score, sample size calculation was done using the formula of continuous outcome variables for a randomized controlled trial. Keeping power of study 80% and 95% confidence interval, sample size was calculated to be 100 patients, scheduled for laparoscopic cholecystectomy in the surgery department. A simple random sampling technique was employed in the study. Patients between 20 and 60 years old of either gender, after obtaining written consent and being scheduled for laparoscopic cholecystectomy in the surgical unit of Shalamar Hospital, Lahore were included using a randomized sampling technique. Patients with American Society of Anaesthesiology (ASA) Grade-III and IV, acute cholecystitis, intra-abdominal adhesions, empyema and gall bladder cancer, coagulopathies, previous history of allergy to local anesthetic agents and abdominal wall infections were excluded. Those who did not give written consent were also excluded from the study.

Following a written informed consent form signed by the patients, the recruited patients were randomized into two groups. Using a computerized "random number table" 48 patients were allocated to an Intervention TAP Group-A and 52 patients to a Control Group-B. Intervention TAP Group-A patients received a TAP block with 20 ml 0.5% Ropivacaine (10 ml in each subcostal region), while the Control Group-B received 20 ml saline solution (10 ml in each subcostal region). Injection of paracetamol 1 gm IV 8-hourly and an injection of ketorolac 30 mg IV 12-hourly were given to both groups. All patients received a general anesthesia regimen that included propofol 2 mg/kg, Nalbuphine 6 mg, and Atracurium 0.5 mg/kg for intubation. The provision of anesthesia was managed with volatile Isoflurane 1-2 MAC in oxygen and air (FiO2 0.5). Standard monitoring incorporated pulse oximetry (SpO2), three lead electrocardiography (ECG), non-invasive blood pressure (NIBP), temperature, capnography, and train-of-four (TOF). As part of multimodal analgesia, all patients received 1 gm Paracetamol and 30 mg ketorolac intravenously following induction. After stabilization of the vital signs, patients received intervention according to the group assigned.

Pneumo-peritoneum was created by the Verres needle and a laparoscope was inserted into the abdomen under direct vision. 18G needle was used for insertion at both sides of the abdominal wall using typical surface landmarks. After perpendicular insertion, needle tip was placed between the internal oblique muscle and the transversus abdominis muscle, confirmed by direct laparoscopic vision. A dose of

20 ml of Ropivacaine was injected bilaterally in Intervention Group-A. A bulge inferior to the internal oblique muscle and away from the transversus abdominis muscle confirmed the appropriate location of the local anesthetic injection. Control Group-B received 20 ml of normal saline in the same manner. Towards the treatment groups, the surgeon and the patients were blinded so biased results cannot happen during the study. Postoperative analgesia included paracetamol 1 gm IV 8-hourly and Ketorolac 30 mg IV 12 hourly according to hospital protocol for post-operative pain management. Nalbuphine 5 mg IV was administered as a "rescue analgesic" in patients having pain VAS score 4 or above according to hospital protocol for post-operative pain management. Postoperative pain scores (VAS) at rest and on coughing were documented using numerical rating scores at 2, 4, 6, 12, and 24 hours to analyze the efficacy of laparoscopic administered Transversus Abdominis Plane (TAP) block on pain scores and opioid consumption in the first 24 hours in patients undergoing laparoscopic cholecystectomy.

The data were entered and analyzed using SPSS version 22. Descriptive analysis such as frequencies and percentages were done of categorical variables and for numerical variables, mean and standard deviation were used. For qualitative variables, Chi-square test was applied while Mann-Whitney U test was employed for quantitative variables. The level of significance was 5%.

Table 1: Demographic characteristics in both groups

Variables		Intervention (n=48)	Placebo (n=52)
Age (years) (Mean ± S.D)		45.34 ± 9.48	48.28 ± 11.89
Gender [n (%)]	Female	34 (65%)	34 (71%)
	Male	18 (34%)	14 (29%)

Table 2: Mean Pain Scores at rest and at cough between both groups

Time intervals	Rest/Cough	Group-A	Group-B	P-value
2 hours	At Rest	2.75 ± 0.73	3.48 ± 1.62	0.038
	With Cough	2.90 ± 0.72	3.83 ± 1.44	0.000
4 hours	At Rest	2.46 ± 0.50	3.13 ± 1.05	0.000
	With Cough	2.52 ± 0.58	3.35 ± 0.99	0.000
6 hours	At Rest	2.29 ± 1.27	2.58 ± 0.80	0.025
	With Cough	2.42 ± 1.18	2.71 ± 0.85	0.019
12 hours	At Rest	1.83 ± 1.02	2.52 ± 0.92	0.000
	With Cough	1.92 ± 1.01	2.54 ± 0.92	0.000
24 hours	At Rest	1.02 ± 0.70	2.13 ± 0.35	0.000
	With Cough	1.06 ± 0.69	2.21 ± 0.41	0.000

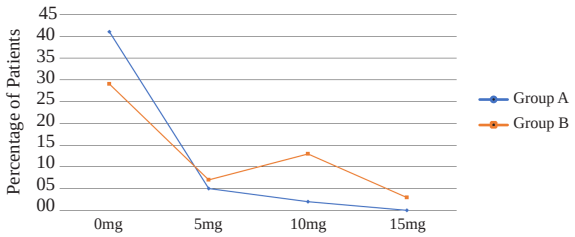
Table 3: Comparison of additional Nalbuphine consumption in both groups

Dose of nalbuphine	Group A	Group B	p-value
	n (%)	n (%)	
0mg	41 (85.4)	29 (55.8)	0.002
5mg	5 (10.4)	7 (13.5)	
10mg	2 (4.2)	13 (25)	
15mg	0	3 (5.8)	

RESULTS

The mean age of patients in Group-A was 48.28 ± 11.89 years and the mean age of patients in Group-B was 45.34 ± 9.48 years. Most of the females were present in both groups A and B. (Table 1). To analyze the efficacy of laparoscopic administered Transversus Abdominis Plane (TAP) block on pain scores and opioid consumption in the first 24 hours in patients undergoing laparoscopic cholecystectomy, the mean pain scores were determined for both groups of patients. It was observed that the difference in means of pain scores at 2, 4, 6, 12, and 24 hours at rest and with cough for both Group-A and Group-B was statistically significant (Table 2). The difference in total Nalbuphine consumption between both groups was statistically significant (p=0.002). This means that the Nalbuphine dose was more used in Group-B patients as the additional drug as compared to Group-A. (Table 3) The graphical representation was shown in Figure 1.

Figure 1: Comparison of additional Nalbuphine consumption in both study groups



DISCUSSION:

The current study has demonstrated the efficacy of laparoscopic administered TAP block for postoperative analgesia. It is significantly linked with lower postoperative pain VAS score and reduced opiate analgesic consumption. The findings of our study are consistent with earlier research showing that, following TAP block in laparoscopic cholecystectomy, there was an alleviation in opioid requirement and lowered pain scores.[13] As depicted in a few other studies, the TAP block method was employed in the laparoscopic form of ultrasound-guided four-quadrant dual-block. So according to the results to provide adequate analgesia, multiple point injection block is highly efficacious.[17,18] Additionally, L-TAP made the hospital stay shorter. Also, the outcomes were predictable if L-TAP is integrated into an Enhanced Recovery After Surgery (ERAS) program. This outcome further affirms past studies that, when added to an ERAS program, L-TAP leads to shortened emergency clinic stay post-procedure, without expanding complexities or subsequent re-admission risk.[18,19] There were no complications observed for TAP block in the present study, indicating that TAP block can exhibit effective

analgesia for upper abdominal laparoscopic surgery.[19,20] Tihan et al.[21] also reported laparoscopic TAP block to be an easy and effective procedure, reducing the operational time and having low risk of adverse effects making it an ideal choice especially in elderly patients.

It was clinically indicated that nalbuphine's analgesic efficacy is comparable to that of morphine, with only a slight breathing depression and a phenomenon known as capping. Our findings suggested that due to its modulatory action on central ê-receptors, nalbuphine can reduce postoperative analgesic requirements and NRS scores related to generalized pain.[22] The requirement for analgesia is the unintended indicator of post-operative pain in the postoperative period. According to the results of the TAP block, it not only reduced the number of patients who required rescue analgesia, but it also significantly reduced the "rescue analgesic" necessity with respect to the other group. So, our outcomes are similar to the recent studies.[23] There has been much focus on Enhanced Recovery After Surgery (ERAS) over the last decade. An effective perioperative pain control strategy is of paramount importance for enhanced recovery.[24] According to a recent study, 20 ml of Bupivacaine, Ropivacaine or Levobupivacaine could be the optimal dose for TAP block with 0.4 mL/kg infiltration at port site, because a low number of side effects, adverse events, and complications.[23] In past studies, TAP block resulted in decrease in pain score (8 mm on a 0 to 100 mm VAS scale) on coughing and a 2.5-mg decline in opiate analgesic necessity in the first 2 hours post-surgery.[25] The present study has certain limitations that should be considered also. Based in a single institution, the present study had a relatively small sample size therefore the results may be not applicable to the entire general population. However, the present study is unique in terms of providing a detailed perspective of TAP block, its effects, and complications during laparoscopic cholecystectomy in a developing country like Pakistan with limited resources. We recommend that further studies should be conducted to explore and compare effectiveness of TAP in other surgeries using the findings of our study as baseline information.

CONCLUSION:

We conclude TAP block to be an easy-to-use, effective and safe technique in laparoscopy surgery that decreases the intensity of post-operative pain, aids in speedy recovery, timely discharge from the hospital, enhanced patient well-being and satisfaction following laparoscopic cholecystectomy.

Authors Contribution:
Sadaf Ishaque: Conception and design, Data collection, Analysis and interpretation of the data, Literature review and drafting of the article
Sarmad Masud: Conception and design, data analysis and interpretation, Critical review and revision of the article
Rizwan Ahmed Khan: Conception and design, Data collection, Literature review and drafting of the article
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Original Article **Open Access**

Analysis of Cesarean Section Rates Using Robson Ten Group Classification System in A Tertiary Care Hospital of Peshawar: A Cross-Sectional Study

Maimoona Qadir

ABSTRACT

Objective: To observe CS rates and assess them using Robson's Ten Groups Categorization System in a government tertiary medical facility in Peshawar, Pakistan

Study Design and Setting: From 1st March to 31st August 2023, a cross-sectional study was carried out at the Khyber Teaching Hospital's department of obstetrics and gynecology in Peshawar, Pakistan

Methodology:. The research cohort consisted of 1250 women with CS who were hospitalized throughout the specified study period. Information on maternal features and pregnancy-related details was collected for every patient.

Results: 4227 women sought labor and delivery services during the course of the research. It was discovered that the CS rate was 29.5%. Most common were Groups 1 (7.57%), 3 (8.65%), and 5 (54.66%), which together accounted for around 69% of all CS occurrences. Group 5's CS rate was 80.7%, but subgroup 5.1's (previous CS) women experienced repeat CS at a rate of 65.14%. 95% babies were alive and 5% were stillborns.

Conclusion: Noticeable raise in the caesarean deliveries rate, leading to substantial worse influence in terms of health, finances, and society. Previous CS is the most prevalent sign of CS.CS if performed on primigravidae with a valid indication, the rate of CS may be managed.

Keywords: Primigravida, Caesarean Section, Abruptio Placentae, Multipara, Placenta Accreta

How to cite this Article:
Qadir M. Analysis of Cesarean Section Rates Using Robson Ten Group Classification System in A Tertiary Care Hospital of Peshawar: A Cross-Sectional Study. J Bahria Uni Med Dental Coll. 2024;14(4):251-5 DOI: https://doi.org/10.51985/JBUMDC2024381

INTRODUCTION:

In 1985, the World Health Organization decided that a rate of 10–15% cesarean sections is appropriate.[1] Thirty years after the WHO released its guidelines, there is still debate over the optimal CS rate. Other difficulties in more recent attempts to determine the optimal CS rate were confounders and the lack of external validity.[2] Despite its shortcomings, the proportion of caesarean sections performed as a percentage of the population is an important indicator of how easily accessible obstetric services are in a given country. The risks involved with this potentially life-saving procedure might potentially jeopardize the lives of the mother and the child in this or future pregnancies. Both the short- and long-term effects of CS have been studied; they include lengthier hospital admissions, a higher risk of postpartum hemorrhage, retained placentas, postpartum infections, and stillbirths.[3]

A universally acknowledged taxonomy is necessary for policymakers, program managers, physicians, and administrators to meticulously monitor the frequency of caesarean sections. A comprehensive assessment of the current CS categorization was conducted before, revealing that RTGCS emerged as the most viable alternative among 27 potential classification systems.[5] The Robson categorization system categorizes all CS into 10 groups based on predetermined fetomaternal characteristics.[6] The characteristics encompass parity, prior caesarean section, fetal presentation, number of foetuses, and gestational age. Researchers have hypothesized that societal and economic factors may contribute to the increasing occurrence of non-medically advised cesarean sections, as seen by the large number of such instances. In order to assess and compare cesarean section (CS) rates within and between healthcare institutions, as well as to consistently analyze, monitor, and improve these rates, the World Health Organization (WHO) in 2014 and the International Federation of Gynecology and Obstetrics (FIGO) in 2018 suggested that the Robson Ten Group Classification System (RTGCS) should be adopted as a worldwide standard.[7] The categorization technique relies on the routinely reported obstetric features of each woman, rather than being dependent on the reason for cesarean section (CS). This approach is straightforward to adopt and enables the examination and analysis of CS rates.[8]

Utilizing the Robsons ten group classification method effectively offers several advantages. It has allowed us to identify a specific subgroup within Robson's categorization that has a significant impact on the overall rate of cesarean sections. The importance of this stage of the audit process

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Received: 27-05-2024
1st Revision01-07-2024
2nd Revision05-07-2024
Accepted: 20-08-2024
3rd Revision 20-08-2024

arises from the potential for actions that typically impact the CS rate.[9] The methodology offers a reliable method for comparing inside an institution over time, as well as across institutions at a national, regional, or global level. Furthermore, it can be readily reproduced. RTGCS provides a reference point and historical data on the rates of CS, which may be used to assess the impact of surgery at various levels.[10] The evaluation of Pakistani caesarean section trends has previously been done on a regional level using the RTGCS technique. Our department's deployment of RTGCS is driven by the same purpose, which is to identify the common groups that influence the caesarean section rate and provide meaningful interventions and approval for its improvement. This method is also utilized to construct a database of caesarean section rates in Pakistan.

