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

JBUMDC

Journal of Bahria University Medical & Dental College

Volume 15 Issue 2, April - June 2025

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/
ROAD Directory of Open Access Scholarly Resources at https://portal.issn.org/resource/ISSN/2617-9482
Pakmedinet at www.pakmedinet.com/jbumdc,
Google Scholar at https://scholar.google.com.pk/,
Crossref at https://doi.org/10.51985/aluu2996
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Editor, JBUMDC, Bahria University Medical & Dental College, Adjacent PNS SHIFA, DHA Phase II, Karachi Pakistan
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Published by: Bahria University Health Sciences, Campus Karachi

JBUMDC

Journal of Bahria University Medical & Dental College

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Volume-15, Issue-2. April - June 2025

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Editorial **Open Access**

The Legitimacy of Hiring Professional Medical Writers: Balancing Ethics and Scientific Progress

Iqbal Hussain Udaipurwala

How to cite this Article:

Udaipurwala IH. The Legitimacy of Hiring Professional Medical Writers: Balancing Ethics and Scientific Progress. J Bahria Uni Med Dental Coll. 2025;15(2):69-70 DOI: https://doi.org/10.51985/JBUMDC2024495

The pursuit of scientific knowledge and the dissemination of research findings are at the core of the scientific endeavor and scientific writing is the most crucial means of communicating scientific work.[1] In the realm of medicine and healthcare, where the stakes are often human lives and well-being, the importance of effectively communicating research findings cannot be overstated.[2] Biomedical research holds the key to understanding and addressing health issues, diseases, and their management, ultimately benefiting society as a whole.[3] However, the research cycle is incomplete without the dissemination of its findings, making publication a critical step. Since the introduction of Evidence Based Medicine, number of scientific articles published per year have increased steadily with a rough estimation of 2 million articles per year globally.[4] Incomplete, inaccurate or delayed reporting of medical research may reduce the efficiency and quality of health care. Therefore scientific and clinical research should be reported in a complete, accurate balanced and timely manner.[5]

Despite the undeniable significance of publishing biomedical research, many clinicians and academic scientists face challenges that hinder their ability to effectively communicate their work.[6] Several factors contribute to this reluctance, including; lack of time, inadequate writing skills, language barriers, limited resources and ethical concerns. They often have demanding schedules that leave them with limited time for writing and publishing research papers and thus balancing with patient care, teaching responsibilities, and laboratory work can be overwhelming. Secondly, proficiency in scientific writing is not present inherently in everyone, they may excel in their respective field but may find difficult to convey their findings effectively through writing as the complex scientific ideas require a precise articulation. In an increasingly globalized world of research, language can be a significant barrier, where a non-native English speakers may find it challenging to write in English which is the dominant language of scientific communication.

In light of these challenges, the need for professional medical writers becomes evident. Professional medical writers are individuals with specialized training and expertise in scientific and medical writing. They play a pivotal role in bridging the gap between research and publication as they possess in-depth knowledge of scientific writing conventions, ensuring that research findings are communicated accurately and effectively. They can distill complex information into clear and concise language. By outsourcing the writing process to professionals, researchers can focus on their core duties, such as conducting experiments, analyzing data, and patient care. This not only saves time but also enhances productivity. They can help researchers overcome language barriers and publish in internationally recognized journals. Ethical considerations are paramount in scientific research and they can assist researchers in adhering to ethical guidelines and addressing conflicts of interest transparently. With their knowledge of the publication landscape, professional medical writers can guide researchers in selecting the most suitable journals for their work. They are well-versed in journal submission processes and can improve the chances of acceptance. While the benefits of professional medical writers are evident, it is essential to consider the availability of these services and raise awareness among researchers about their significance. The contemporary era of scientific research demands greater access to professional medical writing support. There should be mechanisms in place to ensure the competence and ethical standards of professional medical writers. Certification programs and professional organizations can play a role in setting industry standards.

In the ever-evolving landscape of medical research and publication, the question of whether it is legitimate to hire a professional medical writer has garnered significant attention. This debate centers on the ethical considerations surrounding the involvement of third-party writers in the scientific process and the potential impact on research integrity. While concerns about transparency and authorship have been raised, it is essential to delve into this complex issue, weighing the benefits and challenges of employing professional medical writers. The ethical dilemma surrounding the legitimacy of hiring professional medical writers centers on several key issues:

1. Transparency and authorship: Involvement of third-party writers may obscure the true contributions of

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Received: 03-02-2025
Accepted: 14-02-2025

authors, potentially compromising transparency and authorship integrity. A high prevalence of authorship problems can have a severe impact on the integrity of the research process.[7]

2. Conflict of interest: When a pharmaceutical company or industry-sponsored research engage medical writers, the fear is that these writers may prioritize corporate interests over scientific objectivity.[8] The term 'ghost writer' or 'ghost author' refers to a person who has prepared or contributed significantly in writing an article but his name is not included in the authors list.[9]
3. Undermining researcher skills: Relying on professional medical writers may discourage researchers from improving their scientific writing and communication skills and over time it could lead to a dependency on external writers.
4. Financial considerations: The cost of hiring professional medical writers can be significant, leading to concerns about the unequal access to such services and potential financial bias in research.

While the ethical concerns surrounding the use of professional medical writers are valid, it is equally important to consider the practical benefits that these writers bring to the scientific community including; enhanced research communication, quality assurance, overcoming language barriers, time efficiency and regulatory compliance. Although ghostwriting is considered as a serious issue with marked impact on public health but the real extent of this problem is still unclear.[10,11] To address the ethical concerns associated with hiring professional medical writers, several strategies can be implemented:

1. Transparency: Researchers should be transparent about the contributions of medical writers in their publications. This includes explicitly acknowledging their roles in manuscript preparation and providing details in the acknowledgments section.
2. Authorship guidelines: Medical journals should establish clear authorship guidelines that emphasize the importance of transparency in acknowledging the contributions of all individuals involved in the research and writing process.
3. Declaration of conflicts of interest: Researchers and institutions should disclose any potential conflicts of interest related to the involvement of medical writers, particularly in industry-sponsored research.
4. Training and education: Institutions should provide training and resources to help researchers improve their scientific writing skills, reducing the need for external writers.
5. Regulatory oversight: Regulatory agencies should ensure that pharmaceutical companies and research institutions adhere to ethical and transparency standards when engaging medical writers in the preparation of regulatory documents.

To conclude, the debate over the legitimacy of hiring professional medical writers is multifaceted, with valid ethical concerns on one side and practical benefits on the other. Striking the right balance between transparency and the need for expertise in scientific communication is crucial. It is not inherently illegitimate to hire professional medical writers; instead, it is essential to ensure that their roles are clearly defined, transparently acknowledged, and ethically conducted. Researchers, institutions, and journals must work together to establish and uphold ethical standards that address the concerns associated with their involvement.

Authors Contribution:
Iqbal Hussain Udaipurwala: Conception, writing, literature search, proof reading

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Editorial **Open Access**

Artificial Intelligence in Healthcare: Replacement or Reinforcement for Clinical Practice

Farzeen Tanwir, Eesha Hameed

How to cite this Article:
Tanwir F, Hameed E. Artificial Intelligence in Healthcare: Replacement or Reinforcement for Clinical Practice. J Bahria Uni Med Dental Coll. 2025;15(2):71-72 DOI: https://doi.org/10.51985/JBUMDC2024461

Since the dawn of the modern age, individuals have created several machines to assist humankind in various tasks. One of the most prominent discoveries in recent ages has been Artificial Intelligence. John McCarthy devised and constructed the term Artificial intelligence in 1956.[1] He fabricated an idea that machines, like humans, could be programmed to think and make decisions independently. Herbert Simon and Allen Newell formulated the , the first AI system, to prove 38 theorems in Russell's *Principia Mathematica*.[2] This field has recently undergone numerous implementations in various sectors worldwide. Today, this technology has evolved from a single program to multiple layers of complex neural networks that can accomplish complex tasks within seconds and produce human-like cognitive ability, which is proven by several pieces of research carried out worldwide.[3] AI models have been used to perform many tasks such as problem-solving, data collection, storage and analysis, automated administrative tasks, risk and fraud detection, and much more. AI has entered almost every global sector nonetheless efforts have been made to incorporate this technology into healthcare as well.

In the 1970's the AI model CASNET (computer-assisted decision-making based on a causal-associational network) was developed for consultation, identification, and prognosis for glaucoma patients.[4] In later years AI experienced breakthroughs in all fields of medicine such as drug discovery and delivery[5], aiding in the diagnosis of multiple sclerosis by helping radiologists analyze large sets of Magnetic Resonance Images (MRI),[6] advent of robotic surgeries with AI modeling,[7] and much more. The incorporation of AI methods started later in dentistry as compared to medicine. AI systems are being used for the diagnosis and assessment of caries, periodontal diseases, orthodontic patients, and treatment planning of implants.[8]

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Received: 03-10-2024
Accepted: 22-11-2024

Structurally speaking, an artificial intelligence model is categorized into three basic layers; input, intermediate, and output layers. For the model to perform the required task independently, the model must undergo the training phase. This phase of AI is still not independent of the clinician because to be trained and validated the system has to be fed with a data set that has to be annotated by an experienced individual regarding the correct diagnosis and identification of given data. Afterward, new raw data is added to the system to perform the validation phase, in which the accuracy of the machine is checked to correspond to the gold standard dictated by the clinician. After initial programming, the machine is then ready to be tested. Data is entered through the input layer and analyzed in the intermediate layer. Finally, the machine independently generates the results in the output layer.[9]

In the age of modern technology clinicians and patients are leaning more towards solutions that are faster and more efficient, selecting a faster treatment option rather than the conventional one, which requires multiple visits, long patient interviews, and clinical examinations. One question that often troubles many clinicians is as the use of AI is increasing rapidly, will it ultimately replace them in the treatment process? There are two ways of looking at this; a study published by Christopher *et al.* recently stated that among nurses, sleep deprivation and fatigue are some of the most common factors leading to medication errors by registered nurses.[10] This is because the burden on healthcare services is more than the number of healthcare professionals available, which leads to overworking of clinicians and healthcare staff. This issue could be easily sorted out by having AI-assisted medical services, however as desirable as this sounds, there are multiple challenges associated with the use of AI. First and foremost, AI systems in their developmental phase are still dependent on the input data. This input data can have biases, have limited generalizability, and be difficult to collect. An AI model trained on a small dataset is bound to make errors. Even if we have adequate input, this input is still preprocessed by humans and thus can be prone to errors. Any error or biases in the development of the model cannot be assessed when the model is in use due to the black box effect.[11] As clinicians deal with conditions that can affect an individual quality of life, complete dependence on any technology without proper protocol breaks the ethics code of non-maleficence.[12] If any clinician

commits medical malpractice, the individual is accountable in court and can ultimately lose their license. There is no such system in place to check that if an AI model makes a misdiagnosis who is accountable? The creator, the doctor, or the institute. Furthermore, machines could be hacked and personal data can be misused. Even the machines could be used for negative purposes.

All of the above-mentioned concerns lead to the conclusion that no doubt Artificial intelligence is a prodigious development, still complete reliance on it on matters that are related to an individual's well-being and quality of life is detrimental. These machines could be used to assist clinicians and reduce their workload, in data storage and processing administrative tasks, however, treatment should always be performed by the clinicians. They could also be used for diagnosis; however, this should also be verified by a clinician. Further studies should be directed towards the role of Artificial Intelligence in assisting clinicians rather than creating machines for their replacement.

Authors Contribution:
Farzeen Tanwir: Supervised and review of the manuscript
Eesha Hameed: Write up of manuscript

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Original Article **Open Access**

Comparison of Hemodynamic Response to Laryngoscopy / Intubation: Intravenous Lidocaine vs Repeat Dose Propofol

Muhammad Salman Maqbool, Hasnain Ameer Hamza, Fahad Zubair, Kainat Irshad, Affifa Saleem

ABSTRACT:

Objectives: The contrast of effectiveness of repeat dose propofol with lidocaine efficacy before laryngoscopy in maintaining stable hemodynamic(pulse and mean blood pressure)pressure values following endotracheal intubation.

Study design and setting: Randomized controlled interventional(purposive sampling) study by the Anesthesia Department at Farooq Hospital Islamabad, ASMC (Rwp)from 21-06-2024 to 04-10-2024.

Methodology: The study was authorised by the Research Committee; Akhtar Saeed Medical College, Rawalpindi on 14th June 2023 Sample size was calculated by sample size calculator(statistics kingdom) employing a normal distribution, with margin of error 0.04, confidence level of 0.80(z-score of 1.28) and standard deviation of 0.24, the sample size was calculated to be 60 total subjects. Random sampling was used and bunched in two groups using the lottery method; patients had co-induction and inj. dexamethasone 4mg, propofol 1.5mg/kg, inj. cisatracurium 0.15mg/kg as muscle relaxant for intubation in both groups. In group A and B, patients also received 0.5mg/kg propofol thirty seconds and 1.5 mg/kg lidocaine three minutes before laryngoscopy respectively. Cardiovascular parameters, i.e. (pulse, blood pressure) were monitored. Paired-sample T test employed with a confidence interval (of 95%)analysing heart rate and mean blood pressure values with determination of significant P-value greater than 0.05. SPSS v 26 was used.

Results: In group-A, 90% of cases more stable heart rate was noted as compared to group-B with a value of (63.3%). No incidence of bradycardia was noted in group-A, whereas in group-B it was 6.7%. Concerning mean blood pressure, raised values were noted in 23.3% cases and 30% cases in Group A and B respectively and stable systolic blood pressure values were seen in 80% and 66.7% cases in Group A and B respectively.

Conclusions: The propofol repeat dose before intubation showed stable hemodynamic (pulse and mean blood pressure) values as compared to lidocaine following laryngoscopy in general anaesthesia.

Key words: Anesthesia induction, Cardiovascular response, Hemodynamics, Propofol

How to cite this Article:
Maqbool MS, Hamza HA, Zubair F, Irshad K, Saleem A. Comparison of Hemodynamic Response to Laryngoscopy/ Intubation: Intravenous Lidocaine vs Repeat Dose Propofol. J Bahria Uni Med Dental Coll. 2025;15(2):73-79 DOI: https://doi.org/10.51985/JBUMDC2024457

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Received: 18-10-24
Accepted: 27-03-25
1st Revision: 27-10-24
2nd Revision: 12-02-25
3rd Revision: 14-03-25

INTRODUCTION:

Despite statistics portraying that various techniques such as: intra-venous local anaesthesia (bier block), regional blocks(e.g. brachial, sciatic block etc.) and central neuraxial blocks(intra-thecal, epidural etc.) can be employed for anesthesia and analgesia in surgical procedures as sole anesthetic technique, but general anesthesia with tracheal intubation is normally preferred for major surgical(thoracic, head and neck, abdominal, cardio-pulmonary and neurosurgical) procedures and not possible without it.[1] Primary focus in general anesthesia at induction is to employ balanced anesthesia technique peri-operatively to maintain homeostasis primarily cardiovascular (pulse, systolic, diastolic and mean blood pressure) and respiratory (assisted manual ventilation to prevent hypoxia and hypercarbia) for patient safety followed by placement of tracheal tube and ensuing controlled ventilation.[2] Induction of anaesthesia carries risk factors involving mainly patient's medical status, anesthetic medications used, hypersensitivity reactions and surgical technique.[3] Medication used for induction may cause peri-

operative hypotension.[1] A 20-30% or greater decline in systolic blood pressure as regard to baseline value(intra-operative hypotension) or mean blood pressure value less than 80mmHg may have unfavorably outcome and affects patients with ischemic heart disease, uncontrolled/labile blood pressure, and arrythmia's due to lowering of cardiac perfusion pressure as quantified in various studies.[4] Various other researches portrayed relation of severe hypotension at induction phase of anesthesia to delayed emergence from anaesthesia or even risk of stroke.[5]

Laryngoscopy and particular tracheal tube placement may cause hypertension and tachycardia due to stretching of pharyngeal /laryngeal structures (involving X and X1 cranial nerves).[1,2,6] Though these responses are usually well in young healthy patients but in patients with co-morbid diseases may cause myocardial ischemia, arrythmia's, left ventricular failure, sub-arachnoid hemorrhage or stroke.

These hemodynamic changes (heart rate, blood pressure) are evident at one minute interval and can last for a few minutes of laryngoscopy.[7] Thus, general anesthesia induces endocrine and immunologic reflex response (mainly cortisol, complement and interleukin) as well as metabolic acid base balance disturbances.[8]

Various induction medications have been advocated in studies, e.g. barbiturates, midazolam, nalbuphine, dexmedetomidine, etomidate, propofol.[1,2,9]

To blunt intubation pressor hemodynamic response, medications/techniques stated in literature include nitroglycerine, lidocaine, inhalational volatile anesthetics, fentanyl, topical anesthetic spray, calcium channel blocker, laryngeal mask airway, video-laryngoscope usage and top-up dose of propofol.[1,2,9]

Also employing a balanced anaesthesia medication approach/technique that will result in a stable hemodynamic (pulse and blood pressure) state per-operatively, particularly following endotracheal intubation.[1,2,9]

Lidocaine is a membrane anaesthetic(amide type), its mode of action(membrane stabilizing effect) is mediated by blockade of sodium channels. It is also used as an adjuvant to tracheal intubation to obtund cerebro-hemodynamic response to laryngoscopy.[2,10] It is usually given in dose of 1.5mg/kg three minutes before intubation.[10] Propofol is widely used nowadays for induction of anaesthesia in adults, with two popular techniques:(a)induction dose of propofol(2-2.5mg/kg) followed by smaller bolus dose and (b)target-controlled infusion technique. Deepening anaesthesia with a bolus propofol dose might be helpful when using a smaller initial dose of propofol(1-2mg/kg), thus it will minimize cardiovascular and respiratory(apnea) depressant effects.[11] As inferred from the above points stabilizing hemodynamics at induction phase of anaesthesia, would circumvent patient morbidity and mortality.

The rationale of this study was to foresee hemodynamic response to induction and laryngoscopy of repeat dose propofol in comparison to lidocaine. As fewer studies are documented in the literature studying hemodynamic effects of incremental bolus dose of propofol at laryngoscopy in general anaesthesia.

Primary outcome variables were: pulse rate, systolic, diastolic and mean blood pressure (with aim to keep them within 15% of baseline values) and noting raised blood pressure, pre-mature ventricular contractions (PVC), bradycardia and tachycardia. Whereas secondary variables covering qualityof anesthesia (intubating conditions) were monitored by noting involuntarypatient movement at laryngoscopy, stylet use, cricoid pressure, bronchospasm, coughing and backward upward rightward pressure (BURP) manoeuvre to aid glottic view and medication needed to control hemodynamic i.e. heart rate changes and blood pressure fluctuations.[9] This study will help to implore technique in hemodynamic pressor control of blood pressure at induction.

METHODOLOGY :

Study protocol was authorized by the Research Advisory Committee& Institutional Review Board (Letter No.RAC&IRB-14/6/2023); Akhtar Saeed Medical College, Main Murree Expressway Bahria Golf City, Rawalpindi in meeting held on 14th of June,2023. Sample size was calculated by sample size calculator (statistics kingdom) employing a normal distribution, with margin of error 0.04, confidence level of 0.80(z-score of 1.28) and standard deviation of 0.24, the sample size was calculated to be 60 total subjects participating in the research divided randomly into two groups by using computer generated allocations from elective surgical schedule (n=30) in each group. This single blind (randomized controlled) interventional study was plotted with random sampling methodology divided into 2 groups by lottery method and convened at Farooq Hospital Islamabad (Rwp), by the Anesthesia Department.

The duration of the conducted study was about five months, and the period was from 21st June 2024 to 4th October 2024.The inclusion criteria of the study being (aged 21-70years) placed on elective general surgical/gynecological/ head and neck procedures like (cholecystectomy, total abdominal hysterectomy, septoplasty etc.) to be done under general anaesthesia (with tracheal intubation).[11] The patients belonging to American Society of Anesthesiologist (ASA) class-1 and 2 of both genders were eligible for the study and fulfilling above stated eligibility criteria were included in study.[12]

The patients were not aware of group allocation. Patients had standard pre anaesthesia assessment and as regard to informed consent patients were explained pertinent information as regard to technique of anesthesia, risks and benefit of anesthesia in simple phrases so that patients were able to make a decision of voluntary participation in research,

which was also taken in written format as well.[1]The exclusion criteria of study were patients with history of difficult airway, acute abdomen, pregnant woman, hypersensitivity to soybean oil, egg lecithin, ischemic and stenotic valvular heart disease patients.[11]

In both groups in the study patients fasted was as per ASA guidelines whereas in operation theatre after intravenous isotonic fluid attachment and cardiac monitors attachment (pulse oximetry, blood pressure, electrocardiograph) patients in both groups had co-induction with (intravenous inj. midazolam 0.05 mg/kg and inj. Nalbuphine 0.1mg/kg)along with inj. Dexamethasone 4mg.[2] Secondly, anesthesia induction was with propofol in a dose of 1.5mg/kg and inj. cisatracurium 0.15mg /kg as muscle relaxant for intubation in both groups. Only difference in both groups at induction being that in group-A patients received 0.5mg/kg repeat dose propofol thirty seconds (n=30) and in group-B patients received 1.5 mg/kg lidocaine (n = 30) three minutes before laryngoscopy.