METHODOLOGY:

At Gynaecology unit of Khyber Teaching Hospital, Peshawar, a cross-sectional research was done. A tertiary care center, Khyber Teaching Hospital handles about 10,000 births annually. In addition, it is a public hospital that primarily acts as a hub for high-risk patient referrals. All mothers who gave birth after 28 completed weeks of gestation between 1st March to 31st August 2023 were included in the research population. We did not include laparotomies performed for uterine rupture or prenatal births. The institutional research committee approved the study (Ref No.270/EC/KTH), and as it was a non-interventional study with no requirement for identify disclosure, informed permission from the mothers was not required.

Data was collected and stored by knowledgeable data collectors using a standardized proforma. This includes factors such as the foetal presentation or position, gestational age (term or preterm), number of foetuses, delivery mode , Parity and prior obstetric history. An obstetric ultrasound performed before to 24 weeks of pregnancy or the menstruation date was used to determine gestational age. When there was no milestone for period of gestation, we used birth weight in place of gestational age. We searched medical records for relevant pregnancy-related information. Nulliparous is defined as the woman who has not given birth to any baby at the time of study whereas multiparous is defined as the woman who has given birth to >2babies.

Version 20 of IBM SPSS Statistics for Windows was used to analyse the information. In the beginning, the organization's total CS rate was determined. Following the entry of all data, women were categorized into one of the 10 Robson categories. It was recorded how big each group was in relation to the overall obstetric population, how much of the CS rate each group contributed, and how much of the CS rate each group contributed overall.

RESULTS:

In all, 4227 women visited for labour and delivery throughout the six months. Two patients were omitted because of uterine rupture, while twenty-five people were not included because of pre-viable babies. Consequently,4,200 births were considered. The average age was 25.3 ± 4.6 years. Table 2 shows that 29.5% of the population had CS. The sampling technique was non consecutive probability sampling and sample size was calculated by Open Epi.

Table 1: Robson's 10 Group Classification

Group	Description
1	Primi,single cephalic,>37 weeks in spontaneous labor
2	**2a**-Primi,single,cephalic,>37 weeks,induced labor **2b**-Primi,single,cephalic,>37 weeks,CS before labor
3	Multi(- prior CS),single,cephalic,>37weeks in spontaneous labor
4	**4a**- Multi,no prior scar,with singleton,cephalic, >37 weeks,induced labor
	4b-Multi,no uterine scar,single, cephalic, > 37 weeks, CS prelabor
5	Prior CS,single,cephalic,>37 weeks
6	Primi,single breech fetus.
7	Multi,single breech fetus (+previous scar).
8	Multiple pregnancies (+ previous scar).
9	Single pregnancy in transverse or oblique lie (+prior scar).
10	Single, cephalic, < 37 weeks(including previous scar).

Table 2: Demographic Characteristics (N=4200)

Characteristics	Frequency	Percentage
Age		
Less Than 20	267	6.5
20-30 Years	3515	83
More Than 30Years	418	10
Parity		
Nulliparous	1761	42
Multiparous	2247	53
Grand Multiparous	192	4.7
Period Of Gestation		
Less Than 37 Weeks	909	22
37Weeks	3291	78
Labor Onset		
Spontaneous	2558	61
Iol	352	8.5
Caesarean Before Labor	1290	31
Presentation		
Vertex	3972	94
Breech	214	5.2
Transverse Or Oblique	14	0.5
Fetal Number		
Single	4190	99.6
Multiple	10	0.35

Group 1 women, accounted for 10.5% of all births and were nulliparous with a single cephalic pregnancy at term in spontaneous labour. Groups 3, which included 8.2% of the total, were followed by Group 10 (which included all women with singleton pregnancy before 37 completed weeks, including women with previous scar) in 11.3% cases, and multigravidae with singleton pregnancy at 37 weeks with cephalic presentation in spontaneous labour without prior scar. Group 5 represented 1.9% of the obstetric population and consisted of all multigravidae having one prior uterine scar and a single cephalic pregnancy at term. This puts it in last place in terms of size. The highest percentage of CS cases were contributed by Group 10 (18.7%), Group 2 (17.5%) (primigravidae with a single cephalic pregnancy at term who either experienced CS before the commencement of labour or an induction of labour), Group 5 (16.3%), and Group 4 (16%).These four categories enabled around 69% of all caesarean deliveries (Table 3).

DISCUSSION:

Caesarean sections have been shown to provide benefits, but there are also recognized hazards, such as hemorrhage, infection, difficulties from anesthesia, and even death. Other factors that may impact subsequent pregnancies include uterine rupture, aberrant placentation, and early birth.[11]Women who were residing in areas with little resources and have insufficient access to high-quality obstetric care are more vulnerable. Thus, in order to optimize outcomes, hospitals should start a comprehensive and intensive examination of their obstetric population. This classification system enables monitoring and auditing inside an organization and may prove to be a valuable resource in a range of scenarios.[12]

Instead of aiming for a specific rate, efforts should be made to perform CS on women only when it is necessary. The Robson classification system is recommended by the World Health Organization (WHO) as a consistent standard for evaluating, monitoring, and comparing cumulative CS rates within and between healthcare institutions. Our department used Robson's Ten Group Classification System for the current study to demonstrate how useful and approachable it is for identifying the critical parameters impacting the CS rate.[13] This made it possible for us to create effective intervention strategies to stop this rate from rising.

The rate of cesarean sections in our research was 29.5%, which is significantly higher than what the WHO advises. However, research conducted at other Pakistani tertiary institutions showed far higher C section rates: 33% in Islamabad, 49% in Karachi, and 54% in Rawalpindi.[14–16] In addition, a study carried done in five hospitals in South Asia found that 36% of C-sections were performed overall [17].Group 3 provided the most to the obstetric population in our study, accounting for 49.3% of all births, as we found after examining the population type. Groups 1 (19.72%) and 5 (10.65%) contributed the next largest percentages. Groups 1 (17.1%), Group 5 (21.4%), and Group 3 (30.7%) were the most prevalent groups in Gilani et al.'s study.[18]

Khan MA et al. found that the majority of obstetric patients belonged to Groups 2 and 5, which contradicts our findings.[19] According to Dhodapkar SB et al., group 2 and group 5 were the most common groupings, accounting for 19.6% and 33.3% of cases, respectively.[20] Every one of these studies shows the trends in the associated institutions' delivery case handling procedures.

Multigravidas were found in Groups 01 through 07 of our research sample in greater numbers (57.45%) than primigravidae (32.4%). Two more local studies found similar numbers (70.1% and 29.9%), while a research conducted in Bihar found that multiparous women (55.92%) were more prevalent than nulliparas (44.08%).[21,22] Of the women, 94.57% had a cephalic fetal presentation, whereas only 5.23% had a malpresentation. These figures are in line with

Table 3: Proportion of Each Robson Groups, CS Rate in Each Group, and their Relative and Absolute Contribution to Overall CS Rate

Robson group	No. of CS in group	No. of women in group	Group CS rate	Absolute group contribution to overall CS rate(%)	Relative group contribution to overall CS rate(%)
1	141	977	18	3.2	9.1
2a	47	159	19.5	0.8	2.4
2b	109	369	22.5	5.5	16.2
3	85	587	14.5	1.3	3.9
4a	29	98	24.5	4.6	13
4b	120	406	21.5	3.2	9.1
5	294	387	76	10.5	30
6	47	159	21.5	3.5	10
7	52	176	29.5	2.6	7.2
8	26	88	22.5	3.4	14
9	20	67	30	1.4	3.4
10	282	754	27.5	6.6	18
Total	1250	4227	29.5	29.5	100

a local study that discovered that, respectively, 93.4% of the women and 6.6% of the unusual presentations.[23] Around the world, there is a noticeable variation in the prevalence of CS. It ranges from 5% in sub-Saharan Africa to 42.8% in Latin America .[24] This might be explained by differences in the population's demographics, local obstetric practices and legislation, and the challenges of providing healthcare.

When all is said and done, the rates of CS have increased since 1990.In the Indian research, Group 2—rather than Group 01—was the next prevalent group after Group 5 because of the increased risk of CS associated with induction of labor. Group 5 is frequently thought to have contributed the most to the total CS rate because of its scarred uterus.[24] Groups 1, 2, 5, and 10 account for the majority of CS in all worldwide research projects. Group 10, which includes all preterm babies, is the fourth greatest contributor.[25] Due to regional differences in labor induction procedures, Groups 1 and 2's contribution appears after Group 5's in a number of studies. Future research must concentrate on these four areas in order to optimize the CS rate.

The vaginal delivery after caesarean section is decreasing because of concerns for uterine rupture, even though RCOG guidelines support the safety of VBAC in carefully chosen instances.[26]

In our study, the stillbirth rate was 24.5/1000 live births, which is far less than Pakistan's stillbirth rate of 43.1/1000 live births. Just 8% of the stillbirths in this research occurred intrapartum, whereas 92% occurred antepartum. The high rate of antepartum stillbirths is indicative of the province's inadequate health system, low socioeconomic status of women, illiteracy, and poverty, as well as of their inability to access health facilities for adequate prenatal care.

The high sample size and full data availability for analysis are two of this study's strengths. The study's findings may be used as baseline information to track changes in our institution's CS rate over time.

Our study has very few limitations. We define fetal viability as a birth weight of 1,000 g or a gestation length of 28 weeks. This may have an effect on the proportionate size of Robson's groups and the rate of CS. We now understand exactly "who" is receiving CS, but not "why," at the time of the procedure. The limitations of our research stem from the omission of important components such as maternal and perinatal outcomes and indications.

CONCLUSION:

The concerning global raise in the rate of cesarean sections is cause for significant concern since it depletes surgical health resources and is linked to major consequences for the fetus and mother. The Robson's classification is a helpful tool because it identifies the main groups that contribute to the CS rate and makes recommendations for interventions and strategies based on those findings. This allows for the optimization of the CS rate, with the main objectives being the reduction of primary CS and, when practical, the encouragement of women to participate in TOLAC.

Authors Contribution:
Maimoona Qadir: Data collection, analysis, compilation proof reading

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Original Article **Open Access**

Immunohistochemical Expression of Cyclin D1 in Invasive Breast Carcinoma

Tabish Hassan, Nadeem Zafar, Akhter Ali Bajwa, Rabia ahmed, Muhammad Umair, Mubina Qayyum

ABSTRACT

Objective: This study was conducted to determine the immunohistochemical expression of cyclin D1 in invasive breast carcinoma and its association with already established prognostic parameters like estrogen receptor (ER), progesterone receptor (PR), HER2/Neu, and Ki67 status.

Study Design & Setting: Cross sectional Observational. Department of Pathology, Armed Forces Institute of Pathology, Rawalpindi

Methodology: The study included 350 cases of invasive breast cancer diagnosed between January 2023 and December 2023. Data collected included patient age, histological subtype, molecular subtypes, tumor size, and the presence of estrogen (ER) and progesterone (PR) receptors, as well as HER2/Neu and Ki67 status. Patients who had undergone chemotherapy, received radiation to the breasts, or experienced relapse were excluded from the study. Immunohistochemistry was conducted using a Cyclin D1 antibody to assess Cyclin D1 expression in tissue samples. The expression levels were categorized as negative, weak, moderate, strong staining in tumor cells. Data analysis was performed using SPSS 29.0, and statistical comparisons were made between Cyclin D1 staining and ER, PR, HER2/Neu, and Ki67 status.