Patient's cardiovascular hemodynamic parameters, i.e. (systolic, diastolic and mean blood pressure), heart rate and respiratory pulse oximeter were monitored at pre-induction (baseline value) and after endotracheal intubation at[1,3,7] and 10-minute intervals. Patients were manually ventilated for 2.5 minutes before laryngoscopy and an appropriately sized cuffed-tracheal tube placed and controlled ventilation was commenced after confirmation of tracheal tube placement, using visual placement of endotracheal tube, capnograph tracing, bilateral chest auscultation, according to ASA guidelines and standard general anesthesia techniques employed maintaining hemodynamic stability in both groups.[12] All patient data was recorded on the anesthesia proforma and patient confidentiality was fully ensured. Hypotension (defined as a mean arterial pressure <60 mmHg or >30% reduction from baseline) was treated by fluid administration first, if not corrected then by intravenous 50 mcg bolus of phenylephrine; bradycardia (heart rate less than ? 40) was treated by inj. Atropine 0.5mg intravenously. The primary outcomes noted were systolic, diastolic blood pressure changes: particularly rise in mean arterial blood pressure (of 30mmHg) and heart rate variations and noting rise in heart rate (up to 25 beats per minute) as intubation pressor response, bradycardia, hypotension, and secondary outcome, intubation condition as well as medications to control cardiovascular hemodynamic changes to normal baseline values. Researcher in the study only knew about the medication administered to the subject, and a specialist anesthetist who was not participating in the trial outcome performed lottery-generated randomization of groups and gave study medications in a sealed envelope and unbiased handling of data was ensured. Paired-samples T test was used with confidence interval (of 95%) to analyze variables (heart rate and mean blood pressure) in both groups and to seek significant P-value greater than 0.05.[13]The study hypothesis was the assessment of superiority of repeat dose propofol in comparison with lidocaine in maintaining stable hemodynamic variables following intubation. SPSS v 26 was used for statistical analysis.

RESULTS:

The study parameters, demographic along with intubating conditions of both groups are depicted in Table 1.

There were no cases of any stylet/ bougie use, i.e. any difficult airway case in both groups under study. The hemodynamic data(mean / standard deviation) at the time line in a study is represented in Table 2. The variations of hemodynamic parameters(heart rate, systolic and mean blood pressure) noted while conducting the study are depicted in Table 3. The data provides evidence for a clinically important systolic and stable heart rate value as stated in Table 3 in favour of group-A, supported by Paired-samples T statistical analysis test as shown in Table 4.

DISCUSSION:

Study by Ghomeishi A and colleagues compared stress hormone effects on hemodynamic variables in patients undergoing laparoscopic gallstones surgery under general anaesthesia (propofol 75µg/Kg/min vs dexmedetomidine 0.5 µg/Kg/min infusion) started peri-operatively and continued for ten minutes into post-surgical recovery area. They inferred that propofol employed had good effect on inflammatory surgical stress level (epinephrine being the neurotransmitter), but no difference can be inferred in hemodynamic variables i.e. heart rate, blood pressure readings from graphical data in first five minutes after intubation in both groups; though continued infusion showed that dexmedetomidine group had more stable long term effect on heart rate and mean arterial blood pressure readings in comparison to propofol group ($P < 0.001$) on repeated ANOVA test analysis.[14]In our study group-A propofol use resulted in stable heart rate and systolic blood pressure parameters noted in 27 subjects(90.0%) and 24 subjects(80%) respectively.

Seangrung R conducted study to foresee blood pressure and heart rate change still ten minutes post-intubation, using 0.5mg/kg propofol given 30 seconds before intubation along with lidocaine 1.5mg//kg at induction showed that occurrence of hypotension was 15.09% as compared to 52.83% and also less episodes of bradycardia (0%vs 18.87%, P=0.001) than the dexmedetomidine(1 ìg/ kg given at induction) group.[15] Same additional dose of 0.5mg/kg propofol(group-A) was used in our current study with no incidence of bradycardia observed, whereas in lidocaine group-B in 2 cases (6.7%) bradycardia occurred.

Prospective, randomized, double-blind research by Kwon MA and colleagues compared 3 induction doses of propofol, i.e. 1.5mg/Kg in group A and B and 2mg/Kg in group C. Whereas 0.5mg/Kg of bolus dose of propofol was given 45

Table-1: demographic / intubating parameters(n=30)

	Parameters	Group-A	Group-B
Age(years)	mean/standard deviation	45.70/14.34	46.86/12.71
	Minimum/maximum	21/69	23/70
ASA-classes (frequency/percentage)	Class-1	23/76.7	7/23.3
	Class-2	14/46.7	16/53.3
Gender (frequency/percentage)	Males	8/26.7	5/16.7
	Females	22/73.3	25/83.3
Intubating conditions (frequency/percentage)	Involuntary patient movement noted	Nil	1/3.3
	No movement noted	30/100	29/96.7
	Bronchospasm noted	Nil	1/3.3
	BURP maneuver applied for glottic view	Nil	5/16.7

Table 2: Statistical hemodynamic data (mean / standard deviation) at the time line in both groups(n = 30)

	Group	Time Interval (minutes)	Mean / Standard deviation
Heart rate	A	Baseline	89.67/18.05
		1	85.90 / 14.96
		3	81.17 / 12.10
		7	78.80 / 11.33
		10	79.27/ 10.48
	B	Baseline	91.10/18.37
		1	94.40 / 18.13
		3	93.93 / 19.61
		7	89.07 / 17.39
		10	84.50 / 12.74
Mean blood pressure	A	Baseline	103.20/20.57
		1	94.43 / 16.71
		3	85.13 / 16.46
		7	82.47 / 13.48
		10	81.13 / 15.44
	B	Baseline	112.30/23.98
		1	99.90 / 24.46
		3	99.53 / 26.03
		7	94.23 / 19.90
		10	89.50 / 18.32
Systolic blood pressure	A	Baseline	143.53/20.97
		1	125.53 / 17.85
		3	118.20 / 20.94
		7	111.97 / 16.48
		10	113.27 / 16.88
	B	Baseline	150.20/25.68
		1	136.07 / 30.56
		3	134.13 / 34.05
		7	124.20 / 25.06
		10	119.70 / 20.76

Table-3: Variations in hemodynamic data.(n=30)

			Group -A	Group -B
			(Frequency / Percent)	
Hemodynamic parameters	Blood pressure (Systolic)	Normal	24 / 80	20 / 66.7
		Low	2 / 6.7	3 / 10.0
		High	4 / 13.3	7 / 23.3
	Bradycardia	No	Nil	28 / 93.3
		Yes		2 / 6.7
	Tachycardia	No	27 / 90.0	19 / 63.3
		Yes	3 / 10.0	11 / 36.7
	Mean blood pressure	Normal	22 / 73.3	21 / 70.0
		Raised	7 / 23.3	9 / 30.0
		Low	1 / 3.3	Nil

Table - 4: Statistical Paired-samples T test of both groups. (n=30)

		Paired Differences 95% Confidence Interval of the Difference				
		Lower	Upper	t	df	Sig. (2-tailed)
		Group-A / Group-B				
Pair 1	Pre-Induction heart rate - Heart Rate at 1 minute	-1.316 /-9.312	8.849/2.712	1.516 / -1.123	29	.140 / .271
Pair 2	Heart Rate at 3 minutes- Heart Rate at 10 minutes	-1.783/ 2.861	5.583/ 16.005	1.055 / 2.936	29	.300 / .006
Pair 3	Pre-Induction mean BP - Mean BP at 1 minute	.744 / 4.726	16.790 / 20.074	2.235 / 3.305	29	.033 / .003
Pair 4	Mean BP at 3-minutes - Mean BP at 10 minutes	-2.910 / 1.515	10.910 / 18.551	1.184 / 2.409	29	.246 / .023

seconds before laryngoscopy in group B. Intubating conditions and hemodynamic stability (blood pressure, heart rate) were noted. They noted satisfactory intubating conditions of 91.1% in group B in comparison to 61.8% and 58.8% in group A and C respectively. They concluded that a repeat dose propofol of 0.5mg/Kg before laryngoscopy improves intubating situations with less concern about the occurrence of hypotension.[16]Similar protocol of repeat dose propofol was employed in our study. Though no premature ventricular contractions were observed after intubation and no hypoxia was observed in both groups of our study at the time of assisted manual ventilation before intubation. Vasopressors were used in group A and B in 1 case (3.3%) and 3 cases (10%) respectively. In group-B, in 1 case (3.3%) atropine was used to treat bradycardia, whereas in group-A, no bradycardia was reported.

In study by Safavi M on hemodynamic variability and intubating conditions employing three infusions of propofol i.e. 0.5mg,1mg and 1.5mg/kg on laryngoscopy in addition to initial induction dose of 1mg in 2nd and 3rd group respectively with 2mg/kg induction single dose in 4th group only, with no additional propofol infusion dose, intubation conditions in group Ist,2nd,3rd and 4th, were 91.4%, 94.2%, 97.1% and 68.5% respectively; they noted no statistical differences in heart rate mean value between all groups in baseline and after laryngoscopy readings. The mean arterial pressure was profoundly low in group D in comparison to group A(P=0.015). Whereas in other groups, mean arterial blood pressure was not statistically different.[17]In our study, in group-A, more stable mean heart rate at one minute after laryngoscopy was 94.43±16.71 in comparison to a baseline value of 89.67±18.05, while the same values in group-B were 94.40 ± 18.13 and 91.10 ±18.37 respectively.

In study by K Zou Y and colleagues studying hemodynamic response to intubation employing balanced anesthesia (midazolam/sufentanil as adjunct) technique; effect of lidocaine doses (1 and 1.5 mg/kg with placebo) along with propofol induction and cisatracurium as muscle relaxant, noted lidocaine attenuated increase in blood pressure, but effective in controlling heart rate upto five minutes of intubation.[22]We in our study employed similar balanced anesthesia technique.

Ivascu R, in study on reviewing surgical stress response to surgery pointed that propofol impacts the stress response by inhibiting mainly sympathetic nervous system; the agent used in our study protocol.[4]A study comparing conventional dose (2-2.5mg/kg) of propofol versus titrated propofol administration in ASA I and II cases in general anaesthesia, the titrated propofol group had low post-laryngoscopy hypotension incidence of (9 vs. 19 cases with p value of 0.04). They inferred that in comparison to the conventional induction dose of propofol, the titrated propofol dose reduces

hypotension incidence.[4] A similar dosage schedule was used in our study. In another comparative study done by Balasubramanyam V and colleagues on hemodynamic adverse changes at endotracheal intubation, it was inferred that both esmolol and propofol are equally effective in blunting intubation hemodynamic reflex response.[19] Finding was similar to our study. A retrospective cohort study was done by Kawasaki to ascertain propofol induction dose prediction formula (employing age, female gender, body weight and fentanyl dose)and found it to help decrease hemodynamic fluctuations at anaesthesia induction.[20]

Sekiguchi R in their studyfound no statistical difference in hemodynamic parameter between remimazolam and propofol use i.e. mean arterial blood pressure percentage value of 35% and 55% (?than 65mm/Hg); but non-significant p value of 0.341)respectively as induction agents; stating that it is not only the choice of induction agent rather also dose and usage of adjunct anaesthetic medication as important factor in determining hemodynamic stable state at induction.[21]Similar titrated dose of propofol(lower induction followed by repeat dose) schedule was used by us with effective results. A study by Vale AGG and colleagues on arterial hypotension incidence at induction of general anesthesia observed that propofol is routinely given by bolus dose or manually or target controlled infusion system, they in their study stated that patients who had bolus induction dose of propofol showed lower blood pressure values(mean) in comparison to target controlled infusion technique in their study, though interaction in both study groups remained inconclusive. But in our study a lower induction dose of propofol with a bolus before laryngoscopy had stable pulse and mean blood pressure values.[22]Patients who received propofol bolus injection exhibited a lower mean arterial pressure, a greater variation in the level of consciousness, and a higher suppression rate compared to those who received it as a target-controlled infusion. However, the interaction effect between groups and time remains inconclusive.

CONCLUSION:

The propofol repeat dose before intubation showed stable hemodynamic (pulse and mean blood pressure) values as compared to lidocaine following laryngoscopy in general anaesthesia.

Authors Contribution:
Muhammad Salman Maqbool: Concept & Design of Study, Drafting, Revisiting Critically, Data collection & Analysis, Final Approval of Version
Hasnain Ameer Hamza: Drafting, Revisiting Critically, Data collection & analysis
Fahad Zubair: Drafting, Revisiting Critically, Data collection & analysis
Kainat Irshad: Drafting, Revisiting Critically, Data collection & analysis
Affifa Saleem: Drafting, Revisiting Critically, Data collection & analysis

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Original Article **Open Access**

Assessment of Necessity of Retrograde Filling during PCNL Tract Dilatation

Syed Ali Raza Jaffry, Javed Altaf Jat, Waqar Ahmed Memon, Abdul Qayoom Ghangro, Ahsan Ali Arain, Tamoor Jatoi

ABSTRACT

Objective: To investigate the impact of retrograde filling on tract dilatation and associated outcomes among patients presenting at a tertiary care hospital, Pakistan.

Methodology: A prospective cohort study was conducted at a tertiary care hospital's urology department from February 2022 to February 2023. A total of 126 patients undergoing elective PCNL were included, categorized into exposed (retrograde filling utilized) and unexposed (standard PCNL without retrograde filling) groups. Patient demographics, stone characteristics, and procedural details were recorded. Comparative analyses were performed to assess ease of tract dilation and infection rates using appropriate statistical tests.

Results: The use of retrograde filling did not significantly influence the ease of tract dilation during PCNL. Moreover, the exposed group exhibited a significantly higher rate of post-procedure infections (55.4%) compared to the unexposed group (36.5%). Multivariate logistic regression analysis, controlling for potential confounding variables, confirmed that retrograde filling was associated with a substantial increase in the odds of post-operative infection (adjusted odds ratio of 2.48).

Conclusion: Retrograde filling during PCNL is associated with risk of post-procedure infections and does not provide significant benefits in terms of ease of tract dilation. Moreover, the study emphasizes the economic and logistical implications of incorporating retrograde filling, including increased costs and the need for additional personnel. Therefore, urologists are advised to carefully consider the potential drawbacks and benefits before deciding on the adoption of retrograde filling in PCNL procedures.

Keywords: Ease of tract dilation, Percutaneous Nephrolithotomy (PCNL), Renal calculi, Retrograde filling, Tract dilatation, Normal saline infusion

How to cite this Article:
Jaffry SAR, Jat JA, Memon WA, Ghangrom AQ, Arain AA, Jatoi T. Assessment of Necessity of Retrograde Filling during PCNL Tract Dilatation. J Bahria Uni Med Dental Coll. 2025;15(2):80-85 DOI: https://doi.org/10.51985/JBUMDC2024450

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Received: 03-10-24
Accepted: 26-03-25
1st Revision: 05-11-24
2nd Revision: 19-02-25
3rd Revision: 25-03-25

INTRODUCTION

Renal calculi afflict a substantial portion of the global population, with an estimated prevalence of 10% to 15%, making them a prevalent urological condition. [1-3] The incidence rate, influenced by various factors including dietary habits and genetics, underscores the persistent need for effective and efficient stone removal techniques.[4,5]

As the leading approach in addressing complex renal calculi, Percutaneous Nephrolithotomy (PCNL) has become the gold standard, presenting a minimally invasive stone removal technique.[6] PCNL is proved to be associated with lesser morbidity, decreased complications rate and greater success rates.[7] PCNL involves the creation of a nephrostomy tract into the renal collecting system, followed by stone fragmentation through this tract to allow safe and efficient removal of stones.[8]

Percutaneous nephrolithotomy (PCNL) has emerged as a cornerstone in the management of renal calculi, particularly for stones larger than 2 cm. The procedure's evolution has led to the integration of various techniques aimed at enhancing efficacy and minimizing complications. Among these techniques, retrograde filling during tract dilatation has

gained attention for its potential benefits in improving access and visualization during the procedure. This essay explores the role of retrograde filling in PCNL tract dilatation, examining its implications for surgical outcomes, complications, and overall patient management. The supine position during PCNL has been advocated for its advantages in airway control and ventilation, which are crucial for high risk cardiac patient.[9] In this context the combination of retrograde and antegrade approaches can be done in supine position, known as endoscopic combined intrarenal surgery (ECIRS), has demonstrated promising results in enhancing stone-free rates, particularly for complex stone burdens.[10]

Recent advancements in PCNL technique introduced the concept of retrograde filling during tract dilatation. Retrograde filling, often utilizing normal saline or non-ionic contrast is the process of instilling a fluid medium into the renal collecting system prior to making the tract followed by continue filling during tract dilatation. This technique has gained attention due to its benefits, including facilitating tract dilation, minimizing trauma & if water is coming out to the dilators that means the tract is perfect, that potentially reducing the risk of injury to adjacent structures.[11]

The necessity of retrograde filling remains a subject of debate and very limited data is available on it. Hence, the use of retrograde filling, particularly with regard to the use of normal saline, the allocation of additional technician, and the risk of infection, need thorough investigation. Thus, this study aims to see the effect of retrograde filling on tract dilatation during PCNL among patients presenting at tertiary care hospital. The findings can guide the adoption or refinement of retrograde filling practices, contributing to the optimization of PCNL outcomes.

METHODOLOGY

This was prospective cohort study conducted at the department of Urology, LUMHS, Pakistan from Feb 2022 to Feb 2023. Sample size of 126 was estimated using Rao Soft sample size calculator, by taking statistics of stone free rate after PCNL as 85%, margin of error as 6% and 95% confidence level. Patients who were undergoing elective PCNL, aged 18 years and above of either sex were included in the study. Patients who underwent emergent or urgent PCNL procedures due to acute complications (e.g., obstructive uropathy, sepsis), pregnant patients, patients with history of PCNL, hypertension, diabetes, chronic kidney disease and patients with compromised immune systems were excluded from the study. Patients were selected consecutively for the study.

Institutional review board (IRB) approval was sought prior to study commencement (Ref# LUMHS/REC/48). Informed consent was obtained from all participating patients. Patients were divided into two groups, exposed group: patients undergoing PCNL with the utilization of retrograde filling (normal saline / non-ionic contrast infusion) during tract dilatation and unexposed group patients undergoing standard PCNL without retrograde filling.

Baseline demographic information (age, gender), stone characteristics (size, location), and surgical details (time of procedure and site of puncture) were collected. During the PCNL procedure with and without retrograde filling, time required for tract dilatation, data on ease of tract dilation and hospital stay was noted. Patients in both groups were followed up postoperatively to monitor for the development of infections for 2 weeks. The presence of a high-grade fever (>100°F), a WBC count >11,000, and a positive urine culture was classified as a urinary tract infection.

Descriptive statistics were summarized for patient characteristics and baseline demographics. Comparative analyses for numeric and categorical variables between the exposed and unexposed groups using independent samples t-test/Chi-square/Fisher exact test. Multivariate logistic regression was applied to see the association between infection and potential confounding factors. Odds ratio along with 95% Cis were reported. A p-value less than 5% was considered as significant.

RESULTS

Total 137 eligible participants were recruited for the study. Among them 9 patients lost to follow-up. Total 126 patients were included in the final analysis. Out of 126 patients, 74 patients were in exposed group and 52 patients were in unexposed group.