Results: Cyclin D1 moderate to strong staining was seen in 173/352 (49.14%) cases of invasive BC. Cyclin D1 expression was slightly statistically significantly associated with ER (x2 = 7.78, *P* value <0.051) and Ki67 positivity (÷2 = 7.27, *P* value <0.064).

Conclusion: Cyclin D1 has the potential to serve as a prognostic marker. Incorporating it into the routine IHC workup for breast cancer could enhance patient management, especially with the development of new targeted therapies that inhibit the Cyclin D-CDK4/6 axis.

Keywords: Breast carcinoma; cyclin D1; ER; PR; HER2; KI67

How to cite this Article:
Hassan T, Zafar N, Bajwa AA, Ahmed R, Umair M, Qayyum M. Immunohistochemical Expression of Cyclin D1 in Invasive Breast Carcinoma. J Bahria Uni Med Dental Coll. 2024;14(4):256-61 DOI: https://doi.org/10.51985/JBUMDC2024384

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Received: 27-05-2024
1st Revision 22-08-2024
Accepted: 20-09-2024
2nd Revision 12-09-2024

INTRODUCTION:

Prevalence of breast cancer (BC) is 23.8% in women and 31.3% in Pakistan as of in year 2022.[1] A number of innovative therapeutic methods are currently being investigated in order to broaden the range of treatment choices available for breast cancer. An examination into the expression of genes has led to the discovery of a new classification system for breast cancer. This classification system includes luminal A, B, HER2-positive, and basal-like subtypes.[2]. A better understanding of the molecular alterations and genetics of breast cancer, as well as focused treatment, outcomes have improved even in patients who are in advanced stages.[3,4]

Oestrogen receptor (ER)-á positive breast tumours account for around 70 percent of all breast cancers, which means that endocrine therapy is the major treatment for these individuals. There is a relapse rate that is significantly greater in advanced breast cancer cases, even though tamoxifen reduces the incidence of recurrence by fifty percent. Approximately thirty percent of patients will experience a relapse either during or after treatment with tamoxifen. Consequently, both acquired and de novo resistance to tamoxifen present important obstacles in the therapy process

that must be addressed.[5] Standard endocrine treatments are completely ineffective against triple-negative breast cancer, which is another interesting fact. Consequently, the identification of biomarkers that can predict the response to endocrine therapy is critically important for the selection of different therapeutic options.

On 11q13, the CCND1 gene is responsible for regulating the cell cycle.[6] Cyclin D1, an essential G1 cell cycle regulator, is produced by this type of gene. It accomplishes this by binding to CDK4/6, which increases the rate at which the retinoblastoma protein (Rb) and other substrates are phosphorylated, so accelerating the process of cell proliferation.[7] For a comprehensive knowledge of the transitions from the G1 to S phase in tissue, it is vital to have a solid understanding of the intricate cell cycle mechanics. The activation of CDK4 during the G1 phase is a crucial function of cyclin D1. Cyclin-CDK complexes are activated as a result of this activation, which causes the cell cycle to progress into the S phase. Cyclin D1 mutations can hasten the proliferation of cells by disrupting essential processes, which can ultimately result in the development of cancer.[8] There are also actions that cytokine D1 can perform that are not related to CDK. These actions have the potential to trigger ER-mediated transcription regardless of oestrogen and to affect oestrogen and anti-estrogen responses.[9] The CCND1 gene is amplified in a significant number of breast tumours, and the majority of breast cancers that originated in the breast contain Cyclin D1 overexpression.

As per authors knowledge, there are no research conducted in Pakistan that investigate the expression of Cyclin D1 in breast cancer and its relationship with other factors that influence the prognosis. In the current investigation, the objective is to examine the expression of cyclin D1 in breast cancer patients using immunohistochemistry and to discover whether there is a probable association between this expression and other well-established prognostic criteria such as ER, PR, HER2/NEU, and Ki67% status.

METHODOLOGY:

This is a comparative cross-sectional study and was conducted in the Department of Pathology at Armed Forces Institute of Pathology, Rawalpindi between Jan 2023 and Dec 2023. Ethical approval was obtained from the institute's ethical committee. Based on the prevalence of breast carcinoma in Pakistan, which is around 35%, sample size of 350 BC was estimated using the formula $Z_{1-a/2}^2(p)(1-p)/d^2$, where $Z_{1-a/2}$=1.96, p=0.35 and d=0.05 with 95% confidence interval.[10] All patients having histological diagnosis of invasive breast carcinoma on breast core biopsy or lumpectomy were included in the study. Paraffin embedded tissue blocks received for ER, PR, HER2 and Ki67% were also included in the study. Patients having diagnosis of carcinoma in situ and post neoadjuvant chemotherapy samples were excluded from this study.

After fixation of tissue in 10% buffered formalin, specimen was processed in the TissueTek® tissue-processing equipment. After embedded in paraffin wax, 5µm-thick sections were prepared on a semi-automated rotary microtome. These sections were mounted on glass slides and stained with the conventional haematoxylin-and-eosin dyes. Mounted sections were viewed on the microscope for selection of cases having diagnosis of invasive breast carcinoma.

We selected optimal breast cancer tissue blocks for immunohistochemistry (IHC). Citrate buffer antigen retrieval was done in a pressure cooker. The main antibodies used were anti-human Cyclin D1, ER alpha, PR, HER2/neu, and Ki-67 (Clone EP12, EP1, PgR 636, MIB-1, Dako). This study's positive controls comprised tonsil sections for Cyclin D1 expression, endometrial tissue for ER and PR, previously established breast cancer tissue with high HER2/neu positivity, and skin for Ki-67. To eliminate observational bias, two independent pathologists used high power field (HPF) to examine the sections.[11]

Positive cyclin D1 staining was observed when at least 10% of tumor cells displayed nuclear expression with moderate to strong intensity. The intensity of Cyclin D1 was evaluated using a scale ranging from 0 to 3: Assigning numerical values to different levels of intensity: 0 represents a negative level, 1 indicates a weak level, 2 signify a moderate level and 3 represents a strong level. An evaluation of ER and PR was conducted using the Allred score, where positive scores range from 3 to 8.[12] The assessment of ER and PR immunoreactivity involved analysing the percentage of tumor cells displaying nuclear staining. A positivity threshold of more than 10% was used.[13] The HER2 staining was evaluated using the guidelines set by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP). A positive result (3+) was determined if there was moderate to strong complete membrane staining in 10% or more of tumor cells.[14] A Ki-67 labeling index of 10% or higher was classified as positive.[15]

Data was analyzed using SPSS v 29.0. Cyclin D1 staining was used to tabulate age, histological type, tumor grade, ER, PR, HER 2, Ki67, and molecular classification for all patients. The correlation between cyclin D1 expression and histopathological characteristics was determined using Pearson's Chi-square test. The quantitative data was reported as mean ± SD and the qualitative data as f (% age). The results were statistically significant at $P < 0.05$ and highly significant at $P < 0.01$.

RESULTS:

The various histological and molecular subtypes of invasive breast carcinoma included in the study along with cyclin D1 staining spectrum are listed in Table 1 and Table 2. A total of 352 cases of breast carcinoma were included in the study. Age of the patient ranged from 35 to 67 years, and

all were females. Most common histological subtype reported was Invasive breast carcinoma of no special type (NST), 52% (n=184) of the total cases. Similarly, the most common molecular subtype of breast devised from ER, PR, HER2 and Ki67 status was Triple negative breast carcinoma, 22% (n=78).

Table 3 shows BC cyclin D1 expression and its connection with ER, PR, HER 2, and Ki67. Cyclin D1 moderate to strong staining was found in 173/352 (49.14%) invasive BC patients. Cyclin D1 expression was modestly linked to ER (÷2 = 7.78, P < 0.051) and Ki67 positive (÷2 = 7.27, P < 0.064). Our investigation found 78/352 (22%) triple-negative BC (TNBC) cases (Table 2). 43/78 (55%) TNBC cases had moderate to strong Cyclin D1 positive absent. In 35/78 (44%) TNBC instances, cyclin D1 expression was weak to negative.

Table 1: Cyclin D1 Staining in various histological types of breast carcinomas

Histological Classification	Negative N (%age)	Weak N (%age)	Moderate N (%age)	Strong N (%age)	Total N (%age)
Invasive Breast Carcinoma, NST	51.00(27.71)	49.00(26.63)	42.00(22.82)	42.00(22.82)	184.00(100)
Microinvasive Carcinoma	8.00(30.76)	6.00(23.07)	9.00(34.61)	3.00(11.53)	26.00(100)
Invasive Lobular Carcinoma	4.00(12.50)	10.00(31.25)	11.00(34.37)	7.00(21.87)	32.00(100)
Tubular Carcinoma	7.00(50.00)	3.00(21.42)	1.00(7.14)	3.00(21.42)	14.00(100)
Mucinous Carcinoma	3.00(14.28)	7.00(33.33)	5.00(23.81)	6.00(28.57)	21.00(100)
Invasive Micropapillary Carcinoma	3.00(23.07)	1.00(7.69)	5.00(38.46)	4.00(30.76)	13.00(100)
Carcinoma with Apocrine Differentiation	5.00(38.46)	3.00(23.07)	2.00(15.38)	3.00(23.07)	13.00(100)
Encapsulated Papillary Carcinoma	3.00(27.27)	2.00(18.18)	2.00(18.18)	4.00(36.36)	11.00(100)
Metaplastic Carcinoma	6.00(17.64)	7.00(20.58)	10.00(29.41)	11.00(32.35)	34.00(100)
Adenoid Cystic Carcinoma	0.00(0.00)	1.00(25.00)	0.00(0.00)	3.00(75.00)	4.00(100)
Total	**90.00(25.56)**	**89.00(25.28)**	**87.00(24.71)**	**86.00(24.43)**	352(100)

DISCUSSION

During our research, we investigated the immunohistochemical expression of Cyclin D1 in invasive breast cancer and its correlation with various prognostic factors, such as ER, PR, HER2/Neu, and Ki67 status. Within the range of moderate to strong Cyclin D1 positive, approximately 49.14% of invasive breast tumours met the criteria. There was a correlation that was statistically significant between the expression of Cyclin D1 and the presence of ER and Ki67 positive cells.

It is commonly accepted that cytokine D1 is associated with the development of breast cancer. This is because cytokine D1 stimulates cell proliferation and differentiation by speeding up the transition from G1 to S phase and interacting with nuclear receptors. Using an antibody that is specific to the cyclin D1 protein, it is possible to identify an increased expression of the protein, even in situations where there is no discernible increase in the number of copies that are present.[16] As a result of the findings of our ongoing inquiry, immunohistochemistry was able to identify moderate to strong expression of Cyclin D1 in 173 out of 352 samples, which is equivalent to 49% of the total. The expression of cyclin D1 has been found to be positive in around sixty to eighty-five percent of breast cancer cases, according to a large number of researches.[17-20] One possible explanation for the decrease in expression is that this particular centre does not have access to CCND1 gene amplification services, which are necessary for establishing true negative instances. According to the findings of the current inquiry, there is a significant statistical connection between the expression of Cyclin D1 and the existence of ER and Ki67 positive cells. The results of this study lend credence to the findings of other studies that have demonstrated the influence of cyclin D1 on the maturation and differentiating of cells.[21] Furthermore, the statistical analysis showed that there was no significant correlation between HER 2 positive and cyclin D1 expression (p=0.527). This was the conclusion reached by the researchers. In accordance with the findings of prior research carried out by Peurala et al[22] and Sarkar et al[18], this finding is consistent.