The mean age in both groups was similar: 36.25 years in the exposed group and 35.92 years in the unexposed group, with p-value=0.829. In both groups, majority of the patients were males. The size of stones was similar between the exposed and unexposed groups, with means of 3.01 cm and 3.19 cm, respectively (p-value=0.098). The most common stone location was the pelvis, observed in 38.1% of all cases. There were no significant differences in stone location between the exposed and unexposed groups, except for a slightly higher prevalence of stones located in the pelvis in the exposed group. The mean duration of the procedure also showed insignificant difference between both groups (p-value=0.075). The majority of punctures were performed in the lower pole of the kidney (72.2% of cases), followed by the upper pole (23.8%). Similar distribution of puncture sites was observed between the exposed and unexposed groups. (Table 1)

The time required for tract dilatation was comparable between the exposed and unexposed groups, with means of 2.74 minutes and 2.83 minutes, respectively (p = 0.437). The percentage of cases involving successful "first go tract in" was slightly higher in the exposed group (98.6%) compared to the unexposed group (90.4%), although this difference did not reach statistical significance (p = 0.081). The occurrence of "first go tract out" was rare, observed in only 1.4% of the exposed group and 9.6% of the unexposed

group. The duration of hospital stay was similar in both groups, with means of 1.51 days in the exposed group and 1.44 days in the unexposed group (p = 0.435). The exposed group showed a higher infection rate (55.4%) compared to the unexposed group (36.5%), with a statistically significant difference (p = 0.037). Moreover, the odds of infection was 2.15 folds higher among patients undergoing PCNL with the utilization of retrograde filling as compared to odds of infection in patients undergoing standard PCNL without retrograde filling (OR=2.15, 95% CI=1.04-4.46). (Table 2)

Given the significant difference in infection rates between the exposed and unexposed groups, the logistic regression was conducted to explore the association between the exposure and the likelihood of infection, while considering potential confounding factors. After adjusting the potential confounding factors for infection in a multivariate logistic model, patients with retrograde filling had a statistically significant increased odds of post-operative infection (p = 0.026). The adjusted odds ratio was 2.48, with a 95% CI of 1.11-5.53. This implies that patients with retrograde filling were 2.48 times more likely to experience post-operative infection compared to those without retrograde filling. Neither age (p = 0.335) nor gender (p = 0.723) exhibited a statistically significant association with post-operative infection. The adjusted odds ratios for age and gender were 0.98 (95% CI: 0.95-1.01) and 0.86 (95% CI: 0.38-1.94), respectively. Stone location, as categorized, did not show statistically significant associations with infection rates. Stone size also did not exhibit a statistically significant association with post-operative infection rates (p = 0.276). The adjusted odds ratio for stone size was 1.43 (95% CI: 0.76-2.63). (Table 3)

DISCUSSION

Renal calculi remain a significant burden globally,

Table 1: Baseline characteristics of patients in both groups (n=126)

	Overall	Exposed group (n=74)	Unexposed group (n=52)	p-value
Age in years	36.25±14.26	36.49±15.44	35.92±13.51	0.829
Gender				
Male	84 (66.7%)	50 (67.6%)	34 (65.4%)	0.789
Female	42 (33.3%)	24 (32.4%)	18 (34.6%)	
Size of stones (cm)	3.01±1.03	2.88±1.08	3.19±0.94	0.098
Location of stones				
Pelvis	48 (38.1%)	34 (45.9%)	14 (26.9%)	0.124
Lower Pole	8 (6.3%)	4 (5.4%)	4 (7.7%)	
Pelvis+Lower Pole	34 (27%)	16 (21.6%)	18 (34.6%)	
Pelvis+Upper Pole	21 (16.7%)	14 (18.9%)	7 (13.5%)	
Pelvsis+Lower Calyx	1 (0.8%)	1 (1.4%)	0	
Pelvis+Upper Calyx	9 (7.1%)	3 (4.1%)	6 (11.5%)	
Pelvis+Middle Calyx	5 (4%)	2 (2.7%)	3 (5.8%)	
Time of procedure (mins)	69.56±12.96	67.78±12.46	72.02±13.36	0.075
Site of puncture				
Lower Pole	91 (72.2%)	55 (74.3%)	36 (69.2%)	0.796
Middle Pole	3 (2.4%)	1 (1.4%)	2 (3.8%)	
Upper Pole	30 (23.8%)	17 (23%)	13 (25%)	
Middle Pole+Lower Pole	2 (1.6%)	1 (1.4%)	1 (1.9%)	

Table 2: Comparison of outcomes between both groups (n=126)

Outcomes	Exposed group (n=74)	Unexposed group (n=52)	p-value	OR (95% CI)
Time required for tract dilatation (mins)	2.74±0.66	2.83±0.47	0.437	0.70 (-0.129-0.296)
Access tract management				
First go tract in	73 (98.6%)	47 (90.4%)	0.081	7.76 (0.88-68.56)
First go tract out	1 (1.4%)	5 (9.6%)		
Hospital stay (days)	1.51±0.50	1.44±0.50	0.435	-0.07 (-0.25-0.11)
Infection				
Yes	41 (55.4%)	19 (36.5%)	0.037	2.15 (1.04-4.46)
No	33 (44.6%)	33 (63.5%)		

Table 3: Multivariate logistic regression analysis for post-procedure infection

	p-value	Adjusted OR (95% CI)
Retrograde filling		
No		1
Yes	0.026	2.48 (1.11-5.53)
Age in years	0.335	0.98 (0.95-1.01)
Gender		
Male		1
Female	0.723	0.86 (0.38-1.94)
Location of stones		
Pelvis		1
Lower Pole	0.115	0.166 (0.018-1.54)
Pelvis+Lower Pole	0.843	0.87 (0.24-3.16)
Pelvis+Upper Pole	0.997	1.00 (0.19-5.30)
Pelvis+Lower Calyx	0.999	-
Pelvis+Upper Calyx	0.394	0.42 (0.06-3.01)
Pelvis+Middle Calyx	0.240	4.40 (0.37-52.17)
Stone size (cm)	0.276	1.43 (0.76-2.63)

necessitating efficacious stone removal techniques.[12,14] Evidence showed that the prevalence of renal stones is 16% in Pakistan, mostly affecting people of age more than 30 years.[4,15] In past decades, PCNL, as a minimally invasive approach for complex renal calculi, has demonstrated superior outcomes compared to other methods, prompting continuous refinement of its techniques.[13,14] Recently, the utilization of retrograde filling during tract dilatation has gained attention.[6,16,17] Many studies have been conducted to assess the effect of PCNL on renal stones, but to best of our knowledge no study is conducted to see the association of retrograde filling during PCNL tract dilatation with post-procedure outcomes. Therefore, the present study sought to see the effect of retrograde filling on tract dilatation during PCNL among patients presenting at tertiary care hospital, Pakistan.

Evidence showed that PCNL is significantly associated with systemic inflammatory response syndrome. Almost 26% to 40% of the patients get infected after PCNL, even if pre-operative prophylactic treatments were given and almost 0.4% to 3% suffered from sepsis.[18] The idea of using retrograde filling for the ease of tract dilatation during PCNL may further increase the odds of infection. This is due to the possibility of extravasation of normal saline into the retroperitoneum and renal pelvis with the bacterial dissemination during retrograde filling, which could consequently lead to bacterial sepsis.[19] In the current study, we also observed that the odds of infection was significantly higher in patients who had retrograde filling for tract dilatation during PCNL as compared to those who had not, even after controlling for potential confounding factors. This finding prompts careful consideration of the benefits and risks associated with retrograde filling. The introduction of external substances like normal saline into the body, even when performed under controlled conditions, can inadvertently disturb the body's equilibrium and immune responses, rendering patients more susceptible to microbial invasions.[2]

In the current study, we found insignificant differences in ease of tract dilation between the exposed and unexposed groups. This observation aligns with the notion that the primary goal of retrograde filling—streamlining tract dilation—may not yield appreciable advantages in terms of ease of the procedure, as evidenced by the negligible variance in tract dilation experiences between the two groups. The absence of significant differences in ease of dilation contradicts the potential notion that retrograde filling could inherently enhance tract expansion. This implies that, at least in terms of ease of tract dilation, the use of retrograde filling might not present substantial added value. However, the adoption of retrograde filling may inadvertently introduce economic implications by adding to the procedure's cost due to the usage of extra normal saline. Additionally, this practice could demand the involvement of an extra technician to oversee the administration of retrograde filling.

The effectiveness of retrograde filling during tract dilatation can be attributed to its ability to enhance the visibility of the renal anatomy. Studies have demonstrated that retrograde pyelography can significantly aid in identifying the optimal access point for nephrostomy, particularly in challenging anatomical situations[18]. Furthermore, the use of retrograde filling may reduce the risk of complications associated with blind puncture techniques, such as vascular injury or inadvertent damage to surrounding structures. By providing real-time feedback on the anatomy, retrograde filling can facilitate more precise needle placement and tract dilation, ultimately leading to improved surgical outcomes. The choice between standard PCNL and mini-PCNL is also influenced by the use of retrograde techniques. Mini-PCNL, characterized by smaller nephrostomy tracts, has been associated with reduced morbidity and shorter recovery times compared to standard PCNL[19]. However, the success of mini-PCNL often hinges on the surgeon's ability to achieve adequate access and visualization, which can be enhanced through retrograde filling. The integration of retrograde techniques in mini-PCNL procedures has been shown to improve stone-free rates while maintaining a favorable safety profile [20]. This is particularly relevant for patients with complex stone anatomies, where traditional approaches may fall short. Complications remain a significant concern in PCNL, with bleeding, infection, and organ injury being the most common adverse events reported.[21] The incorporation of retrograde filling during tract dilatation may mitigate some of these risks by improving the accuracy of needle placement and reducing the need for extensive dissection. Studies have indicated that the use of retrograde techniques can lead to lower complication rates, particularly in high-risk populations, such as those with anatomical abnormalities

or prior surgical interventions.[22] Moreover, the ability to visualize the renal collecting system in real-time allows for immediate identification and management of potential complications, further enhancing patient safety. The role of retrograde filling extends beyond the initial access phase of PCNL. During the procedure, continuous retrograde irrigation can help maintain visibility and prevent the formation of clots or debris that may obstruct the surgical field.[23] This is particularly important in cases involving large stone burdens or complex stone morphologies, where the risk of intraoperative complications is heightened. By ensuring a clear view of the surgical site, retrograde filling can facilitate more efficient stone fragmentation and removal, ultimately leading to improved stone-free rates. In addition to its technical advantages, retrograde filling during PCNL has implications for postoperative outcomes. Studies have shown that patients undergoing PCNL with retrograde assistance experience shorter hospital stays and faster recovery times compared to those who do not receive such interventions.[24] This is likely due to the reduced need for additional procedures or interventions to address complications arising from inadequate access or visualization. Furthermore, the enhanced stone-free rates associated with retrograde filling may translate into lower rates of recurrent stone formation, thereby improving long-term patient outcomes.[25] The integration of retrograde techniques into PCNL protocols is not without challenges. The need for skilled personnel proficient in both retrograde and antegrade techniques can complicate the implementation of these approaches, particularly in resource-limited settings.[26] Additionally, the learning curve associated with mastering these techniques may pose barriers to widespread adoption among urologists. However, the potential benefits of retrograde filling in terms of improved access, reduced complications, and enhanced patient outcomes warrant further investigation and training in this area. In conclusion, retrograde filling during PCNL tract dilatation represents a significant advancement in the management of renal stones.[27-29] By enhancing access and visualization, this technique has the potential to improve surgical outcomes while minimizing complications. As the field of urology continues to evolve, the integration of retrograde techniques into standard PCNL protocols may become increasingly common, ultimately benefiting patients with complex renal stone burdens. Future research should focus on optimizing these techniques and evaluating their long-term impact on patient outcomes, paving the way for more effective and safer management of renal calculi.

The current study brings several strengths to the forefront. Firstly, the study's prospective cohort design lends itself to robust data collection and minimizes recall bias. Our study has few limitations. Firstly, the study's single-center design may limit the external validity of the findings to other healthcare settings. Secondly, the absence of blinding among the surgical team and patients introduces the potential for performance and detection bias. Furthermore, the short follow-up duration of two weeks might not capture delayed infections that could manifest beyond this timeframe. It is recommended that urologists carefully weigh the advantages of retrograde filling against its potential drawbacks. While retrograde filling may not significantly influence ease of tract dilation, its introduction could lead to increased procedural costs due to the use of normal saline and necessitate the involvement of an additional technician. Therefore, adopting retrograde filling should be driven by a judicious assessment of its benefits in relation to these potential costs and logistical complexities.

CONCLUSION:

The use of retrograde filling during tract dilatation is significantly associated with post procedure infection. Furthermore, it is not associated with ease of tract dilation, its introduction carries implications for cost-effectiveness and procedural logistics.

Authors Contribution:
Syed Ali Raza Jaffry: Objective, data
Javed Altaf Jat: final approval
Waqar Ahmed Memon: data collection
Abdul Qayoom Ghangro: data entry, write-up
Ahsan Ali Arain: Write-up, ethics
Tamoor Jatoi: data analysis

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Original Article **Open Access**

Critical Role of Antental Care in Improving Perinatal and Neonatal Outcomes

Rabia Naeem, Nazma Gul, Sumbal Pervez, Neelam Hassan, Noreen Khattak, Hina Gul

ABSTRACT

Objective: To determine the essential role of antenatal care in enhancing perinatal and Neonatal Outcomes in a Women Attending Obgyn OPD, in Lady Reading Hospital, Peshawar.

Study Design and Setting: Descriptive cross-sectional study, carried out in the Obstetrics & Gynaecology Department of Lady Reading Hospital, Peshawar.

Methodology: Six months study conducted from 9th May 2021 to 9th November 2021. A total of 107 women presenting with age between 20 to 45 years, primiparous, with single gestation, any antenatal visits were enrolled. Data was collected and statistically analyzed by SPSS version 21.

Results: Among 107 women, the average age was 27 years ±5.74. Sixty-five (61%) women had =4 antenatal visits, Moreover, 7(7%) babies had fetal distress, 11(10%) babies were admitted to NICU, 6(6%) babies had early neonatal death, 4(4%) babies had low birth weight, 13(12%) babies had pre term birth. perinatal outcomes have no significant difference with antenatal visits as still birth (P=0.366), fetal distress (P=0.549), admitted to NICU (P value = 3903), early neonatal death (P value = 759), low birth-weight (P=0.551), pre-term delivery (P=0.202).

Conclusion: This research highlights the critical role of Antenatal Care (ANC) in reducing adverse perinatal outcomes, aligning with established evidence. ANC enables early identification and management of pregnancy complications, promotes healthy behaviors, and ensures timely interventions.

Keywords: Perinatal Outcome, Antenatal Visit, NICU, Preterm Birth

How to cite this Article:
Naeem R, Gul N, Pervez S, Hssan N, Khattak N, Gul H. Critical Role of Antental Care in Improving Perinatal and Neonatal Outcomes. J Bahria Uni Med Dental Coll. 2025;15(2):86-90 DOI: https://doi.org/10.51985/JBUMDC2024449

INTRODUCTION:

Antenatal care deals with early detection of pregnancy disorders and prevention of these disorders. It actually, is the key to modern obstetrics.[1,2] The common causes of mortality and morbidity among women aged 15 to 49 in underdeveloped nations, are the complications arising during pregnancy and childbirth.[3] Every year, around 287,000 women die due to pregnancy-related causes globally; 99% of these deaths occur in developing countries. Ethiopia ranks first among the developing countries in terms of mortality and morbidity rates in pregnant women.[4] In developing nations, nearly all women during pregnancy receive prenatal care at least once, while in sub-Saharan countries, where women take ANC services at least once, the estimate is about 68%, and the majority of them visit the health facilities on their third visit.[5]

The timing of a woman's first antenatal care (ANC) visit, the total number of ANC visits, and adverse perinatal outcomes may occur because of the failure to attend the recommended ANC services.[6] Maternal health statistics are similarly concerning. Pakistan's maternal mortality rate is high, with 350 deaths per 100,000 live births, though in some rural areas, this figure rises to 700 deaths per 100,000 live births. This translates to approximately 30,000 maternal deaths annually.[7] Several factors contribute to this elevated mortality rate, such as the limited access to prenatal care and skilled birth attendants.[8] Only about 30 percent of pregnant women in Pakistan receive prenatal care, and fewer

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Received: 03-10-24
Accepted: 12-02-25
1st Revision: 28-10-24
2nd Revision: 06-02-25
3rd Revision: 09-02-25

than 20 percent of deliveries are attended by trained health professionals.[9] In rural areas, approximately 90 percent of deliveries are handled by untrained or semi-trained traditional birth attendants. The total fertility rate is 4.1 births.[10] There are numerous impediments to the early commencement and use of prenatal care. Financial hurdles to early antenatal care include a lack of health insurance, difficulty arranging an appointment, distances from care venues, a lack of transportation, and childcare issues. Young maternal age, poor social status, low parental income, and high parity have all been shown as sociodemographic barriers to early prenatal care initiation.[11]

Many studies have shown that ANC has a positive influence on perinatal outcomes, including lowering the risk of low birth weight, postpartum hemorrhage (PPH), premature birth, and perinatal mortality. Recommends four consecutive ANC visits for all low-risk pregnant women.[12] The total adherence rate of women to ANC visits was 49.9%, and the perinatal outcomes of stillbirth, low birth weight, early and late neonatal death, were about 24.3%, 7.5%, 12.3%, 12.7%, and 11.9%, respectively.[13] Improving community-based prenatal care services can increase child survival.[2] the majority of neonatal and maternal deaths are avoidable; antenatal care is one of the strategic and important key steps for reducing pregnancy-related mortality and morbidity, by prompt detection and treatment of complications in earlier pregnancy periods. To improve the health of pregnant women during childbirth and encourage utmost care, ANC is a widely utilized strategy. To determine the frequency of Perinatal and Neonatal Outcomes in a Women Attending Obs and Gynae Unit in Lady Reading Hospital, Peshawar. The findings will help enhance antepartum fetal well-being surveillance and inform local health researchers on the importance of intensive intrapartum fetal monitoring and postpartum care in our population.

METHODOLOGY:

This descriptive cross-sectional study was conducted in the Obstetrics & Gynaecology Department of Lady Reading Hospital, Peshawar, over six months period, from May 9, 2021, to November 9, 2021. The sample size was 107, calculated using a 7.5% proportion of low birth weight,[14] a 95% confidence level, and a 5% margin of error, determined via the WHO sample size calculator. Ethical approval was obtained from the Institutional Review Board (Ref. No. 546/LRH/MTI on dated 29-07-2020), and informed consent was collected from all participants. Participants were recruited using a non-probability consecutive sampling technique. All women aged 20 to 45 years, primiparous, carrying a single fetus, and attending antenatal check-ups at the hospital from 24 weeks onward based on their last menstrual period (LMP) were included. Both new and follow-up patients who met the inclusion criteria were recruited from the clinic. Women were recruited upon their arrival for antenatal check-ups, and their inclusion was determined at that point. Those who delivered either vaginally or through cesarean section (CS) within the first 24 hours postpartum were included in the study. Exclusion criteria consisted of women with pregnancies involving congenital anomalies, known medical comorbidities, preterm or obstructed labor, antepartum hemorrhage, or chorioamnionitis. Antenatal Care Contacts, defined as the number of antenatal visits made by the pregnant woman to the healthcare facility during her pregnancy. In this study, antenatal care contacts were categorized based on the number of visits and analyzed in relation to perinatal outcomes. Perinatal Outcomes included neonatal intensive care unit (NICU) admissions, early neonatal deaths (deaths within the first 7 days of life), stillbirths (fetal deaths occurring at =28 weeks of gestation), and other adverse fetal outcomes. Gestational age was calculated using the LMP or the earliest available obstetrical ultrasound. Data was recorded on a structured form, capturing detailed patient history, clinical investigations, and perinatal outcomes.

Data analysis was conducted using SPSS version 21. Continuous variables, such as age, were presented as means and standard deviations, while categorical variables, including perinatal outcomes and the number of antenatal care contacts, were expressed as frequencies and percentages. Perinatal outcomes were stratified by age and antenatal care contacts frequency to identify potential effect modifiers. Post-stratification, a chi-square test was applied, with a P-value of =0.05 considered statistically significant.

RESULTS:

The demographic analysis of the present study revealed a mean maternal age of 27 years ± 5.74, indicating a relatively young reproductive age group. Furthermore, the antenatal care utilization patterns showed that 65 (61%) mothers had four or fewer visits, while 42 (39%) had more than four visits (Table 1). This distribution highlights the varying levels of prenatal care adherence among the study participants. The majority of mothers attended fewer than five antenatal visits, which is consistent with the World Health Organization's recommended minimum of four visits for low-risk pregnancies. However, the 39% with more than four visits may indicate complications or high-risk pregnancies requiring closer monitoring.

This study perinatal outcomes revealed a range of frequencies, highlighting areas of concern for maternal and fetal health. Specifically, the data showed that 5% of births resulted in stillbirths, 7% experienced fetal distress, 10% required NICU admissions, 6% resulted in early neonatal deaths, 4% had low birth weight, and 12% were preterm births (Table 2). These rates underscore the prevalence of adverse perinatal outcomes in our study population. Notably, the stillbirth rate aligns with global averages, while the preterm birth rate exceeds recommended thresholds. The frequencies of fetal distress, NICU admissions, and early neonatal deaths also warrant attention, emphasizing the need for targeted

interventions to improve perinatal care.

Our analysis yielded a notable finding: no significant correlation existed between maternal age and adverse perinatal outcomes. Specifically, we observed no significant associations between maternal age and stillbirth (P = 0.7580), fetal distress (P = 0.5936), NICU admission (P = 0.8403), early neonatal death (P = 0.9867), low birth weight (P = 0.4804), and preterm birth (P = 0.6949). This suggests that, within our study population, maternal age may not be a predictive factor for these adverse outcomes. These results align with previous research indicating that other factors, such as prenatal care quality, socioeconomic status, and pre-existing medical conditions, may play a more significant role in determining perinatal health (Table 3). This study analysis revealed another crucial finding: no significant association existed between the number of antenatal visits and adverse perinatal outcomes. Specifically, we found no significant correlations between antenatal visit frequency and stillbirth (P = 0.3665), fetal distress (P = 0.5494), NICU admission (P = 0.3903), early neonatal death (P = 0.7599), low birth weight (P = 0.5518), and preterm birth (P = 0.2025), as detailed in Tables 4. This suggests that, while antenatal care is essential, the mere number of visits may not be a reliable predictor of perinatal outcomes. Other factors, such as care quality, patient engagement, and underlying health conditions, may play a more significant role in determining perinatal health (Table 4).

Table 1: Number of Antenatal Visits (n=107)

Antenatal Visits	%(n)
= 4 visits	61 (65)
>4 visits	39 (42)
Total	100 (107)

Table 2: Perinatal Outcome (n=107)

Perinatal Outcome	**%(n)**
Still birth	5 (5)
Fetal distress	7 (7)
NICU	10 (11)
Early neonatal death	6 (6)
Low birth weight	4 (4)
Preterm birth	12 (13)

DISCUSSION:

Our study shows that ANC plays an important role in reducing adverse perinatal outcome. A study by Akbar *et al.*, demonstrated a highly significant correlation between the number of antenatal visits and neonatal mortality and morbidity.[15] Mothers who attended four or more antenatal visits had notably better pregnancy outcomes.[16] The infants of these mothers (booked) experienced significantly lower morbidity rates compared to those of mothers who had fewer than four antenatal visits (unbooked). Statistically significant differences were found between booked and unbooked mothers in terms of prematurity (p=0.001), low birth weight (p=0.001), birth asphyxia (p=0.001), neonatal sepsis (p=0.001), pneumonia (p=0.001), diarrhea (p=0.019), congenital malformations (p=0.01), seizures (p=0.001), and post-term births (p=0.001). A comparison of outcomes between resident and attending obstetrician deliveries revealed significant differences. Residents had a lower rate of severe

Table 3: Stratification of Perinatal Outcomes with Respect to Age Distribution

Perinatal Outcome		**18-30 Years**	**31-45 Years**	**Total**	**P-value**
Still Birth	Yes	3 (4%)	2 (6%)	5	0.7580
	No	68 (96%)	34 (94%)	102	
	Total	71 (100%)	36 (100%)	107	
Fetal Distress	Yes	4 (6%)	3 (8%)	7	0.5936
	No	67 (94%)	33 (92%)	100	
	Total	71 (100%)	36 (100%)	107	
NICU Admissions	Yes	7 (10%)	4 (11%)	11	0.8403
	No	64 (90%)	32 (89%)	96	
	Total	71 (100%)	36 (100%)	107	
Early Neonatal Death	Yes	4 (6%)	2 (6%)	6	0.9867
	No	67 (94%)	34 (94%)	101	
	Total	71 (100%)	36 (100%)	107	
Low Birth Weight	Yes	2 (3%)	2 (6%)	4	0.4804
	No	69 (97%)	34 (94%)	103	
	Total	71 (100%)	36 (100%)	107	
Pre-term Birth	Yes	8 (11%)	5 (14%)	13	0.6949
	No	63 (89%)	31 (86%)	94	
	Total	71 (100%)	36 (100%)	107	

maternal morbidity (7.8% vs 9.9%) and severe neonatal morbidity (8.3% vs 15.1%) compared to attending obstetricians.[17] Another study by Haftu *et al.,* found that women's overall adherence to antenatal care visits was 49.9%, while perinatal outcomes such as stillbirth, low birth-weight, early and late neonatal death were 12.3%, 7.2%, 10.3%, and 2.7% respectively.[12] Out of the study population, 6.5% experienced maternal mortality (four cases) and 67.8% experienced perinatal mortality (42 cases). Additionally, 16.1% of patients (ten individuals) required postoperative intensive care. Notably, maternal and perinatal mortality rates were substantially higher among patients with unscarred uteruses, with statistical significance ($p = 0.0001$ and $p = 0.026$, respectively).[18] Similarly, Jaleta *et al.,* reported that 576 (74.1%) were between the ages of 21 and 34. 771 (99.2%) were married, and more than half (55.3%) lived in cities.[19] The average maternal age was 26 years, with an interquartile range (IQR) of 7 years. Nearly half of the participants, 382 (49.2%), were multigravida, and 97% had attended at least one ANC follow-up, with 75.8% of the women attending one to four ANC visits. The overall rate of adverse perinatal outcomes was 31.5%, including 6.4% stillbirths and 5% early neonatal deaths. The incidence of small for gestational age, preterm birth, and low birth weight combined was 16.6%. According to a five-year study, nearly two-thirds (66.4%) of deliveries resulted in at least one neonatal complication. Notably, the incidence of complications decreased over the study period, dropping from 76% in 2009 to 66% in 2013 - a significant 13.2% reduction. The most prevalent complications included stillbirths, prematurity, respiratory distress syndrome, and low birth weight, accounting for 30.2%, 32.8%, 37.9%, and 30.2% of cases, respectively. These findings highlight areas for continued improvement in neonatal care and suggest progress in reducing complications over time.[20] Abbas *et al.,* reported that the group with regular ANC visits had a significantly higher mean birth weight ($p=0.000$).[21] The irregular ANC group showed higher rates of preterm births, lower birth weight babies, stillbirths, and neonatal intensive care unit (NICU) admissions compared to the regular ANC group (13% vs. 3.6%, 10% vs. 1.8%, 25.4% vs. 7.5%, and 8.5% vs. 1.8%, respectively; $p=0.000$). A study revealed significant adverse fetal outcomes, including low Apgar scores in 17.8% of cases, low birth weight in 17.8%, birth asphyxia in 32.9%, brachial plexus injuries in 12.5%, and fetal distress in 11.4%.[22] The study revealed various adverse fetal and neonatal outcomes. Specifically, 16% of cases experienced fetal distress, while 18.5% resulted in macrosomia (excessive birth weight). Additionally, birth asphyxia occurred in 18.1% of cases, meconium aspiration syndrome affected 8.4%, and 9.1% required admission to the Neonatal Intensive Care Unit (NICU).[23] In a study of 78,166 women, researchers found that 2.2% underwent pre-labor cesarean sections (CS), while 97.8% attempted a trial of labor. Of those who attempted a trial of labor, 87.5% delivered vaginally, and 12.5% required an intrapartum CS. The study revealed that pre-labor CS significantly reduced the risk of stillbirth or neonatal death within the first day of life, with an odds ratio of 0.2. However, no significant differences were found in maternal mortality or neonatal mortality after Day 1 between women who had pre-labor CS and those who attempted trial of labor. Notably, women who underwent intrapartum CS or operative vaginal delivery during trial of labor faced higher risks of maternal mortality and morbidity, as well as neonatal mortality after Day 1, compared to those who delivered spontaneously vaginally.[24]

In a resource poor communities of Pakistan, we need to improve ANC on focusing effective referral system and to conduct workshops on regular basis to train health care providers to manage delivery complications for the better perinatal outcomes. The reasons for NICU admissions were not examined to determine whether antenatal visits contributed to these admissions. Since the study was limited to a single department, the findings cannot be generalized, highlighting the need for further research. Future research should consider a larger population and focus on the impact of adequate and regular antenatal care on improving perinatal outcomes.

CONCLUSION:

These findings suggest that factors other than maternal age and antenatal visit frequency may influence perinatal outcomes. Future research should explore additional variables, such as socioeconomic status, healthcare quality, and pregnancy complications, to better understand the complex relationships driving perinatal health. This study underscores the vital role of Antenatal Care (ANC) in mitigating adverse perinatal outcomes, aligning with existing evidence that emphasizes the importance of prenatal care in ensuring optimal maternal and fetal well-being. Although our analysis did not reveal a statistically significant correlation between ANC and perinatal outcomes, this finding does not diminish the significance of ANC in improving health outcomes. Rather, it suggests that other factors, such as socioeconomic status, access to healthcare, and quality of care, may influence the effectiveness of ANC in reducing adverse perinatal outcomes. Further research is warranted to explore these interactions and identify opportunities to enhance the impact of ANC on perinatal health.

Authors Contribution:
Rabia Naeem: Study design, data collection
Nazma Gul: Data collection, data analysis
Sumbal Pervez: Data intrepretation, Data analysis
Neelam Hassan: Drafting and data analysis
Noreen Khattak: Drafting, and data collection
Hina Gul: Data collection, critical review and approval

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Original Article **Open Access**

Transcatheter Palliative Balloon Pulmonary Angioplasty in Symptomatic Patients with Tetralogy of Fallot and its Outcome at Tertiary Care Setting

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ABSTRACT

Objective: To analyze transcatheter palliative balloon angioplasty's safety, efficacy, and clinical outcomes by a single operator in symptomatic Tetralogy of Fallot (TOF) patients in tertiary care.

Study Design and Setting: This is a case series study. It was carried out at the Pediatric Cardiology Department PNS SHIFA Karachi and the Armed Forces Institute of Cardiology (AFIC/NIHD) Rawalpindi, Pakistan, from November 2022 to May 2024.

Methodology: This study selected patients from the pediatric database using non-probability consecutive sampling. A sample size of n=30 was taken. Symptomatic infants of TOF requiring palliation for (right ventricular outflow tract) RVOT obstruction were included and infants with predominant valvular narrowing and those not fulfilling the criteria of TOF were excluded. Data was entered and analyzed by using SPSS version-24:00. In descriptive statistics, Mean ± SD was calculated for continuous variables while frequency (%) for categorical variables. The Chi-square test was used to find out the association between categorical variables, p-value of <0.05 was taken as statistically significant.

Results: Out of 30 patients, 11(37%) were males and females were 19(63%). The median age was 24 months. Immediate improvement in saturation was noted in all patients and transient arrhythmias 5(16%) was the most encountered complication.

Conclusion: Transcatheter palliative balloon angioplasty is becoming the first line of treatment for patients with Tetralogy of Fallot due to its physiologic improvement in blood flow to the lungs and reciprocal increase in saturation. It is safe and requires much less hospital stay in a professionally sound environment.

Keywords: Balloon Angioplasty, Congenital Heart Disease, Palliative Treatment, Tetralogy of Fallot, Transcatheter Intervention.

How to cite this Article:

Shaikh AA, Sadiq N, Hasnain MR, Ata I, Ullah N, Anwar S. Transcatheter Palliative Balloon Pulmonary Angioplasty in Symptomatic Patients with Tetralogy of Fallot and its Outcome at Tertiary Care Setting. J Bahria Uni Med Dental Coll. 2025;15(2):91-96 DOI: https://doi.org/10.51985/JBUMDC2024491

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Received: 18-12-24
Accepted: 13-03-25
1st Revision: 20-01-25
2nd Revision: 03-02-25
3rd Revision: 03-03-25

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease accounting for 7-10% of all congenital heart diseases.[1] It includes ventricular septal defect (VSD), overriding of the aorta, pulmonary stenosis, and right ventricular hypertrophy.

Associations of TOF are with 22q11 microdeletions, trisomy 21, Alagille's syndrome, Cat Eye syndrome, or CHARGE and VATER associations. The severity of symptoms depends upon the right ventricular outflow tract (RVOT) obstruction. Many symptomatic young infants are treated by either the complete surgical repair or by the palliative methods early in their life. The mainstay of treatment for patients with TOF is complete surgical repair and it has long-term survival rates of more than 90% after 25 years of surgery.[2] Despite these impressive outcomes, access to timely surgical repair remains a challenge in resource-limited settings, highlighting the critical role of interim palliative measures. Early intervention can mitigate life-threatening hypoxemic spells and improve overall clinical stability in affected infants.[3]

As more patients with repaired Tetralogy of Fallot reach

adulthood, the long-term effects of isolated, surgically induced pulmonary valvular insufficiency or insufficiency and mild stenosis (as is more typical with smaller transannular patches) are still being defined. A to-and-fro murmur at the left sternal border is present in many patients following tetralogy repair and in all patients undergoing transannular patch repairs.[4] Patients with more severe or prolonged pulmonary valve insufficiency may also develop tricuspid regurgitation when the tricuspid valve annulus dilates. A holosystolic murmur at the lower left sternal boundary will occur in these patients. While smaller degrees of residual obstruction typically do not require reintervention, patients with a moderate to severe residual gradient (stenosis) across the right ventricular obstruction typically require surgery. The pulmonic listening post, located on the left upper sternal border, is the ideal place to hear the quiet, high-pitched, early diastolic decrescendo murmur caused by pulmonic regurgitation.[5]

Palliative methods are kept reserved for those patients who are not fit for open surgery.[6] A study of the data showed that the most important element was the medicine dose rather than the patient's age. Results have improved so much over the last 60 years that with repair surgery, almost 95% of neonates with this condition should live to adulthood. As an alternative to the surgical technique of a modified Blalock-Taussig shunt to promote pulmonary artery growth in cyanotic children with tetralogy of Fallot, right ventricular outflow tract (RVOT) stenting has surfaced recently.[7] Palliative methods include surgical palliation in the form of modified Blalock Taussig BT-shunt and transcatheter palliation in the form of Balloon Pulmonary Angioplasty and RVOT stenting.[8] Transcatheter Balloon Pulmonary Angioplasty is the standard method of emergency treatment of RVOT obstruction and has decreased the postoperative hospital stay and shown good results of growth of pulmonary valve and arteries.[9-11] Balloon angioplasty facilitates the anterograde pulmonary blood flow and enhances oxygen saturation at its standards by promoting the growth of pulmonary arteries.[10] The procedure involved the use of a balloon inserted through a guide wire and the balloon is set at the narrowest portion of the pulmonary stenosis and is inflated by low pressure.[11]

However, every procedure has its side effects, so some are minor ones ranging from bleeding from a punctured site, arrhythmias (tachycardia and bradycardia), infundibular spasm, pulmonary edema, etc.[13] In experienced centers, careful patient selection and adherence to procedural guidelines have minimized the incidence of complications, reinforcing the value of balloon angioplasty as a viable palliative approach. We have routinely practiced balloon angioplasty in symptomatic young infants with TOF. This study aimed to assess the immediate results of percutaneous balloon angioplasty in symptomatic infants diagnosed with TOF in a tertiary-care setting.

METHODOLOGY

This case series study was conducted at the Pediatric Cardiology Department, Tertiary Cardiac Care Center PNS SHIFA/AFIC, from November 2022 to May 2024 by a single operator. The study was conducted by selecting patients from the pediatric database using non-probability consecutive sampling. Inclusion criteria included (1) Symptomatic TOF patients having frequent spells with specifically valvular narrowing, (2) Small Branch Pulmonary arteries, (3) Asymmetrical Pulmonary arteries, (4) Small Left Ventricle, (5) Multiple VSDs. Exclusion criteria included: Patients with predominant infundibular narrowing.

The study was conducted on consecutive patients who met inclusion criteria after approval of parents/ guardians and getting informed written consent. Patients were selected using non-probability consecutive sampling. All symptomatic patients with Tetralogy of Fallot meeting the inclusion criteria were enrolled in the study in the order they presented for treatment at the tertiary care center. No randomization was performed, and every eligible patient who sought medical attention within the study period was included until the sample size was reached.

The sample size of 30 was determined based on the availability of eligible patients within the study period, as well as feasibility constraints. Since this was a case series study, a formal sample size calculation was not performed. Instead, the number was chosen based on prior similar studies in the literature and the expected number of cases presenting to the tertiary care center during the study duration

The study was conducted following ethical guidelines, with approval from the hospital's Ethical review committee. Data and information of patients were kept confidential. All patients were admitted to the hospital after baseline investigations and 2D echocardiography. The procedure was explained in detail to the family with pros and cons. Interventions were performed at the discretion of the attending cardiologist. General criteria for intervening included discrete angiographic stenosis (as opposed to diffuse hypoplasia), typically with a pressure gradient across the stenotic vessel. Elevated central pulmonary artery pressure was a consideration in decision-making but was not necessarily present. Technical considerations, such as balloon type, size, inflation pressure, number of inflations, etc, were at the discretion of the interventional cardiologist. Because balloon inflation pressure was documented selectively, there was insufficient data for robust analysis. In general, our preference is to avoid pulmonary artery stents in this population, particularly in the peripheral branches.

All procedures were done under general anesthesia, and a guide wire was accessed through the femoral vein to the inferior vena cava to the right atrium to the right ventricle to the pulmonary artery. The balloon size was taken by pulmonary valve annulus in the range of 1.5-2:1 ratio of the pulmonary valve. In 2 patients, MAPCAs coiling was also

done in the same setting, 2 patients had branch PAs stenosis as well, so balloon angioplasty of branch Pas was done, and 6 patients required two balloons as after first ballooning there was no substantial increase in flow to pulmonary arteries so larger size balloon was taken with good result. In patients with asymmetrical pulmonary arteries (Figure 1), the balloon angioplasty of the branch pulmonary artery was done (Figure 2,3) with good results. There is severe stenosis as shown in Figure 1. After successful balloon dilation, the waist is disappeared in Figure 2. Post-procedure angiogram image shows patent flow to the left pulmonary artery (LPA) as shown in Figure 3.

These patients otherwise require a modified BT shunt for the growth of pulmonary arteries. All the procedural details were noted down. After the procedure, all patients were monitored in the post-catheterization ICU for any complications and course of recovery. Vital signs, oxygen saturation, catheter site, limb perfusion, blood gas analysis, x-rays, and echocardiography were continuously monitored. Data was entered and analyzed by using Statistical Package for the Social Sciences (SPSS) version 24:00. For descriptive statistics, mean ±SD was calculated for continuous variables while frequency (%) for categorical variables. To find out the association between categorical variables, the Chi-square test was applied. P-value of =0.05 was taken as statistically significant.

RESULTS

Out of 30 patients who underwent RVOT palliation balloon angioplasty, 11(37%) were males and 19(63%) were females. The median age and hospital stay of the study participants was 24 months (4 months-25 Years) and 24.3±6.2 hours, respectively (Table 1).

We encountered only transient arrhythmias (16%) and cyanotic spells (.06%) in our patients (Table 2). There were no major complications like perforation, pericardial effusion, pulmonary edema, and cardiac arrest during this study.

Table 1: Demographics and Procedural Parameters of Study Participants

Variables	**Frequency**	
Age (months/year) Median	24 months (4m-25yrs)	
Gender	Male	11(37%)
	Female	19(63%)
PICU Stay (hours) Mean±SD	24.3±6.2 hours	

Table 2 Frequency of Procedural Complications

Complications	**Frequency**
Bradycardia	3
Tachycardia	2
Cyanotic spell	2

Figure 1 Showing 2 wires parked in LPA with balloon angioplasty; there is severe stenosis as marked by the narrowing of the middle part of the balloon (waist).