The expression of cyclin D1 was shown to be moderate to strong in 55% (43/78) of breast cancer cases; however, this has not yet been demonstrated to be a predictive factor.[23] In these patients, there was no research that demonstrated a substantial positive cyclin D1 level. Patients do not accept the traditional endocrine treatment offered. In many instances, the proliferation of breast cancer cells is driven by an excessive amount of activity along the cyclin D–CDK4/6 axis. In recent years, there has been a significant advancement in the treatment of cancer through the emergence of strong, selective, and orally accessible CDK4/6 inhibitors. ER-positive breast cancer is the subtype of breast cancer that is most likely to respond favourably to CDK4/6 inhibition. In addition, excess expression of CCND1, a gene that is directly influenced by the oestrogen receptor (ER), is frequently observed in breast tumours that are ER-positive.[24] In the

Table 2: Cyclin D1 Staining in various Molecular subtypes of breast carcinomas

Molecular Classification	Age Category (Years)	Negative N (%age)	Weak N (%age)	Moderate N (%age)	Strong N (%age)	Total N (%age)
Luminal A	35-55	12.00 (29.26)	8.00 (19.51)	8.00 (19.51)	13.00 (31.70)	**41.00 (100)**
	56-65	7.00 (36.84)	4.00 (21.05)	5.00 (26.31)	3.00 (15.78)	**19.00 (100)**
	>65	6.00 (50.00)	3.00 (25.00)	1.00 (8.33)	2.00 (16.66)	**12.00 (100)**
	Total	25.00 (34.72)	15.00 (20.83)	14.00 (19.44)	18.00 (25.00)	**72.00 (100)**
Luminal B Like (HER2 -ive)	35-55	10.00 (27.77)	8.00 (2.22)	11.00 (30.55)	7.00 (19.44)	**36.00 (100)**
	56-65	2.00 (11.11)	7.00 (38.88)	5.00 (27.78)	4.00 (22.22)	**18.00 (100)**
	>65	1.00 (11.11)	4.00 (44.44)	1.00 (11.11)	3.00 (33.33)	**9.00 (100)**
	Total	13.00 (20.63)	19.00 (30.15)	17.00 (26.98)	14.00 (22.22)	**63.00 (100)**
Luminal B Like (HER2 +ive)	35-55	12.00 (27.27)	15.00 (34.09)	8.00 (18.18)	9.00 (20.45)	**44.00 (100)**
	56-65	5.00 (20.00)	6.00 (24.00)	5.00 (20.00)	9.00 (36.00)	**25.00 (100)**
	>65	0.00 (0.00)	1.00 (33.33)	1.00 (33.33)	1.00 (33.33)	**3.00 (100)**
	Total	17.00 (23.61)	22.00 (30.55)	14.00 (19.44)	19.00 (26.38)	**72.00 (100)**
Non luminal (HER2 +ive)	35-55	13.00 (31.70)	7.00 (17.07)	12.00 (29.26)	9.00 (21.95)	**41.00 (100)**
	56-65	6.00 (33.33)	4.00 (22.22)	3.00 (16.67)	5.00 (27.78)	**18.00 (100)**
	>65	2.00 (25.00)	1.00 (12.50)	3.00 (37.50)	2.00 (25.00)	**8.00 (100)**
	Total	21.00 (31.34)	12.00 (17.91)	18.00 (26.86)	16.00 (23.88)	**67.00 (100)**
Triple Negative	35-55	6.00 (13.63)	11.00 (25.00)	16.00 (36.36)	11.00 (25.00)	**44.00 (100)**
	56-65	7.00 (36.84)	4.00 (21.05)	4.00 (21.05)	4.00 (21.05)	**19.00 (100)**
	>65	1.00 (6.66)	6.00 (40.00)	4.00 (26.67)	4.00 (26.67)	**15.00 (100)**
	Total	14.00 (17.94)	21.00 (26.9)	24.00 (30.76)	19.00 (24.35)	**78.00 (100)**

treatment of ER-positive metastatic breast cancer, the Food and Drug Administration has given its approval to three CDK4/6 inhibitors: palbociclib, ribociclib, and abemaciclib. The addition of these drugs to endocrine therapy has resulted in the highest improvement in progression-free survival in this kind of breast cancer; however, in order to clarify this, additional evidence from clinical trials is required.

There were a number of limitations to the study. The pricey technique of FISH was not successful in detecting the amplification of the CCDN1 gene. HER2 was evaluated solely by IHC. Without the use of fluorescent in-situ hybridisation, it was not possible to determine the presence of uncertain HER2 expression 2+ occurrences. It would be

Table 3: Association of ER, PR, HER2 and KI67 status with Cyclin D1 staining

		CyclinD1 Status				Total	P value
		Negative	Weak	Moderate	Strong		
ER	Positive	47.00(25.40)	56.00(30.27)	46.00(24.86)	36.00(19.45)	185.00(100)	0.051
	Negative	43.00(25.74)	33.00(19.76)	41.00(24.55)	50.00(29.94)	167.00(100)	
	Total	90.00(25.56)	89.00(25.28)	87.00(24.71)	86.00(24.43)	352.00(100)	
PR	Positive	39.00(23.92)	40.00(24.54)	43.00(26.38)	41.00(25.15)	163.00(100)	0.851
	Negative	51.00(26.98)	49.00(25.92)	44.00(23.28)	45.00(23.81)	189.00(100)	
	Total	90.00(25.56)	89.00(25.28)	87.00(24.71)	86.00(24.43)	352.00(100)	
HER2	Positive	48.00(26.66)	47.00(26.11)	47.00(26.11)	38.00(21.11)	180.00(100)	0.527
	Negative	42.00(24.41)	42.00(24.41)	40.00(23.25)	48.00(27.90)	172.00(100)	
	Total	90.00(25.56)	89.00(25.28)	87.00(24.71)	86.00(24.43)	352.00(100))	
KI67	Low	43.00(24.71)	35.00(20.11)	45.00(25.86)	51.00(29.31)	174.00(100)	0.062
	High	47.00(26.40)	54.00(30.33)	42.00(23.59)	35.00(19.63)	178.00(100)	
	Total	90.00(25.56)	89.00(25.28)	87.00(24.71)	86.00(24.43)	352.00(100)	

beneficial to conduct longitudinal research on cytokine D1 expression and clinical outcomes. This may improve the statistics regarding the development of Cyclin D1 disease and the prognosis. In breast cancer, it is important to investigate the clinical implications of Cyclin D1 expression. Patients who have a high level of Cyclin D1 expression may be candidates for the investigation of targeted Cyclin D-CDK4/6 axis inhibitors, which could serve to construct individualised therapy regimens.

CONCLUSION

Cyclin D1 has the potential to serve as a prognostic marker. Its inclusion in the standard immunohistochemistry (IHC) analysis of breast cancer cases can assist in the right management of patients, especially with the introduction of new targeted therapies that block the cyclin D-CDK4/6 axis. Cyclin D1`expression in TNBC patients could explore an additional treatment option like selective CDK4/6 inhibitors in these patients. However large scale placebo control, randomized trial are needed to determine prognostic significance in these TNBCs cases.

Authors Contribution:
Tabish Hassan: Data Collection and tabukation
Nadeem Zafar: Topic selection
Akhter Ali Bajwa: Abstract writing
Rabia Ahmed: Data interpretation
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Original Article **Open Access**

Prevalence of Dentine Hypersensitivity in Vital Abutment Teeth being prepared for Fixed Partial Dentures or Crowns

Maria Komil Ghuuman, Miral Shad, Ammara Sharafat, Maira Afzal, Rida Anjum, Saira Ibrahim

ABSTRACT

Objective: To determine the prevalence of dentine hypersensitivity during the preparation of vital abutment teeth for Fixed Partial Dentures or Crowns and its association with patient's gender, age, and location of tooth.

Study Design & Setting: This is a descriptive cross-sectional study of patients with 150 abutments of either crown or fixed partial dentures, carried out in the department of Prosthodontics at Armed Forces Institute of Dentistry (AFID) Rawalpindi from June to December 2021.

Methodology: The Dentine Hypersensitivity was recorded on a VAS (Visual Analogue Scale) of 0-10 after the patient reported pain during exposure to thermal stimulus i.e. cold water from a 5cc syringe at 1cm distance during or just after the tooth preparation.

Results: In this study, the prevalence of Dentine Hypersensitivity was 13.3% with a mean dentine hypersensitivity score (VAS) for cold water test (Mean ± SD) of 0.61±1.756. Independent samples t-tests were used to determine the difference in hypersensitivity between genders, two age groups, and type of tooth (anterior/ posterior). It showed significant results with p-values of 0.002, 0.002, and 0.003 respectively.

Conclusion: Within the limitations of this study, it was highlighted that the preparation of vital teeth for conventional porcelain fused to metal (PFM) crown or fixed dental prosthesis results in dentine hypersensitivity in a considerable number of cases, with a higher incidence in women, younger patients, and vital anterior abutments.

Keywords: Crown, Dentine Hypersensitivity, Fixed Partial Dentures, Vital abutment.

How to cite this Article:
Ghuuman MK, Shad M, Sharafat A, Afzal M, Anjum R, Ibrahim S. Prevalence of Dentine Hypersensitivity in Vital Abutment Teeth beingprepared for Fixed Partial Dentures or Crowns. J Bahria Uni Med Dental Coll. 2024;14(4):262-7 DOI: https://doi.org /10.51985/JBUMDC2024390

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Received: 14-06-2024 1st Revision: 06-09-2024
Accepted: 20-09-2024 2nd Revision 12-09-2024

INTRODUCTION:

Sensitivity is a quite common yet complex condition that continues to challenge dental professionals and affect patients' quality of life. It is a complicated variable and has many controversies existing around the ideal or correct terminology. A few such terms are 'dentine sensitivity', 'dental sensitivity' and 'hypersensitivity'. However, there is no evidence that the dentine labelled as hypersensitive will histologically differ from a normal dentine and not all exposed dentine causes sensitivity. The pulpal response of a hypersensitive tooth does not differ from a normal one.[1] Among pulpal responses, sharp pain for a short duration elicited due to dentine exposure is described as dentine hypersensitivity. This pain, although transitory, can surely impact the quality of daily life. Dentine sensitivity can adversely affect the simple day to day activities by making it difficult to eat, drink, speak, or perform oral hygiene measures which might trigger sensitivity.[2] Various factors, directly or indirectly, may affect its occurrence like age, gender, type, and position of tooth. When replacing missing tooth structure in younger individuals, the abutments are mostly vital.[3] Interestingly, dentine hypersensitivity is not a widely studied condition, especially in the context of tooth preparation for crowns and FPDs. Research on this subject remains limited despite

its importance, given that vital abutment teeth are often preferred for prosthetic rehabilitation. Few studies have focused on the incidence of dentine hypersensitivity after tooth preparation. Gumus HO found the total incidence of pulpal exposure to be 0.66% (80 teeth with pulp exposure out of 11993 preparations).[4]

Evaluation of pulpal health is of paramount importance before any restoration-involving crown or bridges.[5] Replacement by fixed dental prosthesis is a favorable choice due to numerous advantages like quick fabrication, the familiarity to both the dentist and the patient, satisfactory mechanical properties, comparable natural contour, comfort, function, aesthetics, speech, and health. However, if the preparation goes in too deep there could be several adverse effects like sensitivity, pulp necrosis, caries, periodontitis, and root fractures. It is postulated that the fixed dental prosthesis with vital abutments can comparatively have a higher survival rate and mean life span as well. The reason behind this fact may be that endodontic failure, which is the leading cause of failure of non-vital abutments, is not among the causes of failure in vital abutment teeth being prepared for the same restoration[1,5].

Despite following recommended protocols for tooth preparation, sensitivity can still occur, particularly in cases involving vital abutment teeth. The decision to proceed with elective endodontic treatment or to preserve tooth vitality is a critical one that must be made by weighing the risks and benefits. Many prosthodontists elect to perform root canal treatments before preparing teeth for crowns or FPDs, especially when achieving parallelism and proper alignment is challenging. However, it is not always necessary to devitalize teeth that are not severely mal-positioned or supra-erupted, as doing so can increase the risk of hypersensitivity and compromise the strength of the abutment. Dentin sensitivity has remained an ongoing clinical challenge that significantly impacts both the quality of life for patients and the practice of clinicians.[6]

The rationale of this study is to identify the predisposing factors associated with dentine hypersensitivity in the Pakistani population, specifically in patients undergoing tooth preparation for crowns or FPDs. By understanding these factors, clinicians can make more informed decisions about whether to preserve the vitality of abutment teeth or proceed with elective endodontic treatment before preparing it for a crown or bridge. The findings of this study are expected to contribute to the existing body of knowledge on dentine hypersensitivity and help guide clinical practice in managing this very common but challenging condition.

METHODOLOGY:

This is a cross-sectional study conducted in department of Prosthodontics at Armed Forces Institute of Dentistry over a period of 6 months from June to December 2021. After obtaining ethical approval from the Ethical Board Committee and written consent from the participants the data was collected using nonprobability consecutive sampling technique. Participating patients of both genders, within age range of 21-50 years and having vital abutment teeth (both anteriors and posteriors) undergoing rehabilitation by fixed partial dentures (FPDs) or single crowns were included in the study. Patients with endodontically treated, periodontally compromised, malposed, tilted, supra erupted, attritioned, previously carious, heavily restored abutment teeth or teeth with short clinical crowns were excluded from the study. Patients with neuromuscular diseases like Parkinsonism and dental phobia were also not included.

The sample size (n) of 150 was calculated using World Health Organization sample size calculator with the absolute precision of 0.1, confidence level of 95%, mean 3.36 and standard deviation of 1.26.[3] And a total of 80 abutments of male and 70 abutments of female patients were included in the study following the exclusion and inclusion criteria.

The vital teeth selected as abutments for single crowns or primary abutments for fixed partial dentures were prepared following the standard protocols for tooth preparation for PFM crown or FPD.[7] Teeth were prepared by a single operator using diamond burs with a high-speed hand piece under an air and water coolant. Occlusal reduction of approximately 1.5 mm for non-functional cusp and 2.0 mm for functional cusp, followed by a buccal subgingival shoulder margin of 1.5 mm and lingual supra gingival margin with chamfer of 0.5mm.