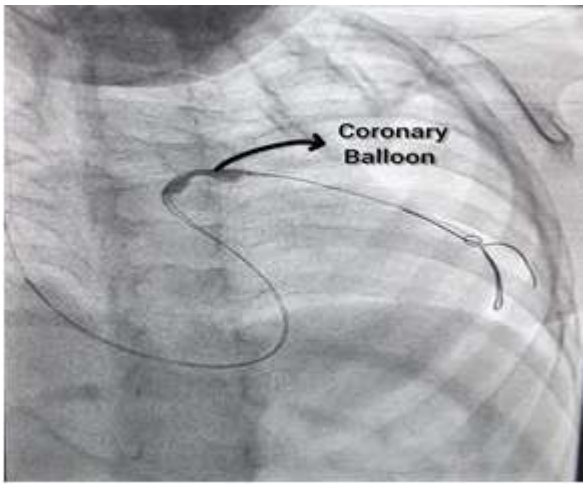


Figure 2 Angiogram showing dilation of balloon with disappearance of waist as it was significant in figure 1

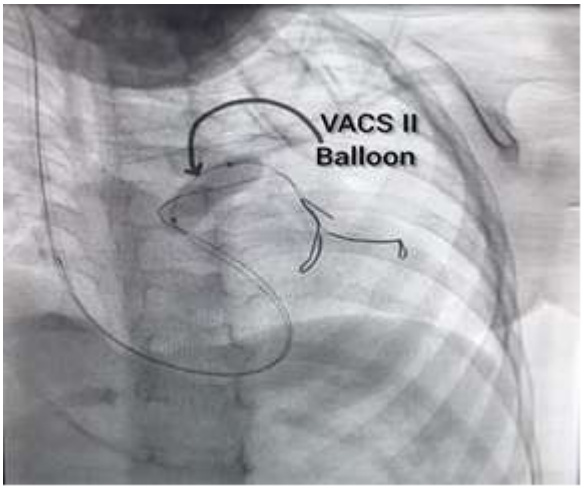
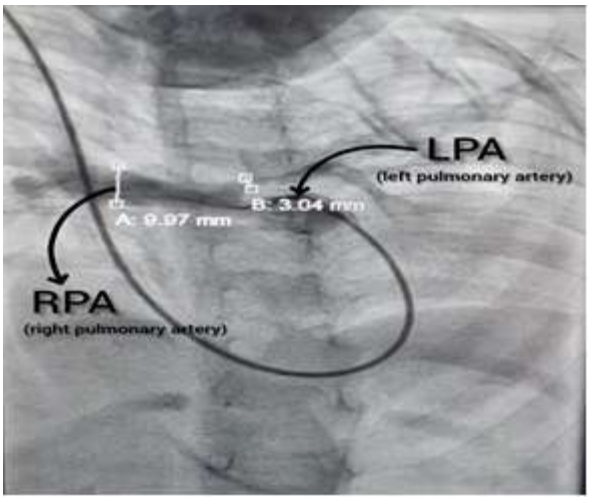


Figure 3 Post-ballooning Angiogram showing good flow to LPA



DISCUSSION:

TOF is commonly observed cyanotic congenital heart disease in clinical practice and surgical repair is done during infancy in most developed centers.[14] However, in our scenario where several reasons result in late surgeries including late diagnosis/referrals, financial constraints, a smaller number of centers/expert hands, etc. In several patients, the anatomy is considered unsuitable for complete repair, requiring palliation to improve the symptoms and underlying pathology as well. A portion of patients will experience symptoms early on and will either receive a full neonatal repair or staged palliation, even if the majority of individuals remain asymptomatic until surgical repair.

Historically, surgical phased palliation which dates back to the original Blalock-Taussig-Thomas (BTT) shunt—was carried out. Although other surgical palliations have been carried out, many patients now receive phased palliations in the catheterization lab before full surgical repair because of advancements in catheter-based technology and outcomes. Patients with TOF can benefit from three common treatments that enable stepwise palliation: patent ductus arteriosus (PDA) stenting, RVOT stenting, and balloon pulmonary valvuloplasty. Selecting an intervention is unique to each patient and institution. A minimally invasive surgery known as balloon valvuloplasty was initially reported for patients with valvar pulmonary stenosis, but it has also been extensively documented in patients with TOF.

Patients with pulmonary valve stenosis or severe narrowing who have TOF may benefit from this. The palliative procedure is usually offered in patients with small pulmonary arteries, neonates with frequent spells, small left ventricles, multiple VSDs, etc. In our centers, we preferred to have transcatheter palliation for these patients rather than going for the surgical option due to multiple reasons including length of hospital stay, financial issues, expert surgical hands, etc. The balloon angioplasty is the best out of all palliation as the immediate results are marvelous in our study with only fewer minor complications. A catheter with a deflated balloon at its tip is introduced into the femoral vein and guided to the location of the pulmonary valve during balloon valvuloplasty. The balloon is positioned and then inflated to widen the constricted valve, which enhances blood flow from the RV to the PA (pulmonary artery). It is usually advisable to have an angiography that displays the valve before proceeding with balloon sizing. The stenotic pulmonary valve's obstruction will be relieved through the treatment, improving blood flow to the lungs. This can help people with symptoms including dyspnea and cyanosis. The stenotic pulmonary valve's obstruction will be relieved through the treatment, improving blood flow to the lungs. In patients with TOF, this helps lessen symptoms including dyspnea and cyanosis. The anesthesia team and the operator need to be prepared for the possibility that the patient may experience a severe episode of hypercyanotic spell during balloon valvuloplasty. Although our team was vigilant and successfully managed such scenarios, we emphasize that pre-procedural planning and immediate access to emergency medications are critical for optimizing outcomes.[15] It is crucial to remember that the suitability of balloon valvuloplasty for patients with TOF depends on several variables, such as the degree of stenosis, the structure of the heart, and the patient's general health. These individuals frequently have other areas of stenosis (typically infundibular blockage), which makes balloon valvuloplasty ineffective in treating their condition.

Transcatheter balloon angioplasty provides a naturally increased pulsatile flow to branch pulmonary arteries with immediate improvement in saturation as in all patients the saturations rose from 40-50% to 80-90%.[16] RVOT stenting is a procedure that is increasingly being used for patients with TOF. The goal of RVOT stenting in patients with TOF is to relieve the obstruction by covering the valvar, supravalvular, and infundibular stenoses; this will all help to improve blood flow from the RV to the PA. After the patient has an RVOT stent placed, the obstruction to the pulmonary circulation is relieved, and it can be managed similarly to other patients with TOF until the full surgical repair is completed. Although RVOT stenting is another transcatheter palliation it has a higher rate of complications and requires antiplatelet therapy after the procedure.[17]

The balloon palliation is considered a more suitable option for patients of TOF as also supported by other published literature on this topic.[18] It not only improves oxygen saturation significantly but also promotes better pulmonary arterial growth, which facilitates later elective repair at low-risk age. Thus, short/medium-term palliation in RVOT ballooning should be considered as the first-line option in patients with TOF with valvular stenosis who are initially considered high risk or not suitable for total correction or those with late presentation as in developing countries. Furthermore, the role of balloon angioplasty in addressing long-term outcomes, such as improved exercise tolerance and reduced complications associated with hypoxic spells, underscores its utility in carefully selected cases.[19] In certain situations in which there is a disparity of branch pulmonary arteries and patients require palliation like BT shunt, we have done balloon angioplasty of selected pulmonary artery, as it can be a feasible option. In our investigation, we discovered that while some patients experienced serious complications the majority of them were minor issues like transient arrhythmias, accounting for 16%. While selecting a patient for balloon angioplasty one must keep in mind that the stenosis is at a valvular level as our patients all have valvular narrowing and the patient with infundibular narrowing do not respond to ballooning and it might be counterproductive in some cases and usually done with RVOT stenting as depicted by existing literature.[20-21]

A small percentage of patients can have a fever, sepsis,

thrombosis, bleeding, and cyanotic spells during balloon angioplasty but we did not have such minor complications in our patients. Other serious complications like pulmonary edema and pericardial effusion can occur during such procedures and patients with pulmonary edema should be managed promptly with diuretics, afterload-reducing agents, fluid restriction, and respiratory care.[22-23] We recommend integrating multidisciplinary teams in managing such complications to ensure swift decision-making and better patient outcomes. In some rare cases, death can be a dreadful complication, but we did not observe any death in our subset of patients.[24]

Despite potential risks, our findings reinforce that balloon angioplasty offers a highly favorable risk-benefit profile, making it a valuable option in resource-constrained settings.[25] We discovered a statistically negligible percentage of minor problems among our patients and overall balloon angioplasty can be considered as a palliative procedure in selected patients as being adapted as a first-line option in many institutions.[26]

CONCLUSION

Palliative balloon angioplasty emerges as a promising and safe intervention for symptomatic patients with Tetralogy of Fallot (TOF), particularly in resource-limited settings or when definitive surgical repair is delayed. Our study highlights its efficacy in improving oxygen saturation and pulmonary arterial growth, with minimal procedural complications, making it an excellent alternative to traditional surgical palliation. By offering immediate physiological improvement and reducing hospital stays, this technique not only stabilizes high-risk patients but also optimizes their candidacy for future corrective surgery. As advancements in interventional cardiology continue, palliative balloon angioplasty may establish itself as the first-line option for managing TOF patients with valvular stenosis, ensuring better short-term outcomes and paving the way for definitive repair at a more opportune time.

Authors Contribution:
Ahsan Ali Shaikh: Conceptualization of Study Design, Writing
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Muhammad Rashid Hasnain: Data Analysis and Interpretation
Imrana Ata: Literature Search
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Saqlain Anwar: Data Collection and Analysis

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Original Article **Open Access**

Effect of Propofol on Postoperative Nausea and Vomiting in Patients Undergoing Elective Cesarean Section under Spinal Anesthesia: A Randomized Clinical Trial

Atif Nazir, Ayesha Shahid, Atiya Chaudhry, Syed Makarram Ahmed Bukhari, Azher Munir, Meamoona Shabbir

ABSTRACT

Objective: To analyze anti-emetic effect of sub-hypnotic dose of Propofol in patients undergoing cesarean section.

Study Design and Setting: Prospective, Interventional Randomized Clinical trial done at PAF Hospital Islamabad, from 1st August 2021 to 31st January 2022.

Methodology: A total of 60 patients undergoing elective cesarean under spinal anesthesia were selected for the study. Selected patients were randomly allocated either of the two groups. Patients included in the Group A received sub hypnotic intravenous dose of Propofol as per their body weight, whereas the Group B patients received intravenous saline (0.9%). Postoperative nausea and vomiting was assessed during patients' PACU stay of 1 hour using the subjective feelings of the patients. If the patient complains of vomiting in PACU, an intravenous dose of 10mg Metoclopramide was given as rescue antiemetic.

Results: Mean age of patients was 30.73±4.51 years. APFEL score 3 was observed in 15 (50.0%) in group A and 15 (50.0%) in group B. Score 4 was observed in 4 (13.3%) in group A and 08 (26.7%) in group B(p-value 0.33).Vomiting was observed in 06 (20.0%) in group A and 24 (80.0%) in group B respectively(p-value of <0.01).Nausea was found in 08 (26.7%) in group A and 25 (83.3%) in group B (p-value <0.01).

Conclusion: Propofol in sub-hypnotic dose is effective in the prevention of postoperative nausea and vomiting in patients undergoing cesarean section under spinal anesthesia.

Key words: Elective cesarean, Postoperative nausea and vomiting, Propofol, Spinal anesthesia

How to cite this Article:
Nazir A, Shahid A, Chaudhry A, Bukhari SMA, Munir A, Shabbir M. Effect of Propofol on Postoperative Nausea and Vomiting in Patients Undergoing Elective Cesarean Section under Spinal Anesthesia: A Randomized Clinical Trial. J Bahria Uni Med Dental Coll. 2025;15(2):97-102 DOI: https://doi.org/10.51985/JBUMDC2024488

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Received: 11-12-24
Accepted: 27-03-25
1st Revision: 24-12-24
2nd Revision: 18-03-25
3rd Revision: 25-03-25

INTRODUCTION:

Lower segment cesarean section remains the most commonly performed surgical procedure in obstetric population worldwide.[1]Spinal anesthesia is the choice of anesthesia in majority of cases owing to its safety and fast speed of recovery. Nausea and vomiting in postoperative period is an unpleasant experience, often described as side effect of anesthesia and surgery. It is very common in women undergoing spinal anesthesia for cesarean section. Incidence of nausea and vomiting after cesarean section may vary from 35 to 60% and is different in varying age groups. After postoperative pain, it is the next most common complain after surgery.[2] It is one of the major concerns in Post Anesthesia Care Units after lower segment cesarean section. The etiology of nausea and vomiting in postoperative period is multifactorial and is divided into patient factors, intra operative and post-operative factors. Various patient factors are obesity, female gender, non-smoking, history of postoperative nausea and vomiting, motion sickness as well as genetic predisposition. Surgical factors involves nature, site and duration of surgery. Anesthetic factors are type of anesthesia, use of opioids, inhalational agents and nitrous oxide. Literature shows that a 30-minute increase in surgical time can increase the incidence of nausea and vomiting by

60%. As duration of surgery prolongs, use of drugs like narcotics, sedatives and inhalational agents increases. These drugs tend to stimulate the chromaffin cells in gastric mucosa resulting in release of neurotransmitters and activation of vagus nerve. This initiates the vomiting reflex through chemoreceptor trigger zone in medulla. Smoking is a protective factor for postoperative nausea and vomiting. Tobacco contains nicotine and polycyclic aromatic hydrocarbons. They have the ability to decrease nerve receptor function. They cause activation of cytochrome P-450 and increase tolerance of body for narcotics.[3]APFEL scoring is based on four independent factors named female gender, non-smoking, opiods, history of postoperative nausea and vomiting or motion sickness. Each variable carries 1 score. APFEL score ranges from 0,1,2,3 to 4 predicting the possibility of developing postoperative nausea and vomiting as approximately 10%, 20%, 40% or 80%.[4]

Incidence of postoperative nausea and vomiting (PONV) in cesarean section was 24% and 14% respectively as quoted in literature search .[5]Postoperative nausea and vomiting increases the risk of dehiscence of wound, postoperative bleeding, aspiration of gastric contents causing pneumonitis, dehydration due to fluid loss, electrolyte imbalance and delay in starting oral feeding. It increases duration of hospital stay thus causing financial burden for patients. Patients reported that postoperative nausea and vomiting is even more troublesome than postoperative pain. Though difficult to completely avoid postoperative nausea and vomiting, it can be significantly reduced by opting multimodal non-opioid based analgesia, total intravenous anesthesia technique and using antiemetic prophylaxis as part of premedication [6]. Review of literature shows use of both medication and as well as non-medication therapies. Various drugs used are ondansetron, metoclopramide, droperidol while non medication therapy includes ginger, acupressure and acupuncture.[7]Propofol (2,6-diisopropylphenol) is used as intravenous induction agentin general anesthesia. It has relatively fast onset of action and short duration. In addition to its use as induction agent it has got antiemetic and antipruritic effects. However, its mechanism of action for antiemetic role is still not clear. Propofol has anti-emetic effects at sub hypnotic dose both in bolus or continuous infusion form in susceptible individual, however the exact mechanism of this effect is yet not known. [8]

The antiemetic actions of Propofol have been shown in previous investigations, whether administered as a bolus dosage or as a continuous intravenous infusion.[9] In addition, very few clinical trials strengthen the evidence that Propofol when given as infusion in a low dose (1.0 mg/kg/h) is effective in prevention of postoperative nausea and vomiting in patients undergoing cesarean section. But they did not mentioned treatment specifics for the pregnant patients who had acute nausea and vomiting, nor did they analyze the neonatal behavior linked with postoperative nursing in the case of the other women. A continuous intravenous infusion of Propofol, in conjunction with small bolus doses for immediate control, was expected to be beneficial and safe in reducing the incidence of postoperative nausea and vomiting in parturients after cesarean delivery as compared to a control group receiving placebo.[10]This study aims to evaluate the effectiveness of Propofol in reducing postoperative nausea and vomiting (PONV) in parturients undergoing cesarean sections under spinal anesthesia, as current literature lacks sufficient evidence on its efficacy in this setting in Pakistan. Given the high incidence of PONV and its negative impact on patient recovery, this study will assess whether Propofol can serve as a viable alternative to conventional antiemetic treatments.

METHODOLOGY:

The study was conducted as a prospective interventional randomized clinical trial at PAF Hospital Islamabad affiliated with Fazaia Medical College (IRB no CPSP/REU/ANS-2020-137-2419dated 30th April 2021) from 1st August 2021 to 31st January 2022.The study was registered with ClinicalTrials.gov No NCT05071794. Patients undergoing elective lower segment cesarean section under spinal anesthesia were recruited for the study. A total of 60 patients were included in the study while dividing them in two groups of 30 patients each. Sample size was calculated by using WHO calculator, taking population percentage 8.7%, test value of population proportion 93.9%, level of significance 5% and power of test as 95%[11]The participants included parturients aged between 18 – 50 years, ASA[12] status II and gestational age more than 37 weeks, planned for elective lower segment cesarean section under spinal anesthesia. Exclusion criteria were ASA Class III and above, allergy to Propofol, patients who refused for spinal anesthesia and anti-emetic drug was administered 24 hours before surgery. Patients included in the study were thoroughly counseled about the procedure, drugs used and significance of antiemetic drugs. Informed written consent as per hospital policy was taken from all the patients included in this trial. Patients were divided in group A and B by table of random numbers. All the patients were kept NPO for 8 hours before surgery. Baseline investigations including blood CP, blood sugar random, liver and renal function test as well as hepatitis screening and coagulation profile was done. Using aseptic measures patients were cleaned and draped for spinal anesthesia in sitting position. Interspinous space was identified and infiltrated with injection lignocaine plain 2%.Spinal anesthesia was administered with injection Bupivacaine hyperbaric 12 mg at space L3-L4. Standard vital monitoring including BP, heart rate, oxygen saturation and ECG was done. Preloading was done with infusion ringer lactate 500 ml. Vital signs' monitoring was done at every 5 minutes interval. Intraoperative hypotension was treated with boluses of injection Phenylephrine 50ug intravenously. Intraoperative bradycardia was managed with injection Atropine 0.5 mg

intravenously. At the time of delivery of baby injection Oxytocin was given as 10 IU followed by infusion of 40 IU in normal saline. Baby was resuscitated by a registrar from the pediatrics' department. Patients included in the Group A received sub hypnotic IV dose of Propofol[13] as per their body weight i.e. 0.5mg/kg whereas the Group B patients received 5 ml saline (0.9%) 10-15 min before end of procedure. Patients were monitored for level of sedation and oxygen saturation. Purposeful verbal response to commands was followed and maintained in all patients. At the end of surgery patients were transferred to recovery room. Nausea and vomiting in postoperative period was assessed by a registrar anesthetist who was blinded for study during stay of patients in post anesthesia care unit. Patients were followed in recovery room for 1 hour. Nausea was defined as subjective uncomfortable feeling of retching and vomiting was defined as forceful expulsion of gastric contents. If episodes of nausea and vomiting were more than 2 minutes apart they were considered as independent events. The findings including demographic data and APFEL scoring[14]were recorded in the Study Performa. APFEL scoring includes female gender, non-smoking, history of postoperative nausea and vomiting, and motion sickness. Each variable was assigned 1 score and scoring varying from 0-4 were recorded. If the patient complained of vomiting in PACU, an IV dose of 10mg Metoclopramide was given as rescue anti-emetic. Relief was considered if more than 50% of symptoms were relieved as documented by patients. Data was collected and analysis was done on SPSS version 25.Mean ± SD was calculated for age. Frequency was calculated for categorical data like APFEL scoring. Frequency was calculated for nausea and vomiting in both groups. P value was calculated for all the variables and less than 0.005 was considered significant.