Sensitivity was recorded on exposure to cold water from a 5cc syringe for 5 seconds at a distance of 1 cm by the same operator immediately after the tooth preparation for fixed partial dentures or single crowns. The pain was recorded on VAS from 0- 10 0= no pain, 4-7 moderate pain, 8-10= severe pain. VAS is a dependable measure because the amount of pain in one patient can be measured by the operator multiple times (at least twice) and outcomes of each test for that individual will correlate well. [3]

RESULTS:

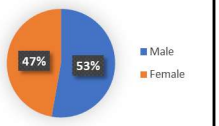
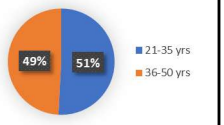
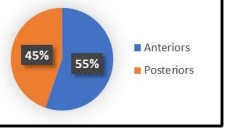
The data was compiled for a descriptive statistical analysis using SPSS (version 23.0). Qualitative variables like gender, frequency, percentage and quantitative variables like age, dentine sensitivity (on VAS) was calculated. Effect modifiers like age and gender were controlled through stratification. Age of the patients was stratified into two groups: 21-35 years of age and 36-50 years of age. Stratification on type of tooth included anterior teeth (Incisors and canines) and posterior tooth (premolars and molars). Independent Sample T-test was used post stratification, for calculating dentine hypersensitivity with respect to considered variables. P-value of = 0.05 was considered significant.

The frequency of distribution of patients according to considered variables for this study are shown in Table-1 Mean ± SD Hypersensitivity as VAS score for cold water

test performed during the tooth preparation phase is stated in Table-2.

Independent samples t-test was used to determine the difference in hypersensitivity (VAS score) between the considered variables are shown in Table-3, 4 and 5 respectively. Our study clearly shows that women, anterior teeth and younger age group reported significantly higher sensitivity.

Percentage Distribution of Patients with Dentine Hypersensitivity

Considered variables	Distribution (n= 150)	
Gender Male Female	 80 (53.3 %) 70 (47.7 %)	
Age Group 21-35 years 36-50 years	 74 (49.3 %) 76 (50.7 %)	
Type of Tooth Anterior Posterior	 83 (55.3 %) 67 (44.7 %)	

Mean Hypersensitivity		
VAS Score	Mean	Standard Deviation
10	0.61	1.756

Following figure shows the prevalence of sensitivity in our sample size

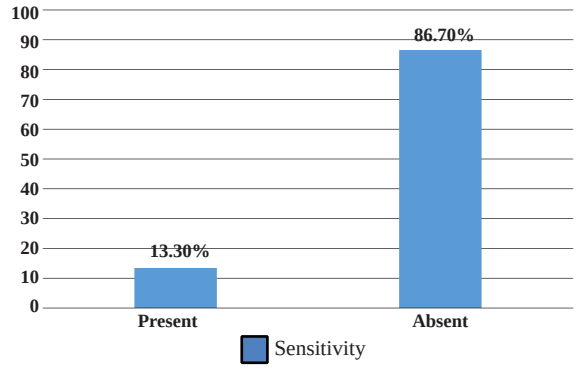


Figure: Prevalence of Sensitivity in study subjects

Table 3: Hypersensitivity (VAS score) in relation to gender

Gender	Cold Water Test (VAS Score) (mean ± SD)	Independent Sample T-test p- value
Male	0.18 ± 0.725	0.002
Female	1.11 ± 2.362	

Table 4: Hypersensitivity (VAS score) in relation to patient age groups.

Age Group	Cold Water Test (VAS Score) (mean ± SD)	Independent Sample T-test p- value
21- 35 years	1.07 ± 2.241	0.002
36- 50 years	0.17 ± 0.915	

Table 5: Hypersensitivity (VAS score) in relation to teeth.

Type of Tooth	Cold Water Test (VAS Score) (mean ± SD)	Independent Sample T-test p- value
Anterior Tooth	1.07 ± 2.241	0.002
Posterior Tooth	0.17 ± 0.915	

DISCUSSION:

Dentine hypersensitivity has been documented to have anincidence in the range of 4 to 74%. This wide variation is due to differencesin the target population, selection criteria, and the method of assessment or diagnosis.[8] A different study supports this wide range of prevalence, showing results between 3-98%.[9] Yet again a novel study anticipates the prevalence of dentine sensitivity spread over a spectrum between 4.8% and 62.3%.[10]

Dentine hypersensitivity is more commonly reported in women than in men. The reason behind this was found to be thefact that women have lower pain threshold, and they have less tolerance to noxious stimuli. Dentine hypersensitivity was most commonly found in age 20- 40 but predominantly during the third decade owing to increased dentinal thickness in old age due to continued formation of secondary dentine and sclerosed pulp chambers leading to decreased dentine permeability.[3,4,11] It has also been reported that anterior teeth, having less enamel thickness, have higher dentine hypersensitivity than posterior teeth.[4, 8, 11, 12, 13, 14]

In this prosthesis, porcelain is veneered to a cast metalsubstructure which perfectly fits over prepared tooth. A minimal reduction of 1.5mm is usuallyindicated (0.3 - 0.5mm for metal and 1.0 - 1.2mm for porcelain). The adequate thickness of porcelain is necessary to create asense of colour depth and translucency and to hide the metalsubstructure and this thickness of metal framework isnecessary for adequate mechanical strength and durability of FDPs.[7] However, there is no possible means of clinically checking the residual dentine thickness during tooth preparation.[1]

Extensive studies have been undertaken to elucidate the causes of dentine sensitivity. Direct Innervation Theory and Odontoblastic Transducer Theory have been widely rejected.[15] and the Hydrodynamic theory better explains the physiology behind dentine sensitivity.[2] First proposed by Gysi and later reinforced by Bra¨nnstro¨m, this theory suggestswhen exposed dentine surface is subjected to a stimulus, whether

thermal, chemical, tactile or evaporative, there is a change in the dentinal fluid flow of dentine tubules. This movement of dentine fluid inside the tubules leads to apressure change, exciting the pressure sensitive nerve receptors across the dentine.[16] During a full crown preparation approximately 1-2million tubules are exposed, and it is found that dentine sensitivity is strongly associated with the number and diameter of exposed dentinal tubules and on the type and duration ofthe stimulus. [17] Most commonly used methods to check for sensitivity are the use of air jet from an air water syringe or using cold water from a 5cc syringe for cold stimulus.It is found that a cold sensation is the most common stimulus in triggering hypersensitivity in patents [9, 16, 18]. A few precautions during tooth preparation, like cooling to counter the heat generation with anair water syringe, keeping dentine wet to prevent desiccation, maintaining thickness of dentine can be applied to reduce this incidence. Two different studies by Davis GR and Stanley and Swerdlow concluded that residual thickness of dentine of more than 2mm aftertooth preparation is required for maintaining vitality of tooth and the remaining thickness of dentine is inversely proportional to pulpal response.[1,7]

Crowns or FPDs are considered as one the most reliable, dependable, convenient and sought-after treatment options in prosthodontics whereas vital teeth have long been considered as preferable abutments because of their intact proprioception. Significantly, there is considerable tooth structure loss during the tooth preparation. In clinical situations like these, the dentist has to make a critical decision, by weighing the risks against benefits of keeping the tooth's vitality intact or carrying out elective endodontic treatment. Many prosthodontists elect to undertake the latter option to ensure that principles of parallelism and correct alignment are achieved before fabricating crowns and FPDs. However, it is not necessary to devitalize intact teeth that are neither supra-erupted nor tilted, as such intervention may increase the chances of sensitivity and compromise the strength of the abutment. [19, 20] A group of clinicians have evaluated incidence of possible endodontic complications during and immediately after tooth preparation phase for PFM fixed dental prosthesis to be around 3-38%.[21] The tooth preparation for porcelain fused to metal FPDs requires a considerable amount of removal of tooth structure, a minimum of 1.5 mm (0.3-0.5mm for the metal substructure and 1.0-1.2 mm for the porcelain layer) has been recommended. And the pulp vitality can be maintained in abutments if principles of tooth preparation are strictly adhered to. Maintenance of vitality of the dentine and minimal pulpal damage are the most important biological considerations in tooth preparation.[7] Despite following the guidelines for tooth preparation like minimal tooth preparation, preservation of biological width, minimizing thermal and mechanical trauma, some complexities may be faced during the preparation of vital abutment teeth. Tooth preparation leaves dentine tubules open, exposing them to noxious stimuli like bacteria, desiccation, cold and heat. Heat is also generated as a result of contact of cutting instruments on tooth structure. [7,22]

Additionally, removal of surface moisture from prepared vital tooth surface due to exposure to air i.e., desiccation can result in extreme sensitivity. Regardless of following the ideal guidelines, there is always a threat to the integrity of vital pulp during the preparation of abutment teeth as all the steps involved have a potential for irritating the vital pulp. [21] The pulpal response to these different procedures is however cumulative.

This study reported a prevalence of sensitivity of 13.3% based on the selected sample size of 150, with a mean ±SD of VAS of 0.61±1.756. A previously documented study showed that there is a wide range (4-74%) in prevalence of dentine hypersensitivity, due to extensive variation in the target population, selection criteria, and the method of assessment or diagnosis. [23] The incidence of any postoperative complication after the tooth preparation is usually undervalued by most dentists. In our study, a higher incidence of sensitivity in a younger age group (age 21-35 years) was observed, as compared to the older age group (36-50 years), P-value=0.002. These results were reinforced by another study by Blaizot et al. reporting highest occurrence of dentine hypersensitivity in the third decade. [11, 23] The reason was attributed to the continued formation of secondary dentine and sclerosed pulp chambers in old age, leading to a decreased dentine permeability and subsequently decreased dentine hypersensitivity. [7, 16] This is further underscored by an in-vitro study by Davis et al who used microtomography and calculated the amount of residual dentin thickness after tooth preparation and found a significant increase in sclerosed pulp chambers in older individuals. [1]

The study revealed a meaningfully higher incidence of sensitivity in female patients with a *p* value=0.002. Therefore, this study reinforces the results of other studies reporting the same.[3, 4] Epidemiological studies have shown that women and men experience and cope with pain and sensitivity differently due to hormonal variation, puberty, reproductive status, and menstrual cycle affecting their pain threshold and perception.[5]

Furthermore, it was reported that anterior teeth, including incisors and canine, showed a significantly higher incidence than posterior teeth, including premolars and molars (P value= 0.003). This has been observed even after strictly following the guiding principles of tooth preparation, maintaining the vitality in anterior teeth was challenging when compared to posterior teeth. Another study conducted by Hammad on the Pakistani population reinforces this statement.[24] It was established that the vitality of most of the posterior teeth being prepared for fixed prosthesis can be preserved without requiring endodontic treatment, if proper guidelines are followed. The results are attributed

to the fact that anterior teeth are smaller in size, having an overall thin layer of enamel and dentine as compared to the posterior teeth. It was affirmed by some studies that the teeth most prone to Dentine Hypersensitivity are canines and premolars. [7, 20] Cheung et al signified further that molars can better tolerate pulpal trauma during tooth preparation than premolars. [25]

Nowadays there is a growing trend towards using minimally invasive preparation methods like air abrasion and laser and fabricating minimum preparation prosthesis thereby decreasing the incidence of dentine hypersensitivity. Also the adoption of digital dentistry tools, such as CAD/CAM systems, is on the rise enhancing the accuracy of crown preparations, potentially reducing the risk of hypersensitivity by ensuring more precise tooth reductions and a better fit for crowns.[7]

The findings of our study, however, cannot be applied to the general Pakistani population, owing to the limited sample size and a certain number of people having access to treatment in this institute. It is felt that further studies in this field are necessary to ascertain the exact prevalence of sensitivity in the Pakistani population keeping in view the significance of the considered variables.

CONCLUSION:

Within the limitations of this study it was concluded that the preparation of vital teeth for conventional porcelain fused to metal crown and fixed dental prosthesis can result in sharp, transient pain known as dentinal hypersensitivity. In our study a prevalence of 13.3% was calculated in a sample size (N) of 150. It was further observed that women, patients of younger age group or patients with prepared anterior teeth reported more dentine hypersensitivity than men, patients of older age group or patients with prepared posterior teeth just after tooth preparation. Needless to say, the low prevalence of hypersensitivity suggests that operators can perform tooth preparation without elective endodontic treatment in most of the cases. Multiple factors, individually and collectively, play a role in the phenomenon of dentine hypersensitivity, which needs further exploration.

Authors Contribution:
Maria Komil Ghumman: Conception and Design of Study, Drafting of Manuscript, Acquisition of Data
Miral Shad: Drafting of Manuscript, Acquisition of Data
Ammara: Analysis and Interpretation of Data
Maira Afzal: Analysis and Interpretation of Data
Rida Anjum: Critical Review of Manuscript
Saira Ibrahim: Critical Review of Manuscript

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Original Article **Open Access**

Efficacy and safety of Dapagliflozin and Glimepiride in combination with Metformin: Randomized clinical trial

Muhammad Kamran Yousuf, Khalid Mustafa Memon, M. Sajid Abbas Jaffri, Mehar Fatima, Mamoora Arslaan, Shizma Junejo

ABSTRACT:

Objective: To identify the effective treatment option between dapagliflozin-metformin and glimepiride-metformin combination in patients with type 2 diabetes who were inadequately controlled with metformin monotherapy.