RESULTS:

Demographic profile regarding age and APFEL scoring is shown in table 1 that show statistically no significant difference among both groups with p value 0.12 and 0.33 respectively. Frequency of postoperative nausea and vomiting was compared among both groups (table 2) that show statistically significant difference (p value 0.01) with less postoperative nausea and vomiting in Propofol group in comparison to placebo group. Stratification was done regarding age by dividing patients in age groups 18-30 years and 31-42 years. There was statistically significant difference in frequency of postoperative nausea and vomiting in both groups considering age. When stratification was done regarding APFEL scoring there was significant difference in frequency of nausea and vomiting in postoperative period in both groups with APFEL scoring 2 and 3, however this difference was statistically insignificant in patients with APFEL scoring 4 that shows that high APFEL scoring is a significant risk factor regarding postoperative nausea and vomiting. (table 3)

Table 1. Demographic profile regarding age in years (mean ± SD) and APFEL scoring

	Group A (n=30)	Group B (n=30)	P-value
Age (years) ± SD	31.63 ± 3.73	29.83 ± 5.09	0.12
APFEL score 2	11 (36.7%)	07 (23.3%)	0.33
APFEL score 3	15 (50.0%)	15 (50.0%)	
APFEL score 4	04 (13.3%)	08 (26.7%)	

Table 2. Frequency of nausea and vomiting and rescue antiemetic

		Groups		P-value
		Group A (N=30)	Group B (N=30)	
Vomiting	**Yes**	06 (20.0%)	24 (80.0%)	0.01
Nausea	**Yes**	08 (26.7%)	25 (83.3%)	**0.01**

Table 3. Stratification regarding age and Apfel scoring with complaint of nausea and vomiting

		Group A (N=13)	Group B (N=17)	P value
Age: 18-30 years	**Nausea**	04 (30.8%)	15 (88.2%)	<0.01
	Vomiting	04 (30.8%)	15 (88.2%)	<0.01
Age: 31-42 years	**Nausea**	04 (23.5%)	10 (76.9%)	<0.01
	Vomiting	02 (11.8%)	09 (69.2%)	<0.01
APFEL score 2	**Nausea**	0	03 (42.9%)	0.02
	Vomiting	0	03 (42.9%)	0.02
APFEL score 3	**Nausea**	04 (26.7%)	15 (100%)	<0.01
	Vomiting	03 (20.0%)	14 (93.3%)	<0.01
APFEL score 4	**Nausea**	04 (100.0%)	07 (87.5%)	0.46
	Vomiting	03 (75.0%)	07 (87.5%)	0.58

DISCUSSION:

Gan et al. performed a trial and established that plasma concentrations of 343 ng/mL and 592 ng/mL of Propofol reduced incidence of nausea upto 50% and 90% patients, respectively. He used a computer-assisted continuous infusion device in the post anesthesia care unit.[15] Moreover he found that 20 mg Propofol was effective for treatment of postoperative nausea and vomiting with shorter post anesthesia care unit stay and higher degree of patient satisfaction. Review of literature shows various studies done on antiemetic potential of Propofol. Mohammad MJ conducted a randomized trial to observe antiemetic efficacy of Propofol in patients undergoing cesarean section. He divided patients in two groups. First group received Propofol as continuous infusion while the second group received normal saline as placebo. He found that there was statistically significant difference in incidence of postoperative nausea (p value 0.003) and vomiting (p value 0.014) in Propofol group as compared to placebo group. Moreover, the requirement of rescue antiemetic was lower in Propofol group than placebo. The results of this study were the same as our trial.[16]

Sprung J retrospectively collected data on patients who underwent procedure under general anesthesia and analyzed whether use of Propofol in intraoperative period was associated with decrease need of rescue antiemetic. He found that those patients who receive Propofol as bolus or as infusion intraoperatively, had less incidence of nausea and vomiting. While there was no significant difference in recovery time in PACU when compared with those patients who didn't receive Propofol intraoperatively however, this effect was dose dependent with no added advantage in dose more than 100ug/kg/ min was noted. Antiemetic effect of Propofol was independentof the type of volatile agent used in surgery, duration of procedure and prophylactic use of antiemetics. At the end of this trial he concluded that intraoperative use of Propofol infusion in volatile based anesthesia not only reducesthe incidence of postoperative nausea and vomiting but this practice can be improvised depending upon patient specific as well as procedure specific factors. Results of this trial were same as our trial however we didn't measure dose dependent effect of propofol.[17]

Pang QY conducted a meta analyses of randomized clinical trials in patients undergoing breast surgeries. He found that those patients who received Propofol based anesthesia had higher requirement of rescue analgesics as compare to inhalational anesthetics, however incidence of postoperative nausea and vomiting as well as rescue antiemetics was significantly less in Propofol group than the inhalational group. This meta-analysis also demonstrated that Propofol has tendency to preserve nature killer cell cytotoxicity, decrease interleukin 6 levels, decrease neutrophil to lymphocyte ratio as well as increase in 2 years' survival rate. However, these long term effects of Propofol need trials to be done on large population.[18]Antiemetic effect of Propofol was also studied in procedures outside the operation theatre. Sakanoue H observedthe incidence of postoperative nausea and vomiting with Propofol infusion in patients undergoing catheter ablation for atrial fibrillation. He found that although Propofol has significant antiemetic effect, however APFEL scoring had low accuracy in predicting incidence of nausea and vomiting after Propofol infusion. This is in contrast to our results where Propofol has significant antiemetic effect in patients with APFEL score of two and three, however results were not significant with APFEL score of 4, indicating that high APFEL score is itself a very high risk factor for nausea and vomiting in postoperative time. [19]

Kampo S conducted a prospective double blind study on patients undergoing cesarean section. He selected 345 parturients and randomly divided them in three groups. All patients underwent cesarean section under spinal anesthesia. One group was given injection Propofol 0.5 mg/kg, second group was given injection Metoclopramide 10 mg and third was placebo group that received normal saline.Patients were followed in recovery room for nausea and vomiting and requirement of rescue analgesia. 10 patients in Propofolgroup, 8 patients in metoclopramidegroup while 108 patients in placebo group experienced postoperative nausea and vomiting. Statistically there was no significant difference in incidence of nausea and vomiting in Propofol and metoclopramide group however when compared to placebo group this difference was statistically significant. Moreover, the requirement of rescue antiemetic was 10%, 37.5% and 97.2% inPropofol, metoclopramide and placebo group respectively.This shows that the requirement of rescue antiemetic was low in Propofol group as compared to metoclopramidegroup. The incidence of postoperative pruritus is also less in Propofol group as compared to placebo. Results of this study are similar to our trial however we didn't measure need for rescue antiemetic as well as postoperative pruritus in our study.[11]

Acharya SA performed a comparative study in patients undergoing laparoscopiccholecystectomy. He compared ondansetron, ramosetron and subhypnotic dose of Propofol and observed patients for nausea and vomiting in postoperative period .He selected 120 patients planned for cholecystectomy and divided them in three equal groups. Group 1 was given ondansetron 4 mg, group 2 was given ramosetron 0.3 mg and group 3 was given Propofol 0.5mg/kg. All patients were given general anesthesia as per standard protocol. Study drugs were given at the time of removal of umbilical ports. Patients were followed in postoperative period for nausea and vomiting. He observed that in first 6 hours postoperatively the difference in incidence of vomiting was statistically insignificant, however from 6-24 hours the incidence of vomiting was much high in Propofol group as compared to other two groups. The incidence of nausea was more or less same in all groups. Results of this trial are same as our study as percentage of vomiting is same as in our study. However, in our study we have compared Propofol with placebo rather than any other anti-emetic. [13]

Bansal T performed a prospective double blind study on patients who underwent elective laparoscopic surgeries under general anesthesia.70 patients were included in this study divided intwo groups of 35 each. After induction of anesthesia one group was given Propofol infusion as maintenance of anesthesia and other group was given combination of Propofol with sevoflurane for maintenance of anesthesia. Incidence of postoperative nausea and vomiting was 33% in Propofol group and 38.7% in combination group that shows statistically no significant difference. Need for rescue antiemetic was 11 in Propofol group and 12 in combination group that was also statistically insignificant. Since there was no placebo group in this study so this trial doesn't measure antiemetic efficacy of Propofol alone.[20]

Zhao TUM conducted a trial on patients undergoing gastroscopy. He selected 112 patients and divide them in two groups. Group C was given Ciprofol 0.4 mg/kg and group P was given Propofol 1.5 mg/kg. Both groups were

augmented with Alfentanil 7 mcg/kg. Patients were discharged after procedure and were followed on telephone for postoperative nausea and vomiting after 24 hours. He found that although both Propofol and Ciprofol could prevent nausea and vomiting, antiemetic effect of Propofol was superior to Ciprofol with p value 0.042.[21]

Admabb BA performed a clinical trial on pregnant patients undergoing cesarean sections. He selected 100 patients who were planned to undergo elective cesarean delivery. He collected data on form that included patient history, anesthesia monitoring chart and standard check list. He analyzed that in his study population patients at low, medium and high risk of postoperative nausea and vomiting were 21%, 33% and 25% respectively. He emphasized on SAMBA guidelines that stated stratification of risk of postoperative nausea and vomiting, baseline risk reduction strategies, no prophylaxis in patients with low risk of postoperative nausea and vomiting, administering 1-2 pharmacological interventions in medium risk and more than two agents in high risk patients. Those patients who did not receive preemptive antiemetic or failed to respond to prophylactic antiemetic should be addressed urgently and every setup should establish some local guidelines for prevention of postoperative nausea and vomiting. He documented that in clinical practice there is a significant performance gap in prevention of postoperative nausea and vomiting. Adherence to SAMBA guidelines may provide a significant tool in prevention of postoperative nausea and vomiting.[22]

Hence prevention of postoperative nausea and vomiting after cesarean section needs both prophylactic as well as therapeutic measures. Prophylactic measures include adequate fasting, head up positioning of patient and prophylactic antiemetic well before surgery. Therapeutic measures include administering right choice of antiemetic well in time and it should be rationalize according to patients need and known risk factors.

CONCLUSION:

When compared with placebo, intravenous administered sub-hypnotic dose of Propofol has shown significant anti emetic activity for prevention of postoperative nausea and vomiting in patients undergoing cesarean section under spinal anesthesia however this effect was not significant in patients with high APFEL scoring.

Authors Contribution:
Atif Nazir: Concept & Design of study drafting, revisiting critically, data analysis, final approval of version
Ayesha: Concept & Design of study, drafting, final approval of version
Atiya Chaudhry: Concept & Design of study, drafting
Sayed Makarram Ahmed Bukhari: Concept & Design of study, data analysis
Azher Munir: Concept & Design of study, data analysis
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Original Article **Open Access**

Association of Platelet Apheresis with Hematological and Electrolyte Abnormalities in Donors: A Pre- and Post-Donation Study

Anum Shabir, Saeed Akhtar Khan Khattak, Kiran Jabbar, Dawood Ahmed, Shahzaib Shaikh, Muhammad Umar

ABSTRACT

Objectives: To assess the association of platelet pheresis with occurrence of abnormalities in hematological parameters and serum electrolyte homeostasis before and after donation.

Study Design and Setting: Prospective cohort study. Department of Pathology, PNS Shifa, Karachi (Jan-Dec 2024).

METHODOLOGY: A total of 126 platelet donors were studied. Patients aged 18–60 years who had a normal CBC, a platelet count of =200,000/µL and a body weight of at least 50kg were included. Individuals with chronic illness history, medication affecting hematological parameters, recent infection, prior platelet donations or surgery within the last 6 months were excluded. Pre-donation CBC and serum electrolytes were measured and then repeated immediate post-donation and then at one-week and one-month. The sample was calculated by WHO calculator with 5% significance (α) and 95% power of the test (1-β) with standard deviation (σ) of 0.385, variance (σ^2) of 0.148225, a mean serum calcium level prior to platelet pheresis of 9.91 mg/dL and a post-plateletpheresis of 9.75 mg/dL.

Results: The median-age at donation was 32.0 (IQR: 10.0) years with 122 (98.6%) patients being male and 19 (15.1%) had a history of previous donations. Haemoglobin (p=0.023), hematocrit (p<0.001), platelet count (p<0.001), serum calcium (p<0.001) and magnesium (p=0.003) were significantly lower in patients immediately after plateletpheresis. At 1-week post-donation, only platelet count (p<0.001) was below baseline levels. One month from the plateletpheresis procedure, all the haematological and electrolyte levels returned to baseline.

Conclusion: Plateletpheresis is a safe procedure with any haematological or electrolyte disturbance post-procedure returning to normal within one week.

Keywords: electrolyte balance, hemostasis, platelet aphersis

How to cite this Article:
Shabir A, Khattan SAK, Jabba K, Ahmed D, Shaikh S, Umar M. Association of Platelet Apheresis with Hematological and Electrolyte Abnormalities in Donors: A Pre- and Post-Donation Study. J Bahria Uni Med Dental Coll. 2025;15(2):103-108 DOI: https://doi.org/10.51985/JBUMDC2025498

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Received: 05-01-25
Accepted: 26-03-25
1st Revision: 15-01-25
2nd Revision: 22-01-25
3rd Revision: 19-02-25

INTRODUCTION:

Platelet apheresis is a critical and highly specialized procedure in the realm of modern medicine, playing an indispensable role in the treatment and management of patients suffering from thrombocytopaenia, malignancies, and other medical conditions that necessitate platelet transfusion. Among these conditions, immune thrombocytopaenic purpura stands out as a significant indication for platelet transfusion therapy.[1] This advanced medical process has gained increasing prominence in the field of transfusion medicine, primarily because of its unique ability to address the specific and individualized needs of patients requiring targeted platelet replacement therapy. Unlike traditional methods of whole blood donation, platelet apheresis is a procedure that involves the selective extraction of platelets from a donor's blood while simultaneously returning the remaining blood components, including red blood cells and plasma, back into the donor's circulation system.[1,2] This sophisticated technique not only yields a significantly higher quantity of platelets suitable for transfusion compared to conventional blood donation methods but also allows donors to participate in the process more frequently, given its minimal theoretical impact on the overall homeostasis and balance of the donor's

blood components.[3,4] Despite these numerous advantages, the exact impact of platelet apheresis on the donor's haematological parameters and overall health remains an area of ongoing research and clinical scrutiny. Researchers and medical practitioners continue to explore the various physiological and biochemical changes that occur during and after the apheresis procedure to better understand its implications for donor health, safety, and long-term well-being.

To safeguard donor health and ensure their well-being, the US Food and Drug Administration (FDA) established comprehensive guidelines in 2005. These guidelines permit up to 24 component donations per year and restrict each individual procedure to a maximum of three components. Additionally, the guidelines impose a limit of no more than two donations per week and require a mandatory minimum interval of 48 hours between consecutive donation sessions.5 These regulatory measures are designed to minimize any potential risks to donors, ensuring that the frequency and intensity of donations do not adversely affect their overall health or long-term physiological stability. While platelet apheresis is widely regarded as a safe and well-tolerated procedure, it is known to induce measurable changes in the donor's blood composition. These changes can persist for varying durations following the donation process.6 The most commonly observed change is a reduction in platelet count, which is an expected and inevitable outcome of the procedure. However, other haematological parameters, including white blood cell counts, hemoglobin levels, plasma protein concentrations, and electrolyte balances, may also be affected to varying extents.[7,8] Understanding the scope, extent, and duration of these changes is crucial for ensuring donor safety, optimizing the frequency of donations, and improving the overall efficacy and outcomes of the apheresis process. Previous research efforts have largely focused on examining the immediate and short-term impacts of platelet apheresis on donors. These studies have documented fluctuations in platelet counts, minor decreases in hemoglobin levels, and occasional alterations in white blood cell counts.?[,10] These findings have provided valuable insights into the acute physiological effects of the procedure, which are generally well-tolerated by the majority of donors. However, the long-term effects of platelet apheresis, as well as the timeline for the complete recovery of haematological parameters following repeated donations, remain less thoroughly explored. This gap in the available data creates a significant knowledge void, particularly with respect to understanding how repeated platelet apheresis sessions may influence donor health over extended periods of time.

This article aimed to address these critical knowledge gaps by conducting a detailed analysis of the effects of platelet apheresis on donors' haematological parameters. The analysis covered both short-term and long-term changes, providing a comprehensive overview of the physiological adjustments experienced by donors. By comparing haematological parameters before the procedure and at various intervals following the donation, this study sought to elucidate the extent and duration of any observed changes. Such an approach allows for a more nuanced and detailed understanding of the physiological processes involved, offering valuable insights that could enhance donor management and safety protocols. For example, identifying trends in recovery times or persistent alterations in specific haematological parameters could lead to recommendations for adjusting donation frequencies or developing personalized donor care strategies. Furthermore, this research not only contributes to the broader scientific knowledge surrounding apheresis but also holds practical significance for clinical practices in transfusion medicine. By shedding light on the physiological effects of platelet apheresis, the findings aim to support the development of evidence-based guidelines that prioritize donor safety while maximizing the availability of life-saving platelets for patients in need. Ultimately, this study highlights the importance of balancing the significant benefits of platelet apheresis with the critical need to protect and preserve the health and well-being of the donors who make this vital medical procedure possible.

METHODOLOGY

This prospective cohort study was carried out in the Department of Pathology at PNS Shifa, Karachi, over a duration of eight months, spanning from January 2024 to August 2024. The ethical review for this study was approved under the reference number ERC No. ERC/2024/PATH-125. The research sample consisted of 126 voluntary donors who underwent plateletpheresis during the study period. Written informed consent was obtained from all participants prior to their inclusion in the study, ensuring that they were fully aware of the procedure and its potential implications. The study was carefully designed and executed in strict adherence to the principles outlined in the Declaration of Helsinki, as well as the ethical standards and institutional guidelines established by our organization. The participants included in the study were selected through consecutive, non-random sampling, a method that allowed for the inclusion of eligible donors as they became available. To determine the appropriate sample size, the World Health Organization (WHO) sample size calculator was employed. The calculations were based on a level of significance (α) of 5%, a test power (1-β) of 95%, a population standard deviation (σ) of 0.385, and a population variance (σ^2) of 0.148225. The mean serum calcium level prior to plateletpheresis was estimated at 9.91 mg/dL, with a post-plateletpheresis mean level of 9.75 mg/dL, as reported in the study by Syal et al.[8]

Inclusion Criteria: The study included donors aged 18 to 60 years who met specific health requirements. All participants were required to have a normal complete blood count, a platelet count of at least 200,000/µL, and a minimum body weight of 50 kg to qualify for participation.

Exclusion Criteria: Individuals were excluded from the study if they had a history of chronic illnesses, were taking medications known to affect haematological parameters, or had experienced recent fever or infection. Additionally, donors who had undergone prior platelet donations or surgeries within the past six months were also excluded to minimize confounding factors.

For each participant, a comprehensive medical history was meticulously recorded at the time of enrollment. Baseline haematological parameters were measured before the donation, including haemoglobin (Hb), haematocrit (Hct), white blood cell count (WBC), platelet count, mean platelet volume (MPV), and serum levels of calcium, magnesium, and potassium. Immediately after the plateletpheresis session, these parameters were reassessed to evaluate any short-term effects of the procedure. To monitor potential long-term changes, additional blood samples were collected at one week and one month post-donation, with the same parameters being tested at each time point.

Plateletpheresis procedures were conducted using a standard apheresis system (Cell Separator Haemonetics; MCS+ USA) following the manufacturer's protocols and guidelines. Each donor participated in a single apheresis session, which lasted for an average duration of 60 to 90 minutes. The volume of platelets collected during each session ranged between 200 and 300 mL, with a minimum target yield of 3×10^{11} platelets per unit to ensure optimal collection efficiency.

The collected data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 27.0. Quantitative variables were summarized using mean and standard deviation or median and interquartile range (IQR), depending on the distribution of the data. Qualitative variables were expressed in terms of frequency and percentage. To compare the parameters measured at different time points, paired samples t-tests were utilized. A *p*-value of =0.05 was considered statistically significant, ensuring robust interpretation of the findings.

RESULTS

Our research study was conducted on a total of 126 individuals who voluntarily participated in plateletpheresis procedures during the study period. The median age of the donors at the time of their platelet donation was 32.0 years, with an interquartile range (IQR) of 10.0 years, reflecting a relatively young and uniform donor population. Notably, the overwhelming majority of participants, amounting to 122 individuals (98.6%), were male, highlighting a significant gender disparity within the donor pool. Additionally, it is important to note that only a small proportion of the participants, specifically 19 individuals (15.1%), reported having a prior history of platelet or blood donations. This suggests that the majority of the donors in our study were first-time donors, which may have implications for the interpretation of their physiological responses to the plateletpheresis procedure. Table-1 provides a detailed summary of the baseline haematological and serum electrolyte parameters for all participants before proceeding with the platelet donation.

Table-2 provides a comprehensive overview of the haematological parameters that were measured at three distinct time points: immediately following the plateletpheresis procedure, one week after the donation, and finally, one month post-donation. The data reveal that haemoglobin levels, haematocrit values, platelet counts, as well as serum calcium and magnesium concentrations, showed a statistically significant decrease immediately after the plateletpheresis session. However, it was observed that these values generally returned to their normal, pre-donation levels within one week of the procedure, with one notable exception—platelet counts.

The recovery of platelet counts was comparatively slower, as they did not return to baseline levels within the one-week timeframe. By one month following the plateletpheresis procedure, however, all haematological parameters, including platelet counts, and all electrolyte levels had fully returned to their baseline values, indicating complete recovery from the physiological changes induced by the procedure. Notably, a mean reduction in platelet count of 23.59 ± 3.97% was observed immediately after the plateletpheresis session. This decline is an expected outcome of the procedure, given the nature of platelet collection during apheresis.

DISCUSSION:

This study was designed to evaluate the effects of plateletpheresis on various haematological parameters and serum electrolyte levels among healthy, voluntary donors. The primary objective was to determine whether this commonly performed procedure induces significant changes in these parameters and, if so, to assess the timeline for their recovery to baseline levels. Our findings suggest that while plateletpheresis is generally well tolerated by donors, it does lead to measurable changes in certain haematological parameters and serum electrolyte levels immediately following the procedure. However, most of these alterations appear to resolve within a recovery period of one week to one month post-donation. These results align with those

Table-1. Patient haematological and electrolyte characteristics prior to plateletpheresis (n=126)

Variable	Value
Haemoglobin (g/dL)	15.0 (IQR: 1.3)
Haematocrit (%)	47.0 (IQR: 5.0)
White Blood Cell Count (/µL)	7.55 (IQR: 3.4)
Platelet Count (/µL)	328.0 (IQR: 112.0)
Mean Platelet Volume (fL)	9.0 (IQR: 5.0)
Calcium Level (mg/dL)	9.2 (IQR: 0.8)
Magnesium Level (mg/dL)	2.0 (IQR: 0.4)
Potassium Level (mg/dL)	4.25 (IQR: 0.8)

Table-2. Patient haematological and electrolyte characteristics after plateletpheresis (n=126)

Variable	Immediately After Plateletpheresis (p-value)	At One Week Post-Plateletpheresis (p-value)	At One Month Post-Plateletpheresis (p-value)
Haemoglobin (g/dL)	15.0 (IQR: 1.30) 0.023	15.0 (IQR: 1.5) 0.195	14.9 (IQR: 1.5) 0.248
Haematocrit (%)	44.0 (IQR: 4.0) <0.001	47.0 (IQR: 5.0) 0.291	47.0 (IQR: 5.0)0.144
White Blood Cell Count (/µL)	7.60 (IQR: 3.4) 0.465	7.7 (IQR: 3.5) 0.744	7.6 (IQR: 3.6) 0.384
Platelet Count (/µL)	247.5 (IQR: 78.0) <0.001	304.0 (IQR: 104.0) <0.001	326.0 (IQR: 115.0) 0.241
Mean Platelet Volume (fL)	9.0 (IQR: 5.0) 1.000	9.0 (IQR: 5.0) 1.000	9.0 (IQR: 5.0) 0.425
Calcium Level (mg/dL)	9.0 (IQR: 1.0) <0.001	9.2 (IQR: 0.8) 0.867	9.2 (IQR: 0.8) 0.904
Magnesium Level (mg/dL)	1.9 (IQR: 0.3) 0.003	1.95 (IQR: 0.4) 0.711	1.9 (IQR: 0.5) 0.251
Potassium Level (mg/dL)	4.2 (IQR: 0.7) 0.264	4.2 (IQR: 0.8) 0.931	4.2 (IQR: 0.8) 0.183

reported in previous studies, which have consistently demonstrated that the effects of plateletpheresis on haematological and electrolyte parameters are transient in nature.[11]

In the current study, there was a statistically significant reduction in haemoglobin (p=0.023) and haematocrit levels (p<0.001) immediately after plateletpheresis. Notably, both parameters returned to their pre-donation levels within one week, indicating a rapid recovery. Our findings are consistent with those reported in earlier research. For instance, Gil-Betacur et al observed a significant reduction in haemoglobin levels by approximately 0.80 g/dL (CI 95%: 0.75–0.86) and a corresponding drop in haematocrit by 2.26% (CI 95%: 2.11–2.41).? Similarly, Ashok et al documented a decrease in haemoglobin of -0.50 g/dL (CI 95%: -0.72–-0.27) and a reduction in haematocrit of -1.36% (CI 95%: -2.05–-0.66).[1°] Sharma et al also reported a modest mean haemoglobin drop of 0.4 g/dL in their study.[14] The reduction in haemoglobin and haematocrit observed during plateletpheresis may be attributed to several factors. These include blood loss associated with the lines and donation circuit, the type of apheresis procedure used, haemolysis during the process, fluid dilution effects, and blood lost at the time of line insertion.[12-15] Despite these potential contributing factors, the observed reductions in haemoglobin and haematocrit were mild, and the lost levels were quickly replenished by the donors' natural physiological mechanisms.

In addition to changes in haemoglobin and haematocrit, the present study found a significant reduction in platelet counts immediately after the procedure (p<0.001). This result is unsurprising given the nature of plateletpheresis, which involves the selective extraction of platelets from the donor's blood. The mean drop in platelet count was 23.59 ± 3.97%, consistent with findings from prior studies. For example, Rajput et al reported that plateletpheresis temporarily reduces circulating platelet levels, while Thokala et al observed a 20–25% drop in platelet counts post-procedure, with full recovery typically occurring beyond the first week.[16,17] Interestingly, studies such as Shima et al have suggested that donors with lower platelet counts prior to plateletpheresis may experience larger drops in platelet levels following the procedure.[18] The mechanism underlying this observation remains unclear, warranting further investigation. Importantly, extended follow-up studies have consistently demonstrated that plateletpheresis does not result in long-term alterations in haematological parameters, further affirming the safety of this procedure for regular donors.[1?]

Serum electrolyte levels were also assessed in this study, with significant decreases observed in calcium (p<0.001) and magnesium (p=0.003) levels immediately after donation. These findings are consistent with studies by Barrientos-Galeana et al and Navkudkar et al, which have similarly reported reductions in calcium and magnesium levels following plateletpheresis.[2°,21] These changes are primarily attributed to the use of citrate as an anticoagulant during the procedure, as citrate chelates calcium and magnesium, leading to transient hypocalcaemia and hypomagnesaemia.[2°–22] However, both calcium and magnesium levels normalized within one week in the present study, indicating that these disturbances are temporary and unlikely to pose any long-term risks to donors. In contrast, potassium levels remained stable throughout the study period, with no significant changes observed. Furthermore, the study found no significant alterations in white blood cell counts or mean platelet volume at any of the time points assessed. This stability suggests that plateletpheresis does not have a meaningful impact on these haematological parameters, further supporting its safety and tolerability. These findings align with those of Nayak et al, who also reported minimal haematological disruption in donors undergoing plateletpheresis.5

In summary, this study highlights that while plateletpheresis induces temporary changes in certain haematological parameters and serum electrolyte levels, these effects are short-lived and resolve within a predictable timeframe. These results reaffirm the safety of plateletpheresis as a viable and effective method for platelet donation, with minimal risk to donor health. Future research should focus on exploring

these effects in more diverse donor populations and over longer follow-up periods to provide even greater clarity and assurance regarding the safety of this critical procedure.

CONCLUSION

Our study provides clear evidence that plateletpheresis induces significant, though transient, changes in several haematological and serum electrolyte parameters, including haemoglobin, hematocrit, platelet count, calcium, and magnesium levels. These alterations, while measurable and statistically significant immediately following the procedure, tend to normalize within approximately one week post-donation. This rapid recovery suggests that plateletpheresis is a safe and well-tolerated procedure, with no apparent long-term adverse effects on the donor's haematological or electrolyte parameters. The findings of our research strongly support the continued and widespread use of plateletpheresis as an effective and reliable method for platelet donation. However, it is important to note that future studies should aim to address certain limitations, including the need to evaluate more diverse donor populations. Furthermore, extending the follow-up periods would provide additional insights into the longer-term recovery process and help identify any delayed effects that might not have been captured within the timeframe of our study. Such extended research would contribute to a more comprehensive understanding of the physiological impact of plateletpheresis and further reinforce its safety profile.

Authors Contribution:
Anum Shabir: Principal Investigator
Saeed Akhtar Khan Khattak: Supervisor
Kiran Jabbar: Topic Selection
Dawood Ahmed: Biostatistics
Shahzaib Shaikh: Strictly limitation
Muhammad Umar: Discussion

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Original Article **Open Access**

Performance of Automatic Urine Analyzer Compared with Manual Microscopy in Urinary Tract Infection Cases in a Tertiary Care Hospital

Shaista Bakhat, Yasmeen Taj, Maria Ali, Sana Barkat Ali Bhayani, Luqman Satti, Hina Wasti

ABSTRACT

Objectives: This study aimed to assess and compare the results of automated urine analyzers and manual urine analysis in the evaluation of urinary tract infections (UTIs) at Pakistan Navy Shifa Hospital Karachi.

Study Design and Setting: A cross-sectional study was conducted from March 2022 to December 2022 in the Microbiology Department of Pakistan Navy Shifa Hospital Karachi.

Methodology: Urine samples were randomly selected, and both automated urine analyzers (Urised, 77 Electronika, Hungary) and manual analysis methods were used for evaluation. Key urine parameters, including red blood cells, epithelial cells, leukocytes and crystals, were analyzed. Statistical analysis was performed using the Chi-square test with p-value less than .05. Sensitivity, specificity, PPV. And NPV were also determined.

Results: A total of 169 urine samples were analyzed. Significant differences were observed between the automated and manual methods for leukocytes (P-value < 0.000). Crystals were determined by both methods, automatic analyzer was unable to describe structure and morphology as compare to manual method.

Conclusions: Automated urine analyzers are essential for efficient and large-scale sample processing and standardization. However, further development is needed to improve the accuracy of identifying certain urinary elements. Manual microscopic examination remains crucial for confirming pathological cases. In high-volume settings like Pakistan, automated systems offer significant time-saving benefits but should be complemented with manual analysis for comprehensive diagnosis.

Key words: cross-sectional study, pH, red blood cells, specific gravity.

How to cite this Article:
Bakhat S, Taj Y, Ali M, Bhayani BA, Satti L, Wasti H. Performance of Automatic Urine Analyzer Compared with Manual Microscopy in Urinary Tract Infection Cases in a Tertiary Care Hospital. J Bahria Uni Med Dental Coll. 2025;15(2):109-114 DOI: https://doi.org/10.51985/JBUMDC2025499

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Received: 06-01-25
Accepted: 28-03-25
1st Revision: 16-01-25
2nd Revision: 27-02-25
3rd Revision: 14-03-25

INTRODUCTION

Urinalysis is an essential tool in clinical diagnostics, widely used for screening and monitoring a range of health conditions, particularly those affecting the kidneys and urinary tract. It ranks third in diagnostic tests, following serum chemistry and complete blood count, due to its non-invasive, cost-effective nature and its ability to provide early indications of renal and genitourinary diseases.[1,2] Urinalysis plays a critical role not only in detecting conditions such as urinary tract infections (UTIs), kidney stones, and glomerulonephritis, but also in identifying signs of systemic diseases such as diabetes mellitus, hypertension, and toxemia of pregnancy. This makes it a vital component of both routine health check-ups and targeted diagnostic investigations for individuals with suspected genitourinary issues.[3]

Urinalysis is particularly valuable for detecting renal and genitourinary diseases in their early stages. Through microscopic examination of urine sediment, it allows the detection of abnormalities like proteinuria, hematuria, bacteriuria, and leukocyturia, which are indicative of underlying pathologies.[4] Despite its utility, traditional manual urinalysis procedures face significant limitations. These include labor-intensive processes, susceptibility to human

error, and challenges associated with large sample volumes, which can lead to inconsistencies and delays in results.[5] Manual urinalysis typically involves a series of steps, including a dipstick test, visual inspection, and microscopic analysis of urinary sediment.[6] While these methods are standardized, they are time-consuming and highly dependent on the skill and experience of the technician performing the analysis. Furthermore, manual procedures are prone to inter-observer variability, as well as potential issues such as cell lysis and the loss of cellular elements during analysis.[7] The centrifugation speed, urine staining quality, and volume of urine available for re-suspension can also affect the accuracy of results. These challenges make manual analysis particularly difficult for large-scale or high-volume clinical testing.[8]

To address these challenges, automated urine analyzers have been introduced to improve the efficiency and consistency of urinalysis. These devices utilize advanced technologies, including image recognition and sensors, to detect urinary elements more accurately and with minimal human intervention.[9] Automated systems offer several advantages, including the ability to process large numbers of samples more quickly and efficiently than manual methods. However, concerns regarding the diagnostic accuracy of automated analyzers persist, particularly when it comes to their ability to match or surpass the results obtained through manual microscopic analysis. In laboratories that have transitioned from manual to automated systems, discrepancies between the two methods have been reported. These discrepancies often raise questions about the reliability of automated systems and whether they can identify urinary abnormalities with the same level of precision as manual methods.[10] As such, further research is needed to compare the diagnostic performance of manual urinalysis with fully automated urine analyzers, particularly in terms of sensitivity and specificity for detecting key markers of genitourinary conditions.

The lack of sufficient research in our region comparing the diagnostic capabilities of manual urinalysis with automated urine analyzers represents a significant gap in literature. This study aims to fill this gap by evaluating the sensitivity of automated urine analyzers in diagnosing genitourinary pathologies, such as proteinuria, hematuria, and leukocyturia, in comparison to manual microscopy. By investigating whether automated systems can reliably detect these urinary abnormalities, the study seeks to determine if they can match or even surpass the diagnostic accuracy of manual methods, particularly in high-volume clinical settings where speed and efficiency are crucial. The results of this study will provide valuable insights into the practical applications and limitations of automated urine analyzers in clinical practice, particularly in regions where manual methods are still commonly used.

By comparing the performance of both manual and automated techniques, this study will contribute to the refinement of urinalysis practices, ensuring that healthcare providers can make more accurate and timely diagnoses of genitourinary diseases. The findings will be particularly relevant in settings where clinical demand is high, and where automation can help streamline the diagnostic process without compromising the quality of care. Ultimately, this research will contribute to better patient outcomes through the adoption of more reliable and efficient diagnostic methods.

METHODOLOGY

This cross-sectional study was conducted in the Microbiology Department of Pakistan Navy Shifa Hospital, Karachi, from March 2022 to December 2022, with approval from the Institutional Review Board of the Bahria University Health Sciences (BUHS) (ERC# 67/2022). The study adhered to ethical standards, and informed consent was obtained from all participants before their inclusion in the study.

To determine the appropriate sample size, the open-source online EPI software (https://www.openepi.com/Menu/OE_Menu.htm) was utilized, ensuring that the sample size was sufficient to obtain statistically significant results. A total of 169 urine samples were analyzed, which were selected using a simple random sampling technique, ensuring an unbiased and representative sample for the study.

The inclusion criteria for the study were specifically defined to ensure that only valid and reliable samples were analyzed. The selected samples included freshly voided midstream urine, with a minimum volume of 30 mL, collected within 30 minutes of urination. These samples were obtained from both outpatients and inpatients, allowing the study to encompass a diverse population. The exclusion criteria were also carefully defined to eliminate any samples that could interfere with the analysis. Excluded were urine samples with a volume of less than 15 mL, contaminated samples, or samples that had spilled out of the collection containers. Additionally, samples that contained preservatives, such as those obtained from 24-hour urine collections, were also excluded. Patients were already on use of antibiotics were excluded from study.

For the analysis, each urine sample was divided into two aliquots, one for manual analysis and the other for automated analysis. The preservative-free midstream urine samples were carefully collected in wide-mouth, spill-resistant containers to ensure that the sample remained uncontaminated during transport to the laboratory. Once the samples arrived at the microbiology department, they were processed by centrifuging at 1500 rpm for five minutes to obtain sediment for microscopic evaluation. This step allowed for the separation of the solid components of the urine, including cells and particles, which could then be analyzed under the microscope.

For the manual analysis, a small drop of the sediment was placed on a glass slide, covered with a cover slip, and examined using an Olympus microscope. The samples were scanned under both low power (100x) and high power (400x)

magnifications. The analysis included the enumeration of red blood cells (RBCs), white blood cells (WBCs), epithelial cells, and yeast cells, with results reported as the number of cells or particles per Low Power Field (LPF) and High Power Field (HPF).

In parallel, the second aliquot was processed using the Urised 77 Electronika automated analyzer, which provided results for RBC count, WBCs, epithelial cells, and yeast cells. This automated method was used to assess the consistency and comparability of the results with the manual microscopy method.

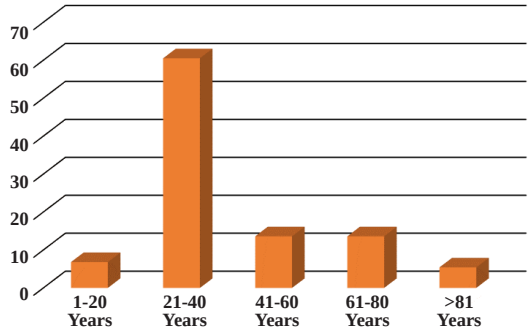
The collected data were analyzed using IBM SPSS version 23, which allowed for the calculation of descriptive statistics. To assess the statistical significance of differences between the two methods, the Chi-square test was applied, with p-value less than .05. Sensitivity, specificity, PPV, NPV was determined.

RESULTS:

A total of 169 cases were analyzed, focusing on demographic and clinical data. The results from the urine automated analyzer were compared with those obtained through manual microscopy. In accordance with the protocol, relevant demographic details, clinical information, and both microscopic and automated findings were recorded and analyzed.

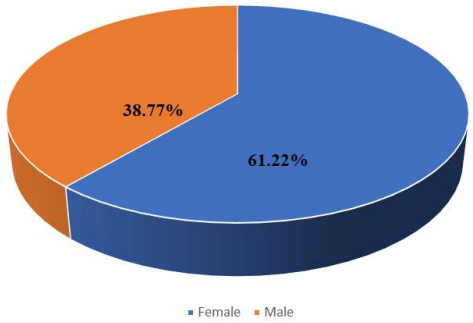
The patients' ages varied widely, ranging from 1 to 90 years. The majority of patients fell within the 21-40 years age group, comprising 60.50% of cases, followed by the 41-80 years age range, which accounted for 13.60% of the cases. The comparison between the WBC counts obtained from the automated analyser and manual microscopy revealed a statistically significant difference, as indicated by a p-value below the significance threshold. The comparison between the RBC counts obtained from the automated analyser and manual microscopy revealed a statistically insignificant difference, as indicated by a p-value. For the RBC count of >100/hpf, automated analyser, reported exact number of cells per high power field, while current study reported “RBC Full field” on manual microscopic examination in same number of cases. These results imply high sensitivity of automated analyser. The comparison between epithelial cells obtained from the automated analyser and manual microscopy revealed a statistically insignificant difference, as indicated by a p-value. For the epithelial cell count of >100/hpf, automated analyser, reported exact number of cells per high power field, while current study reported “epithelial cells Full field” on manual microscopic examination in same number of cases. These results imply high sensitivity of automated analyser. The crystal count result for the 0-10/hpf category was nearly identical between the automatic analyser and manual microscopic examination. However, a difference was observed in the counts for the >10/hpf range. This suggested that the automatic analyser was highly specific in counting crystals per hpf. However, it was unable to identify the type and morphology of the crystals, making manual microscopy necessary for accurate reporting.

Figure 1: Distribution of patients as per age



Majority of patients were females (61.22%) with Male: female ratio of 1:1.57.

Figure 2: Distribution of patients as per gender



Majority of cases presented with burning micturition (40.80%)

Figure 3: Distribution of patients according to clinical features

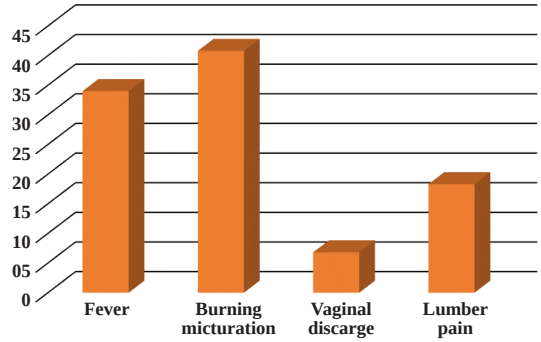


Table 1: Comparison of frequency of WBC per HPF observed in automated analyser as compare to manual microscopy

WBC	Automated analyser	Manual	*p*-value
>5-10/hpf	70	60	0.000
>10-20/hpf	30	20	
>20/hpf	47	40	

Table 2: comparison the frequency of RBC per HPF observed in automated microscopy compare to routine microscopy

RBCs	Automated Analyser	Manual	p-Value
>3-5/hpf	60	50	0.556
>5-10/hpf	20	30	
>10-20/hpf	30	20	
>20/hpf	5	9	
>100/hpf (Automated analyzer)	5	-	
Full field (manual)	-	5	

Table 3: comparison the frequency of epithelial cells per HPF observed in automated microscopy compare to routine microscopy

Epithelial cells	**Automated analyser**	**Manual**	**p-Value**
>15-20/hpf	75	55	0.761
>20/hpf	67	90	
>100/hpf (Automated analyzer)	1	-	
numerous (manual)	-	1	

Table 4: Displaying the frequency of crystals observed in automated microscopy compared to routine microscopy

Crystals	Automatic analyser	Manual	p-value
0-10/hpf	10	12	.032
>10/hpf	3	10	
Absent	134	98	

Table 5: Displaying sensitivity, specificity, PPV, NPV in case of WBC in both methods

WBCs Ranges	Sensitivity	Specificity	PPV	NPV
>5-10/hpf	100%	88.5%	85.7%	100%
>10-20/hpf	100%	92.1%	66.7%	100%
>20/hpf	100%	93.5%	85.1%	100%

PPV (Positive predictive value), NPV (Negative predictive value)

DISCUSSION

Urinary tract infections (UTIs) are one of the most prevalent bacterial infections worldwide, ranking just behind respiratory tract infections. They are frequently encountered in clinical practice, with many cases being asymptomatic, posing a risk of complications like kidney scarring and pregnancy-related issues if left undiagnosed and untreated. Urine, unlike other bodily fluids, lacks lysozyme, immunoglobulins, and complement proteins, making it a favorable medium for bacterial growth. As such, accurate and reliable urinalysis plays a vital role in diagnosing and preventing UTIs and other urinary tract disorders.[12] Early diagnosis of UTIs is essential, as untreated infections can lead to severe renal complications. This study aimed to evaluate the accuracy of an automated urine analyzer (Urised, 77 Electronika, Hungary) in comparison to the gold standard of manual urine microscopy, focusing on physical, chemical, and microscopic parameters.