Study design and setting: The present study is randomized, conducted for 12 weeks at the National Medical center, Karachi, Pakistan.

Methodology: The patients were divided into 2 treatment groups; group A was given dapagliflozin-metformin combination, while group B was given glimepiride-metformin combination. The efficacy endpoint of groups was estimated by hemoglobin A1c and fasting blood glucose levels at 0-, 6- and 12-week. While, safety endpoints were identified by analyzing liver function tests, lipid profile tests, renal function test, and urine analysis. The significant difference of data was analyzed by using statistical package of social sciences (SPSS) version 25. The parametric t-test and paired t-test were performed and considered p-value = 0.05 as statistical significant.

Results: Baseline demographics, clinical features of diabetes, levels of liver enzymes, liver function test, renal function test, lipid profile, and urinalysis of randomized patients were similar in both treatment groups by showing p = 0.05. Followed by the initiation of the respective treatment, the baseline change of mean FBG and hemoglobin A1c levels with dapagliflozin-metformin combination was shown significantly reduce more compared to glimepiride-metformin combination (p = 0.05).

Conclusion: Dapagliflozin-metformin combination therapy was superior and well-tolerated to regulate glycemic control as compare to glimepiride-metformin combination.

Keywords: Type 2 diabetes mellitus, glimepiride, dapagliflozin, fasting blood glucose, glycated hemoglobin

How to cite this Article:
Yousuf MK, Memon KM, Jaffri MSA, Fatima M, Arslaan M, Jenejo S. Efficacy and safety of Dapagliflozin and Glimepiride in combination with Metformin: Randomized clinical trial. J Bahria Uni Med Dental Coll. 2024;14(4):268-73 DOI: https://doi.org/10.51985/JBUMDC2024437

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Received: 28-07-2024
Accepted: 31-09-2024 1st Revision: 30-09-2024

INTRODUCTION

Diabetes mellitus is a chronic metabolic condition defined by insulin resistance that prevents glucose uptake into the cells and ultimately causes hyperglycemia over a prolonged period. Currently, around 463 million people live with diabetes and produce drastic effect on health of individuals of all ages.[1] Therefore, the focus of attention of medical practitioners and researchers is to highlight the agents that control the blood sugar level of type 2 diabetes (T2D) patients and having a decreased probability of causing hypoglycemia and weight loss. According to the American Diabetes Association (ADA) recommendation, metformin is the first-line treatment prescribed in T2D that requires maintaining glycated hemoglobin (hemoglobin A1c) below or around 7%. However, modifications in treatment are strictly needed if the target to maintain hemoglobin A1c is not achieved at maximal tolerated dose over the use of 3 to 6 months. This modification involves the addition of a second oral anti-diabetic drug or initiation of subcutaneous administration of basal insulin.[2] Many FDA-approved therapies control blood sugar levels,[3] but the elucidation of safety and efficacy profile between dapagliflozin-metformin

and glimepiride-metformin combination in patients with type 2 diabetes was unfocused.

Many studies have compared the safety and efficacy profile of sulfonylurea-metformin and SGLT-2 inhibitor-metformin in patients with type 2 diabetes inadequately controlled with metformin. Nauck MA and colleagues compared dapagliflozin *vs.* glipizide (sulfonylurea) in combination with metformin over 2 years. They found greater glycemic stability, weight loss, reduced systolic blood pressure, and low hypoglycemia but frequent genital and urinary tract infections in dapagliflozin-metformin compared with other combinations.[4] Cefalu WT and Del Prato S colleagues study the same combination for 54 weeks and 4 years, respectively, and found consistent results.[5,6] Moreover, Ridderstråle M and colleagues study canagliflozin (SGLT-2 inhibitor) *vs.* glimepiride (sulfonylurea) in combination with metformin and revealed the greater reduction of HbA1c level in canagliflozin group than glimepiride.[7] And Nauck MA and colleagues study empagliflozin-metformin *vs.* glimepiride-metformin and found empagliflozin effective and a well-tolerated option.[8] However, the comparation of dapagliflozin-metformin *vs.* glimepiride-metformin combination was a neglected area.

The clinical studies reveal that glimepiride exhibits a lower association with hypoglycemia and increase weight.[9] Furthermore, it is safer to prescribe in T2D patients suffering from cardiovascular disease (CVDs). It does not produce an effect in the ischemic preconditioning, which is defined as an adaptive physiological mechanism in response to an ischemic event. This eventually delays cardiac infarction and prevents cardiac tissue injury.[10] On the other hand, SGLT-2 inhibitors are also the possible option for the treatment of diabetes and produce a definitive role in the management of diabetes-mediated heart failure. Remarkably, dapagliflozin is the latest generation of anti-diabetic drug and the first FDA-approved regimen for treating heart failure compared with other SGLT-2 inhibitors.[11] The number of studies has highlighted its more prominent role over other SGLT-2 inhibitors to cardiac safety and considered it for opening future floodgates by repurposing from anti-glycemic drugs to anti-heart failure medicine[12,13].

Taken all together, both of these drugs are promising add-on pharmacotherapies, but the selection of effective therapy between these two is a neglected area. Therefore, the present study aimed to study the efficacy and safety profile of dapagliflozin-metformin *vs.* glimepiride-metformin in type 2 diabetes patients given maximum tolerated dose of metformin monotherapy. To the best of our knowledge, this comparative analysis was not investigated before.

METHODOLOGY:

The present study is a randomized control trial conducted for 12 weeks at the National medical center, Karachi, Pakistan. A total of 200 diabetic patients were enlisted in which 190 patients were randomly enrolled according to inclusion criteria and completed the study successfully. The patients were assigned numbers from 1 to 190, and then they were randomly selected using a Google random number generator to be part of either group A or group B. A total of 95 patients were selected for each group. A double-blind method was used to ensure that neither the patients nor the researchers assessing the outcomes were aware of the assigned groups. The patients of group A were taken a fixed dose of 10 mg of dapagliflozin with 500 mg of metformin orally, while the patients of group B were taken 4 mg of glimepiride with 500 mg of metformin orally thrice a day throughout the 12-weeks of treatment. They were strictly restricted to a sugary diet in their meal. Initially, the approval of protocol was obtained by Ethical Research Committee (ERC) of Bahria University, and the written informed consent taken from all the enrolled participants.

The inclusion criteria were based on normal baseline levels of LFT, RFT, lipid profile, and white blood cell count (WBC). The fasting blood glucose (FBG) levels of all recruited participants were = 126 mg/dL, and hemoglobin A1c levels were >7-10%, followed by 1500 mg/day metformin monotherapy last 3 to 6 months. The exclusion criteria were based on hypertension, decompensated or acute congestive heart failure, estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, left ventricular ejection fraction (LEVF) less than 40%, liver impairment, terminal illness, or cancer.

The sample size for the frequency of population was calculated by using the OpenEpi, Version 3. [14] The efficacy endpoints of groups were estimated by quantifying glycated hemoglobin (Hemoglobin A1c) and FBG levels at 0-, 6- and 12-week of treatment. Safety endpoints were identified by analysing levels of LFT, RFT, lipid profile, urinalysis, and hypoglycemic events.

The hypoglycaemic events were divided into five definitions as per the glucose level and symptoms; (i) FBG level = 70 mg/ dL, (ii) FBG level = 54 mg/Dl, (iii) FBG level = 50 mg/dL, (iv) FBG level = 70 mg/dL but an asymptomatic hypoglycaemic event, and (5) FBG level > 70 mg/dL but with another hypoglycaemic episode.

The statistical significance of data was analyzed using the IBM statistical package of social sciences (SPSS) version 25. All quantitative parameters such as FBG, hemoglobin A1c, liver enzymes, bilirubin, lipid profile, blood pressure, and body mass index (BMI) were presented in mean ± standard deviation (SD). The parametric t-test and paired t-test were performed to estimate the significant clinical difference between pre and post findings. P-values less than 0.05 were considered significant in the study.

RESULTS:

All participants in this study were between the age group of 45-55 years. Baseline demographics and clinical diabetes

characteristics of randomized patients were the same in both treatment groups. All patients were Asian and belonged to Karachi, Pakistan, in which a total of 50% were male, and 50% were female. At baseline, the mean age and BMI were 56± 4 years, 31±2.15 kg/m2, respectively. All enrolled patients were previously taking metformin monotherapy of =1500 mg, once or twice in 24-hours from the last 3 to 6 months, and had insignificant FBG and haemoglobin A1c levels between groups at week-0 shown in table 1. Furthermore, the lipid profile, LFT, RFT, and urinalysis levels were similar in both groups, as depicted in Figures 1,2, 4 and 4, and table 3.

The baseline change of mean FBG at 6-week of treatment with dapagliflozin- metformin and glimepiride-metformin combination were shown 137.02±12.30 and 146.23±12.54 levels, and at 12-weeks of treatment were shown 101.40±16.85 and 121.89±9.22 mg/dL levels, respectively. Whereas, mean of baseline hemoglobin A1c at 0-week with dapagliflozin- metformin and glimepiride-metformin combinations were 7.83±0.54 and 8.21±0.45 %, respectively and, at the end of the study (at 12-week) this were 6.91±0.74 and 7.91±0.49 %, respectively. The change in glycemic levels was significantly greater (*P*= < 0.001) in group A compared to group B at 6- and 12-week, thereby demonstrating the superiority of dapagliflozin-metformin over another treatment regimen. A slightly more shift in FBG levels was achieved, followed by the first 6 weeks of dapagliflozin-metformin combination. The glimepiride-metformin combination treatment showed increased reduction at week-12, as shown in Table 1.

Table 1: Glycemic profile at intervals of 0-, 6- and 12-week in treatment regimens

	Dapagliflozin-Metformin (Mean±SD)	Glimepiride-Metformin (Mean±SD)	Mean Difference	P-Value
FBG (mg/dL)				
At Week 0	184.05±14.82	178.19±9.04	5.86	0.067[S]
At Week 6	137.02±12.30	146.23±12.54	-9.210	0.000 [S]
At Week 12	101.40±16.85	121.89±9.22	-20.49	0.000[S]
HbA1c (%)				
At Week 0	7.83±0.54	8.21±0.45	-0.377	0.075[S]
At Week 12	6.91±0.74	7.91±0.49	-1.000	0.000[S]

FBG: Fasting blood glucose, HbA1c: haemoglobin A1c, SD: standard deviation; [S]: statistical significant

Table 2: Blood pressure and body mass index at intervals of 0-, 6- and 12-week in both treatment regimens

	Group A (Mean±SD)	Group B (Mean±SD)	Mean Difference	P-Value
SBP				
At Week 0	184±14.82	178±9.04	5.86	0.052
At Week 6	137±12.30	146±12.54	-9.210	0.064
At Week 12	101±16.85	121±9.22	-20.49	0.073
DBP				
At Week 0	95±0.25	98±0.12	-0.377	0.075
At Week 6	93 ±0.73	97±0.37	-1.000	0.062
At Week 12	92±0.89	98±0.69	-1.000	0.082
BMI				
At Week 0	31±2.15	31±2.15	-0.377	0.071
At Week 6	30±1.82	31±1.06	-1.000	0.052
At Week 12	30±6.12	30±9.15	-0.200	0.08

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, [S]: statistical significant

The safety and tolerability profiles in treatment arms were identified. The analysis was shown that patients did not significantly experience adverse hypoglycemia in both groups during the entire study period of 12-week. No clinically meaningful lipid profile changes were observed between the dapagliflozin-metformin combination group and the glimepiride-metformin group at 12-week by showing p-value >0.05, as depicted in figure 1. Furthermore, insignificant LFT and RFT changes were found in the dapagliflozin-metformin combination group at 6- and at 12-week compared to the glimepiride-metformin combination group (Figure 2 and 3).

Furthermore, urinalysis of A group and B group at 6- and 12-week were similar (Figure 4 and Table 3). In group A, an increased concentration of ketone was found in one patient. Whereas the patient continued the prescribed study regimen. None of the profound adverse effects was observed in both groups.

DISCUSSION:

The present study compared the efficacy and safety profile of dapagliflozin-metformin with the glimepiride-metformin combination is used glycaemic control in type 2 diabetes patients of Karachi, Pakistan. Dapagliflozin-metformin combination was lead to superior improvements in glycaemic management than other treatment regimens followed by 12-week treatment. Previously, many studies have compared the safety and efficacy profile of sulfonylurea-metformin and SGLT-2 inhibitor-metformin in patients with type 2 diabetes who are inadequately controlled with metformin, [4-8]. But none of them reported glimepiride-metformin and dapagliflozin-metformin combination.

Table 3: Glycosuria at 0 week, 6 week and 12 week in treatment regimens

		Mild (n = %)	Moderate (n = %)	Severe (n = %)
Group A	At Week 0	97 (97)	3 (3)	0 (0)
	At Week 6	12 (12)	82 (82)	6 (6)
	At week 12	2 (2)	9 (9)	89 (89)
Group B	At Week 0	96 (96)	3 (3)	1 (1)
	At Week 6	98 (98)	2 (2)	0 (0)
	At week 12	99	1	0

Figure 1: Lipid Profile at week 0, 6 and 12 in both treatment groups.

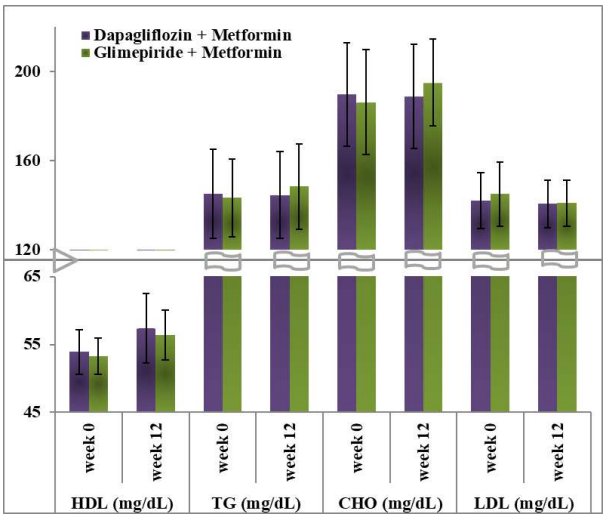
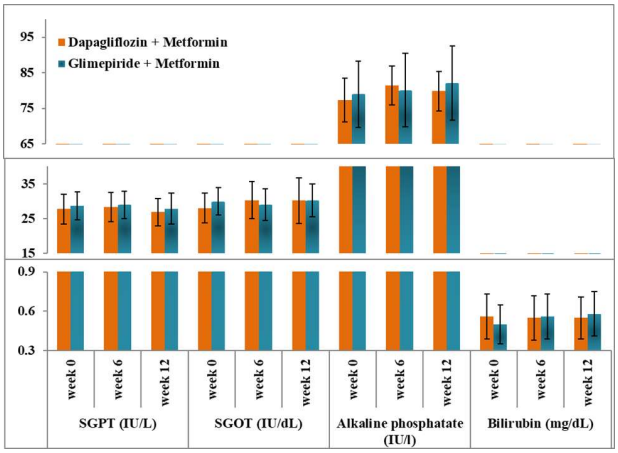


Figure 2: Liver function test at week 0, 6 and 12 in both treatment groups



The glycemic control analysis showed decreased FBS and hemoglobin A1c levels from baseline to week 12, and superiority was met for dapagliflozin-metformin compared with the glimepiride-metformin combination. No statistically significant differences between groups were found for lipid profile, LFT, RFT, urinalysis, and hypoglycaemic events during the complete study. Dapagliflozin-metformin therapy reduced baseline FBS level to a greater extent than glimepiride-metformin combination therapy at week 6. But, both treatment regimens were well tolerated. The findings of glycemic control of dapagliflozin-metformin combination are similar to previously reported study of Bailey CJ and colleagues. They enrolled 546 patients for 102 weeks and given them 2.5 to 5 and 10 mg of dapagliflozin monotherapy. Their results were shown changes from baseline HbA1c from all the treatment doses.Moreover, all dapagliflozin groups sustained decline in baseline FBG levels and weight without producing prominent hypoglycemia. In contrast,

Figure 3: Renal function test at week 0, 6 and 12 in both treatment groups

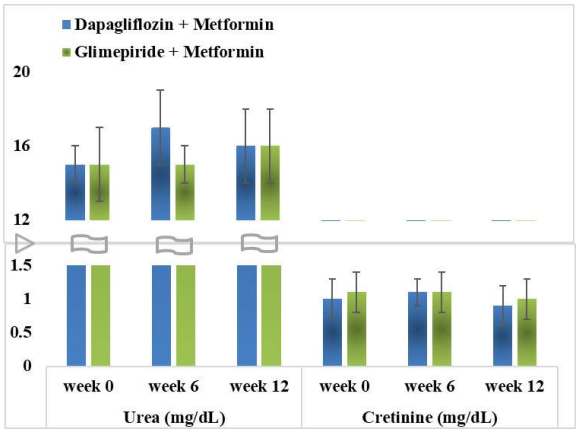
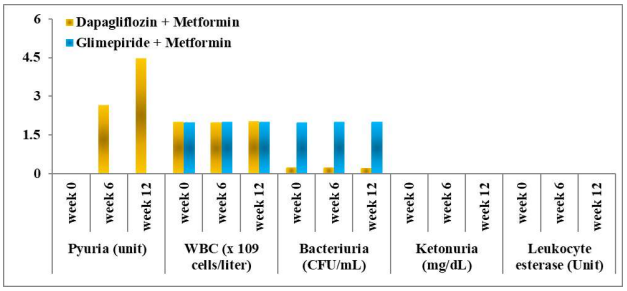


Figure 4: Urinalysis at week 0, 6 and 12 in both treatment groups



some patients experienced genital infections . Another study conducted by Rosenstock J and colleagues is also consistent with our findings. They identified a significant decrease in HbA1c levels in SAXA+DAPA+MET, SAXA+MET, and DAPA+MET combinations. Whereas less than 1% of Urinary and genital infections found in patients receiving SAXA+DAPA+MET combination and hypoglycemia was infrequent, with no episodes of major hypoglycemia. Besides, our results were in accordance with previously reported comparison study of dapagliflozin and many other SGLT-2 inhibitors with sulphonylureas.[4-8]

Dapagliflozin-metformin combination was insignificantly decreased BMI, compared with other therapy which insignificantly increases weight during treatment. Furthermore, the dapagliflozin-metformin combination reduced systolic blood pressure insignificantly. Sjöström CD et al. and Yamout H et al. in their study highlighted the similar effect, and another investigation was concluded that these effects possibly due to the natriuretic, osmotic, and weight-decreasing property of SGLT-2 inhibitors.[17-20] The insignificant findings in the present study may be due to the short period of treatment, and the long-term study will define it more clearly. The earlier study conducted by and colleagues emphasized the importance of control blood pressure in T2DM patients; they analyzed data of 10 mg dapagliflozin as monotherapy and combination therapy and highlighted that increase in blood pressure is greatly associated with

decreased risk of micro-and macro-vascular diabetic impairments, including cardiovascular disease (CVDs).[21]

This study revealed the combination therapy of dapagliflozin-metformin was well tolerated compared to previous studies that reported mild or moderate intensity of urinary tract and tract genital infections in patients who were taking dapagliflozin.[22,23] Numerous hypotheses have been proposed for the underlying mechanism of infection, but the simplest being is the production of glycosuria mediated by SGLT-2 inhibitor.[24]

The preliminary study was shown the transient reductions of lipid profile by SGLT-2 inhibitors, but the present study revealed that patients receiving dapagliflozin-metformin combination experienced insignificantly reduced cholesterol, LDL, and TG than patients receiving the glimepiride-metformin combination; this may be due to the short duration of treatment. Furthermore, the study criteria for withdrawal because of the high lipid profile were strict and modified the treatment if TG, CHO, and LDL-c level were not reversed within 1-week of biochemical analysis. Earlier findings have revealed the reversible effect of SGLT-2 inhibitors on lipid profile and suggested its association with decreased risk of CVDs.[11,12,17]

In the present study, mild hypoglycaemic events occurred in 1 patient out who was given glimepiride-metformin combination. There were substantially no events found in patients taking dapagliflozin-metformin variety. These findings are in line with the previous study of Nauck MA and colleagues.[24] The increase in induction of hypoglycemia is the critical adverse effect of glimepiride-metformin combination therapy, which is greatly associated with various life-threatening complications. Around six times increase mortality rate has been observed attributed to hypoglycemia-mediated impairments, acute neurocognitive dysfunction, retinal cell death, cerebrovascular disease, vision loss, and myocardial infarction. Moreover, it compromises the life quality by producing insomnia, inactiveness in the workplace, and decrease interest in recreational activities (exercise and travel). The clinical spectrum of glimepiride-metformin increases the burden of hypoglycaemia.[25] While none of the hypoglycaemic episodes is the imperative advantage to select dapagliflozin-metformin combination therapy for the treatment of inadequate glycemia. Taken all together, the practical disadvantage of dapagliflozin-metformin combination regimen was not found relative to the glimepiride-metformin combination, which needs constant glucose monitoring and careful titration to maintain good glycemic control.

A key strength of this study is the comparison between dapagliflozin-metformin and glimepiride-metformin combinations for the treatment of glycemia in poorly controlled T2DM patients. This is the first study regarding the comparative effect of these two frequently prescribed medicines to the best of our knowledge. Efficacy of present pharmacological treatment for FBS and hemoglobin A1c were performed. The drug groups' safety profile was closely observed in hepatic functions, urinary tract, and cardiovascular system at intervals of 6th and 12th- week. While possible limitations of the current study include the failure to monitor the long-term efficacy and safety profile of study treatments on liver and heart physiology and heart and restricted population size.

The study included 190 participants, which is a reasonable sample size, but increasing the sample size could improve the generalizability of the findings. Furthermore, the study's results highlight the significance of using the dapagliflozin-metformin combination, which resulted in better improvements in managing blood sugar levels compared to other treatment regimens. Conducting a multi-centre study would allow for a more diverse population to be included and would provide valuable insights on this topic.

CONCLUSION:

In conclusion, dapagliflozin-metformin therapy was superior to the glimepiride-metformin combination in terms of reductions in FBS and hemoglobin A1c levels. This combination produced benefits to control BMI, improved blood pressure, well-tolerated safety profile and was substantially ineffective in producing hypoglycaemic episodes. All of these findings are emphasized for the selection of dapagliflozin-metformin combination therapy in T2DM patients. The long-term follow-up study will define the comparation and safety profile and efficacy among diabetic patients more clearly.

Authors Contribution:
Muhammad Kamran Yousuf: Substantial contribtion to conception and ddesign, acquisition of data analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. Final approval of the version to be published
Khalid Mustafa Memon: Acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published
M. Sajid Abbas Jaffri: Acquisition of data, revising it critically for important intellectual content, final approval of the version to be published
Mehar Fatima: Drafting the article, final approval of the version to be published
Mamoora Arslaan: Drafting the article, final approval of the version to be published
Shizma Junejo: Analysis and interpretation of data, final approval of the version to be published

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Case Report

Open Access

Laser Light Induced Retinopathy in a Young Boy: A Case Report from Eye Care Hospital, Karachi

Mazhar Awan, Madiha Waqar, Ahmed Hafeez

ABSTRACT:

A case report of a 14 year-old-boy who came with a history of direct gazing to laser pointer at Khairun'nisa Eye Hospital, Karachi. A comprehensive eye examination including Slit lamp biomicroscopy, Fundoscopy, optical coherence tomography and Fundus photography was done. Main outcome measure were right eye foveal scarring with normal periphery. Fundoscopy showed right Eye old scar at fovea, exactly like solar retinopathy. Solar retinopathy is a type of retinopathy which is caused by directly looking at sunlight. In this report we are presenting the classical case of retinopathy exactly like solar retinopathy due to gazing directly at laser light for a long period of time.

Key Words: Solar retinopathy, Fovea, Laser Light, Optical Coherence Tomography, Laser Induced Retinopathy

How to cite this Article:
Awan M, Waqar M, Hafeez A. Laser Light Induced Retinopathy in a Young Boy: A Case Report from Eye Care Hospital, Karachi. J Bahria Uni Med Dental Coll. 2024;14(4):274-7 DOI: https://doi.org/10.51985/JBUMDC2024447

INTRODUCTION:

Most cases of laser-induced retinal injury result from accidental exposure to high-energy class IV lasers with military, laboratory, or medical applications used appropriately, low-energy class laser devices pose little risk of retinal injury.[1]

Two factors may have contributed to the development of the macular lesion noted in this patient. First, racial fundus pigmentation may have increased absorption of the laser energy at the level of the retinal pigment epithelium and choroid, accentuating the effect of the low-power laser. Laser Pointer is a device with a power source where the laser emits a narrow coherent low-powered laser beam of visible light. Where, a small bright row of colored waves is spotted when pointing on a target.[2]

Severity of laser induced retinopathy depends on the wavelength of light used. Our eyes are more sensitive to the green light. The beam of laser light can damage our retina and the point where the laser becomes notably dangerous at 5 milliwatts of power, This 5 milliwatts of power laser light can potentially damage the eyes in under 10 seconds.

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Received: 10-09-2024
Accepted: 27-09-2024

This harm mostly results in the light sensitive cells of the eye's retina becoming overloaded and damage to the macula cells, The intense energy generated by laser light can cause an increase in temperature in the tissues it comes into contact with, leading to coagulation, denaturation of proteins, and cellular death. And these laser lights can temporarily blind the person instantly at the exposure of the lights in the eyes. Which can be dangerous for the people in precarious situations or those operating heavy machines or vehicles including planes.[3]

Case Report: A 14 year old boy presented to the OPD of Khairun'nisa Eye Hospital, Karachi with a complaint of decreased vision in right eye for 2 years. It was revealed in history that the young boy had a bet with his friend that among all who could look at the laser light for a long time. He was not wearing any glasses at that time. When he told his parents about his vision declining day by day, his parents thought he was malingering and made up the story of being affected by a laser. When he came to Khairun'nisa Eye Hospital we took his history in detail and get to know that he has no previous history of trauma and surgery. His visual acuity of the right and left eye was 5/60 and 6/6 respectively. His visual acuity of the right eye was not improving even with the pin hole. Although near vision was N14 in right eye and N6 in his left eye. His pupillary reaction was round regular and reaction. On Slit lamp Examination anterior segment was found normal.

However, a Fundoscopy with 90 Diopter lens showed a focal disturbance of the retinal pigment epithelium due to laser burn in his right Eye. Figure 1 and 2 No abnormality was found in the fundus of the left eye. Figure 3 and 4. For further investigation, optical coherence tomography was performed and results clearly showed an old scar in the right eye.Figure 5

Considering the clinical, biomicroscopic and tomographic findings, the diagnosis of right eye solar retinopathy was established, despite no direct sun gaze being documented, it is a type of thermal injury to the retina caused by exposure to high-intensity laser radiation. The thermal energy generated by the laser leads to coagulation and denaturation of retinal proteins and cellular death.No specific treatment was given. He was advised to avoid any further exposure to laser radiation and multivitamin syrup (Lutevit plus one tsp daily) and a healthy diet. He was also counseled on the importance of protective eyewear and the safe use of laser pointers to prevent accidental exposure. No improvement in his right eye vision was seen after 1 month of follow-up with the same 5/60 visual acuity in right eye. On his first follow up he was advised to continue using the same multivitamin syrup for 3 months.

Figure 1 and 2: fundus photographs of right eye showing laser burn

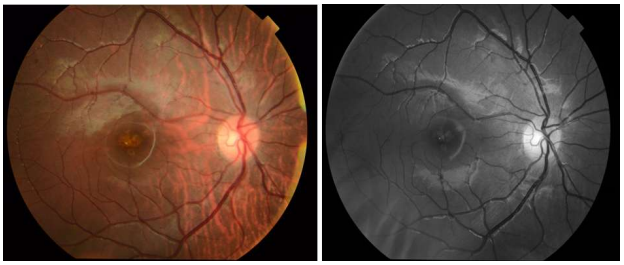


Figure 3 and 4: Fundus photograph of left eye showing no significant abnormality.

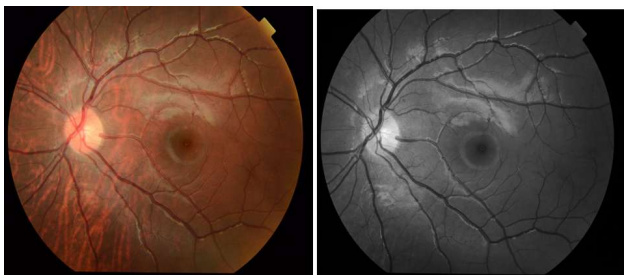


Figure 5: Optical coherence tomography of right eye

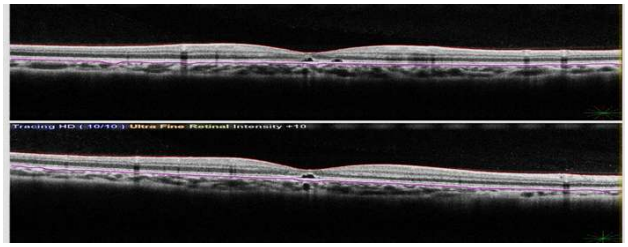
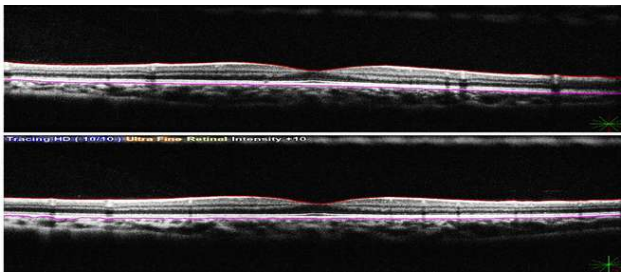


Figure 6: Optical coherence tomography of right eye



DISCUSSION:

Laser light can cause severe damage to the retina, particularly the fovea, which is responsible for our central vision. The retina is the part of the eye that converts light into electrical signals that are sent to the brain to create visual images.[4]

When laser light is directed towards the eye, it can be absorbed by the retina's pigments and converted into heat. This heat energy can then damage the delicate cells in the retina, including those in the fovea, which are particularly susceptible to damage due to their high concentration of photoreceptor cells. This conversion of the laser energy into heat, resulting in a thermal burn and subsequent atrophy of the retina.[5]

The severity of the damage depends on the wavelength, intensity, duration, and size of the laser beam. Higher intensity and longer duration of exposure to laser light can cause more significant damage to the retina, while smaller laser beams can cause pinpoint burns.[6]

The effects of laser light on the retina can range from mild temporary vision loss to permanent damage and blindness. Symptoms of laser-induced retinal damage include blurred or distorted vision, dark or missing spots in the central vision, and sensitivity to light.[7]

To prevent laser-induced retinal damage, it is crucial to wear protective eyewear when working with lasers or being in close proximity to laser beams. It is also important to follow proper safety protocols when using lasers and to avoid pointing laser beams at the eyes.[8]

Due of their increasing curiosity in laser appearances and ignorance of the potential risks, children are more vulnerable to laser eye injuries.[9] Misuse has been linked to deliberate exposure as well as unintentional exposure, such as "games" where kids would compete to see who could keep a laser in their eye longer than everyone else.[10] In addition, compared to adults, youngsters have a clearer ocular medium and are less likely to use the same defense mechanisms blinking and gaze aversion in reaction to lasers pointed directly at their eyes.[11] It has frequently been stated that kids with learning disabilities, behavioral disorders, and mental health concerns are more likely to sustain an eye injury.

Conditions categorized under the general term "photic retinopathy," or conditions secondary to light-related damage from a variety of sources and wavelengths, are examples of ifferentiators.[12] This comprises arc welding retinopathy, solar/eclipse retinopathy, and retinopathy caused by laser pointers. Eclipse maculopathy/solar maculopathy: Both disorders originate directly from prolonged sun exposure, causing retinal damage that can occur in as little as a few

minutes of visible light exposure.[13,14] This causes symptoms and signs akin to laser pointer maculopathy, as well as a retinal appearance. This syndrome typically gets worse when watching solar eclipses for an extended period of time. But it can also happen as a byproduct of religious rituals, outdoor athletic events, and psychotic episodes.[15]

When youngsters do not emerge right away after being injured by a laser pointer, their retinal appearance may lead to a false diagnosis of macular dystrophy.[16] Given these results, it is necessary to ask more focused questions about the case history in order to identify the causal agent. Additionally, the stability of the retinal findings is important in distinguishing this disorder from other bilateral, slowly progressing hereditary macular dystrophies. In addition, family history and genetic tests are critical since, in contrast to laser pointer maculopathy, a hereditary dystrophy may be present in one or more family members. The diagnosis of laser pointer retinopathy relies heavily on OCT imaging. The ellipsoid zone may be disrupted or damaged, leading to the following loss of retinal pigment epithelium, as characteristic observations. Excessively reflecting bands in a vertical orientation can also be seen at the level of the outer retina.

The retinal appearance and sequelae are critical factors in the management of laser pointer maculopathy. If retinal holes are present, they may go away on their own in certain situations, but if they worsen and continue, a pars plana vitrectomy can be required. The previously stated problems can also involve different layers of retinal hemorrhage and vitreous hemorrhage. As they normally go away on their own without treatment, these may usually be seen. The use of oral steroids for laser retinopathy has been supported by case studies and television shows. Steroid usage is supposed to reduce the inflammatory reaction that the laser causes. Unfortunately, the majority of the anecdotal cases in the literature have not been sufficiently studied to determine its clinical utility.

Due to the ease of access to lasers through internet retailers and the lack of awareness regarding their risks, laser pointer retinopathy is a disorder that is becoming more and more common in pediatric and adolescent patients. This instance illustrates how laser viewing can cause detrimental vision issues that children and teenagers may not be aware of, as the condition might go untreated for years before being discovered during a routine eye checkup. While most cases have a good prognosis, some have resulted in significant visual loss. Given the lack of a truly effective treatment, it is essential to raise awareness and educate people about laser pointers. By teaching parents, teachers, caregivers, and kids about safe laser handling practices and how they can have disastrous ocular repercussions if handled improperly, optometrists can play a significant role in the lives of these individuals.[17]

CONCLUSION:

Laser light can cause severe damage to the retina, particularly the fovea, by burning the delicate cells responsible for our central vision. It is essential to take proper precautions to protect the eyes when working with lasers to prevent permanent vision loss. To prevent retinal damage, it is important to use laser pointers responsibly and avoid pointing them directly at the eye.

Authors Contribution:
Mazhar Awan: Conceptualized of work and supervised the study
Madiha Waqar: Manuscript writing, clinical work design of study
Ahmed Hafeez: Manuscript writing, clinical data work and follow-up of patient

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Letter to Editor **Open Access**

Next-Gen Rehab: VR & AI Revolutionize Physiotherapy

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How to cite this Article:
Eman A, Mehmood K, Ali H. Next-Gen Rehab: VR & AI Revolutionize Physiotherapy. J Bahria Uni Med Dental Coll. 2024;14(4): 278
DOI: https://doi.org/10.51985/JBUMDC2024436

The integration of Virtual Reality (VR) and Artificial Intelligence (AI) in healthcare can significantly improve patient outcomes, particularly in physiotherapy. Combining VR and AI enhances accuracy and personalization in physiotherapy, ushering in a new era of patient centered rehabilitation. VR and AR use input devices to gather data on body position, movement, and the environment, and output devices to deliver sensory feedback, including visuals, vibrations, and sounds.[1] By offering a non-pharmaceutical alternative for pain management, virtual reality (VR) can help lessen dependency on conventional painkillers and the negative consequences they are linked with. Pain is a complicated feeling that is impacted by many different things, such as psychological, social, cultural, and physical aspects. VR can assist in diverting patients from their pain, changing their perception of suffering, and enhancing their general well-being by submerging them in interesting, interactive settings. Virtual reality (VR) has shown encouraging results in the field of physical therapy, especially in stroke rehabilitation, where patients are able to restore their independence and motor abilities. Virtual reality (VR) offers a comprehensive approach to treatment and pain management by supporting functional recovery and psychological resilience in addition to managing chronic medical concerns. Children with Cerebral Palsy (CP), a neurological disorder that impairs motor skills, frequently need to get regular physiotherapy in order to enhance their muscle strength, coordination, and general functionality. Conventional approaches usually include splints, stretching, strengthening exercises, and activities that encourage movement. But using virtual reality (VR) in rehabilitation has proven to be a very promising new therapeutic strategy.[2] Children with cerebral palsy benefit from VR-based therapy because it makes their workouts more interesting and dynamic. Research conducted in the last ten years has shown that VR, when paired with conventional physiotherapy, can assist kids in developing new motor skills, preserving the health advantages of physical activity, and enhancing hand functionality. With its potential to enhance both the physical and psychological aspects of rehabilitation, this hybrid method presents a bright future for children with cerebral palsy.[3,4] Integrating VR and AI in physical therapy enhances rehabilitation accuracy and customization. VR creates immersive environments that motivate patients and provide detailed data on their movements and progress, which AI analyzes in real-time to tailor treatment strategies. The Precise monitoring and modifications are made possible by this dynamic feedback loop, leading to more individualised and successful physical treatment. Benefits include more effective interventions, quicker recovery times, tailored treatment plans, and increased patient engagement. High upfront expenses, the requirement for infrastructure, patient acceptability, data protection, and the requirement for more training for healthcare professionals are some of the challenges.[5] In conclusion, the integration of artificial intelligence and virtual reality in physical therapy is a groundbreaking advancement that offers effective and personalised treatment plans. This kind of integration not only makes patients more engaged, but it also makes treatment plans more unique. Despite the challenges, there's a good probability that patient outcomes would get better, which would represent a significant improvement in patient's and the efficacy of rehabilitation as a whole.

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Received: 28-08-2024
Accepted: 31-09-2024

Authors Contribution:
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Kanza Mehmood: Idea conception, final approval
Hassan Ali: Proof reading

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Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482, CODEN: JBUMB7
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