Our study demonstrated a significant level of agreement between manual and automated urine analysis, these findings align with previous studies, such as the work by Ince et al., who reported strong correlations between manual and automatic urine analyzers, especially for components like red blood cells (RBCs), white blood cells (WBCs), and epithelial cells.[13] Bakan et al. also found that the manual and automated approaches were compatible and reliable for detecting these components.[14] These studies confirm the validity and reliability of automated urine analyzers in providing consistent results similar to manual microscopy, particularly for routine urinary parameters.

However, our study also found some differences between the manual and automated methods. The automated analyzer detected a higher percentage of RBCs (71%) compared to manual microscopy (67%). This discrepancy suggests that automated systems may have increased sensitivity in detecting RBCs, which is consistent with findings from Ahmed et al., who noted that automated analyzers performed better than manual microscopy for RBC detection.[15] This suggests that automated analyzers can identify certain elements that may be overlooked during manual examination, potentially improving diagnostic accuracy in specific cases. Similarly, Tantisaranon et al. observed a strong correlation for epithelial cells between both methods, although differences were noted for RBCs and leukocytes.[16] These findings highlight the strengths of automated analyzers in detecting certain elements while acknowledging that manual techniques may still have advantages for others.

Damaged leukocytes are not counted by the automated instrument, but distorted and disrupted cells again may be counted as an artifact. A study by Shayanfar, et al. demonstrates abnormal erythrocytes, such as ghost and dysmorphic cells, are found in some cases with potentially falsely high erythrocyte count due to misclassification of yeast.[17] The blood count needs to be adjusted and Iris iQ200 counts fewer erythrocytes. Wah, et al. reported similar false-positive results. and manual microscopy is therefore the only way of determining urine samples from patients suffering from kidney disorders.[18]

Another significant parameter analyzed in our study was urine color and appearance. Our results showed that the automated analyzer identified straw-colored urine in 63.9% of samples, while manual observation recorded this color in only 46.7%. Similarly, the automated system detected cloudy urine in 64.5% of samples compared to 47.3% in manual observation. These differences, which were statistically significant (p=0.002), suggest that automated systems may be more effective in consistently detecting color and appearance, which could be subject to subjective interpretation in manual analysis. These findings are

consistent with those of Gyamfi et al., who also observed good agreement between manual and automated methods for urine color and appearance.[19]

While automated systems excel at handling large volumes of samples efficiently and reducing laboratory staff burden, they may not always detect certain crucial elements. For example, dysmorphic RBCs, casts, and crystals may be missed by automated analyzers, which are essential for diagnosing complex conditions like glomerulonephritis and nephrolithiasis.[20] We sara chkitti et al. also emphasized the importance of manual microscopy for detecting these elements, which automated systems may fail to identify accurately. Therefore, while automated analyzers are valuable for routine screening, manual examination remains critical for confirming pathological findings and detecting subtle abnormalities that may have clinical significance.[21]

The complementary use of both manual and automated methods is essential for ensuring diagnostic accuracy and reliability. While automated systems can streamline the urinalysis process, especially in high-volume settings, the manual approach provides an added layer of scrutiny that is necessary for detecting rare or complex conditions. This study's findings align with the broader consensus in literature, which suggests that combining both methods offers the most comprehensive and reliable diagnostic approach. This is particularly true in high-demand environments like PNS Shifa Hospital, where the use of automated analyzers can expedite the diagnostic process while still allowing for manual examination in cases where further investigation is warranted.[24] Overall, this study underscores the importance of incorporating both manual and automated urine analysis techniques in clinical practice. The combination of both methods helps overcome the limitations inherent in each and ensures more accurate and reliable diagnoses, particularly in the context of UTIs and other urinary tract disorders. The findings also support the continued use of manual microscopy as a complementary tool in diagnosing more complex or subtle urinary tract conditions, especially in high-volume clinical settings where automated systems are invaluable.

CONCLUSION:

The concordance between the automatic analyzer and manual microscopic examination demonstrated high sensitivity, specificity, positive predictive value, negative predictive value. One notable advantage of the automatic analyser was its "red flag" functionality. It provided specific counts for parameters such as RBCs, WBCs, and epithelial cells, unlike manual microscopy, which often reported a "full field" for large numbers. However, while the automatic analyser could detect and count crystals, it was unable to identify their type or morphology, which still required manual microscopy. Additionally, the automatic analyzer was faster and less labor-intensive than manual microscopy when analyzing urine samples.

Authors Contribution:
Shaista Bakhat: The article was initially written by her, and provided the original statistics
Yasmeen Taj: Made overall modifications to the manuscript
Maria Ali: Contributed to the discussion section and assisted with referencing
Sana Barkat Ali Bhayani: Helped with data collection
Luqman Satti: Supported the gathering of data from PNS Shifa.
Hina Wasti: Helped with the data collection

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Original Article **Open Access**

Effect of Early Essential Newborn Care and Breastfeeding on Reducing Perinatal Morbidity versus Routine Birth Care

Sahiba Dost, Sadia Aftab, Majida Zafar, Sobia Luqman, Kinza Shakeel, Tahreem Sehar

ABSTRACT

Objectives: To compare perinatal morbidity and breastfeeding practices between infants who received Early Essential Newborn Care (EENC) during the first 90 minutes of life versus those who received routine care.

Study Design and Setting: The study design is a comparative cohort study. The study was performed at the Department of Maternal Child Health (MCH), Pakistan Institute of Medical Sciences (PIMS), Islamabad.

Methods: The study involved 600 live singletons vaginally born infants conducted in a hospital setting. Infants were divided into one group receiving routine birth care and the other receiving EENC. The differences between the two groups in terms of health outcomes were analyzed employing Chi-square tests, t-tests, and logistic regression.

Results: EENC significantly reduced the rate of hypothermia compared to the routine care group ($p < 0.001$). Exclusive breastfeeding at discharge was particularly higher in the EENC group ($p < 0.001$), as was breastfeeding within the first hour ($p < 0.001$). The mean length of hospital stay for the EENC group ($p = 0.01$) was also shorter. We performed Logistic regression analysis and found that EENC was independently associated with reduced odds of neonatal infection ($p < 0.001$), respiratory distress ($p = 0.004$), and jaundice requiring treatment ($p = 0.002$).

Conclusion: Early Essential Newborn Care has a major impact on improving neonatal health outcomes with an increase in breastfeeding initiation, reduction in perinatal morbidity, and facilitated faster recovery from illnesses. EENC should be considered an important strategy for promoting newborn health in the hospital setting.

Keywords: Infant, Newborn?, Perinatal Care?, Breast Feeding?, Morbidity?

How to cite this Article:
Dost S, Aftab S, Zafar M, Kuqman S, Shakeel K, Sehar T. Effect of Early Essential Newborn Care and Breastfeeding on Reducing Perinatal Morbidity versus Routine Birth Care. J Bahria Uni Med Dental Coll. 2025;15(2):115-120 DOI: https://doi.org/10.51985/JBUMDC2025500

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Received: 06-01-25
Accepted: 07-04-25
1st Revision: 24-01-25
2nd Revision: 17-03-25
3rd Revision: 20-03-25

INTRODUCTION

According to the World Health Organization (WHO), perinatal morbidity includes illness or conditions that are experienced by the newborn and the mother, defined as 22 completed weeks' gestation until seven days after birth.[1] Perinatal morbidity poses a continued major public health issue worldwide, especially in low and middle-income countries, where neonatal morbidity and mortality are compounded due to deficit access to quality healthcare services and low financial resources.[2] Although neonatal illnesses are largely preventable with appropriate and timely care, they remain one of the primary causes of complications in the long-term health of infants as well as infant deaths.[3] The United Nations Children's Fund (UNICEF) estimates that a large proportion of neonatal deaths are attributable to preventable causes that are related to poor perinatal care practices.[4]

Timely and appropriate Early Essential Newborn Care (EENC) has been shown to significantly reduce neonatal morbidity and mortality. [5] The core components of EENC include early drying and rapid warming of the newborn, early initiation of breastfeeding, and aseptic umbilical cord care. [6] These practices play a crucial role in stabilizing the newborn immediately after birth, reducing the risk of

infections, and fostering mother-infant bonding, which is essential for the baby's physical and emotional development. [7] Several studies have demonstrated that EENC effectively reduces neonatal complications such as hypothermia, infections, respiratory distress, and jaundice—conditions that are among the leading causes of perinatal morbidity and mortality, particularly in resource-limited settings. [8, 9]

A critical component of newborn care is the early initiation of breastfeeding.[10] Breastfeeding within the first hour of life ensures that the newborn receives colostrum, a nutrient-rich first milk containing essential antibodies that protect against infections and strengthen the infant's immune system.[11] Early initiation of breastfeeding has been strongly associated with a reduced incidence of neonatal infections, a major contributor to perinatal morbidity worldwide.[12] Furthermore, establishing breastfeeding early promotes long-term health benefits, including improved cognitive development, reduced risk of chronic diseases later in life, and enhanced maternal health. The WHO and UNICEF recommend exclusive breastfeeding for the first six months of life due to its well-documented benefits for infant growth, development, and survival.

Despite these well-established benefits, routine birth care practices still pose barriers to optimal newborn care in many healthcare settings, particularly in regions with underdeveloped healthcare infrastructure. Traditional practices such as delayed cord clamping, lack of immediate skin-to-skin contact, and late initiation of breastfeeding remain prevalent despite evidence suggesting they are less effective in preventing perinatal morbidity compared to EENC. Moreover, while delayed cord clamping has been linked to improved infant iron levels, it may also contribute to neonatal jaundice and other health complications.

Several studies have investigated the impact of EENC and early breastfeeding on neonatal health outcomes, particularly in low-resource settings where access to advanced medical interventions is limited. However, despite growing evidence supporting the benefits of EENC, there remains a lack of comparative research directly evaluating EENC versus routine birth care practices in terms of perinatal morbidity. Additionally, the long-term health outcomes of mothers and infants with EENC are poorly understood. The purpose of this study is to fill these gaps by comparing EENC, which included initiating exclusive breastfeeding within the first 90 minutes of life, versus routine birth care practices on neonatal health outcomes. The results from this study will contribute to the field of neonatal health by providing recommendations to enhance newborn health practices using evidence-based approaches, especially in resource-limited settings, to improve maternal and infant outcomes on the whole.

METHODOLOGY

In this study, the Early Essential Newborn Care (EENC) with early breastfeeding initiation was compared with routine birth care practices using a comparative cohort design to determine the perinatal morbidity reduction effect. The study was carried out in one of the largest maternity hospitals, the Department of Maternal Child Health (MCH), Pakistan Institute of Medical Sciences (PIMS), Islamabad. The duration of the study was 6 months i-e from 1st April 2023 to 1st October 2023. following the approval of the research synopsis from Ethical Review Board (ERB) No. F, 1-1/2015/ERB/SZABMU/1213, Dated: 30-11-2023.

The sampling technique adopted was non-probability consecutive sampling. The sample size was determined based on an anticipated 7% absolute reduction in perinatal morbidity rates between the EENC and routine care groups. This estimation was informed by previous studies demonstrating significant improvements in neonatal outcomes following EENC implementation.[13] Assuming a 95% confidence level and 80% power, a total of 300 infants per group (n=600) was calculated as the minimum required sample size to detect a statistically significant difference in perinatal morbidity.

The study included vaginally born, live, singleton infants delivered within the study period to control for temporal bias. Eligible mothers were aged between 18 and 45 years, and their newborns had no major congenital anomalies. Infants were excluded if they were born preterm, had severe birth defects, required immediate resuscitation at birth, or if their mothers did not consent to participate.

Data were collected through a combination of prospective observations and retrospective medical records. Maternal demographic and clinical details, including age, parity, gestational age at delivery, and medical history, were recorded. Delivery-related information such as mode of delivery, birth weight, and Apgar scores were also documented. Neonatal outcomes were assessed by measuring body temperature within the first 30 minutes of life to evaluate thermal regulation. The initiation of exclusive breastfeeding within the first hour was noted, and perinatal morbidity was assessed by tracking neonatal infections, jaundice requiring treatment, respiratory distress, and hypoglycemia during the first seven days of life. We also noted the length of the stay in the hospital for those participants who developed complications requiring a longer hospital stay. In addition, health system data were gathered and coded to include healthcare provider practices and infant care patterns of practice related to cord clamping, initiating breastfeeding, and skin-to-skin care.

The 600 infants were designated to the Early Essential Newborn Care (EENC) group or the Routine Care group depending on the care practices at birth. Infants were not randomly assigned but identification followed hospital protocol and maternal preferences. Thus, 300 infants received the EENC protocol and 300 infants were designated to the Routine Care group. Infants who received skin-to-skin contact, an opportunity to breastfeed early, and

thermoregulation as part of the EENC protocol were placed into this group, while those who received the standard routine care were assigned to this group.

To ensure valid and consistent data collection, data from the Early Essential Newborn Care (EENC) group was prospectively documented during the labor and delivery room and the first 90 minutes of life. Observations were regarding key practices such as skin-to-skin contact, initiation of breastfeeding, and thermal care. In contrast, data from the routine care group was retrospectively documented from the medical records, collecting data on initiation of breastfeeding, clamp cord events, and other immediate newborn care interventions. Continued monitoring occurred until discharge from the hospital, with pediatric staff documenting the newborn's health status until discharge, and assessing for any morbidities.

SPSS 25 statistical software was used for the data analysis. Baseline characteristics were descriptively summarized, and bivariate analysis utilized chi-square tests for categorical variables, and t-tests or Mann-Whitney U tests for continuous variables. For confounding variables such as maternal age, parity, and gestational age, a multivariate analysis was performed. Logistic regression was used to evaluate the independent effect of EENC on the outcome of morbidity in neonates, with $p < 0.05$ considered significant.

RESULTS

The demographic and clinical characteristics of the study participants were similar between the EENC and Routine Care groups, with no statistically significant differences observed in maternal age ($p = 0.76$), parity ($p = 0.52$), gestational age ($p = 0.45$), mode of delivery ($p = 0.42$), birth weight ($p = 0.95$), or Apgar score at five minutes ($p = 0.87$) (Table 1).

Neonatal health outcomes were significantly better in the EENC group compared to routine care. Hypothermia was observed in 8.0% of neonates in the EENC group, whereas it was significantly higher at 20.0% in the Routine Care group ($p < 0.001$). Breastfeeding initiation within one hour was notably higher in the EENC group (92.0%) compared to 60.0% in the Routine Care group ($p < 0.001$). Similarly, exclusive breastfeeding at discharge was higher in the EENC group (88.0%) than in the Routine Care group (65.0%) ($p < 0.001$). Perinatal morbidity outcomes also showed significant differences, with neonatal infection occurring in 4.0% of the EENC group compared to 12.0% in the Routine Care group ($p < 0.001$), jaundice requiring treatment in 6.0% versus 15.0% ($p = 0.002$), and respiratory distress in 3.0% versus 10.0% ($p = 0.004$). The length of hospital stay was significantly shorter in the EENC group (3.5 ± 1.2 days) compared to the Routine Care group (4.2 ± 1.4 days) ($p = 0.01$) (Table 2).

Logistic regression analysis further confirmed the benefits of EENC in reducing neonatal morbidity outcomes. The odds of neonatal infection were significantly lower in the EENC group (OR = 0.32, 95% CI: 0.20–0.50, $p < 0.001$). Similarly, the odds of respiratory distress (OR = 0.29, 95% CI: 0.12–0.64, $p = 0.004$) and jaundice requiring treatment (OR = 0.42, 95% CI: 0.25–0.71, $p = 0.002$) were significantly reduced. Additionally, neonates in the EENC group had significantly higher odds of exclusive breastfeeding at discharge (OR = 0.28, 95% CI: 0.16–0.48, $p < 0.001$). These odds ratios were adjusted for sociodemographic variables (Table 3).

DISCUSSION

The present study emphasizes the majority of benefits of Early Essential Newborn Care (EENC) over routine care in the neonatal outcome. Newborn infants who received EENC had improved thermal stability, increased exclusive breastfeeding, and lower perinatal morbidity when compared to newborn infants who received routine care. These results are congruent with previous studies that have emphasized early postnatal interventions (skin-to-skin contact, early breastfeeding initiation, and thermal protection) as postnatal interventions that can reduce morbidity and mortality.

The EENC group observed a significant reduction in hypothermia in the EENC group. Only 8% of the newborns experienced hypothermia compared to 20% of the EENC group ($p < 0.001$). These results are consistent with a study by Mansoor S, et al. (2025) from Jamshoro, Pakistan, who demonstrated that early skin-to-skin contact promotes neonatal body temperature regulation and prevents hypothermia.[14] Likewise, Ramaswamy et al. (2022) conducted a meta-analysis that found immediate postnatal skin-to-skin contact significantly improved thermal stability and decreased rates of neonatal hypothermia.[15] The positive thermal outcomes in the EENC group support WHO recommendations advocating immediate postnatal care interventions for thermoregulation, particularly in resource-limited settings. The results also revealed significant differences in breastfeeding initiation between the two groups. In the EENC group, 92% of neonates initiated breastfeeding within the first hour of life compared to 60% in the routine care group ($p < 0.001$). Additionally, exclusive breastfeeding at discharge was higher in the EENC group (88% vs. 65%, $p < 0.001$). These findings align with previous research by Sangild PT et al. (2021) from Denmark, who found that early breastfeeding initiation reduces neonatal mortality by ensuring early colostrum intake, which provides essential nutrients and passive immunity.[16] Another study by Borg B et al. (2022) from Australia and a literature review by Layuk N et al., (2021) indicated that early initiation of breastfeeding within the first hour significantly decreases the risk of neonatal infections.[17, 18] The high rates of exclusive breastfeeding in the EENC group reinforce the role of early breastfeeding practices in promoting continued breastfeeding beyond hospitalization.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	EENC Group (n = 300)	Routine Care Group (n = 300)	p-value
Maternal Age (years, Mean ± SD)	29.5 ± 5.6	29.6 ± 5.7	0.76
Maternal Parity, n (%)			
Primipara	150 (50.0%)	155 (51.7%)	0.52
Multipara	150 (50.0%)	145 (48.3%)	
Gestational Age (weeks, Mean ± SD)	38.9 ± 1.2	39.0 ± 1.1	0.45
Mode of Delivery, n (%)			
Spontaneous Vaginal	240 (80.0%)	245 (81.7%)	0.42
Assisted Vaginal	60 (20.0%)	55 (18.3%)	
Birth Weight (kg, Mean ± SD)	3.3 ± 0.5	3.3 ± 0.5	0.95
Apgar Score (5 minutes, Mean ± SD)	8.5 ± 0.6	8.5 ± 0.6	0.87

Table 2: Neonatal Health Outcomes by Care Group

Outcome	EENC Group (n = 300)	Routine Care Group (n = 300)	p-value
Thermal Regulation, n (%)			
Hypothermia (temperature <36.5°C)	24 (8.0%)	60 (20.0%)	<0.001
Breastfeeding Initiation, n (%)			
Initiation within 1 hour	276 (92.0%)	180 (60.0%)	<0.001
Exclusive breastfeeding at discharge	264 (88.0%)	195 (65.0%)	
Perinatal Morbidity, n (%)			
Neonatal Infection (sepsis/pneumonia)	12 (4.0%)	36 (12.0%)	<0.001
Jaundice requiring treatment	18 (6.0%)	45 (15.0%)	0.002
Respiratory Distress	9 (3.0%)	30 (10.0%)	0.004
Length of Hospital Stay (days, Mean ± SD)	3.5 ± 1.2	4.2 ± 1.4	0.01

Table 3: Logistic Regression Results for Neonatal Morbidity Outcomes

Outcome	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Neonatal Infection (sepsis/pneumonia)	0.32	0.20 - 0.50	<0.001
Respiratory Distress	0.29	0.12 - 0.64	0.004
Jaundice Requiring Treatment	0.42	0.25 - 0.71	0.002
Exclusive Breastfeeding at Discharge	0.28	0.16 - 0.48	<0.001

Note: Odds ratios were adjusted through multiple logistic regression for sociodemographic variables.

The study demonstrated a significant reduction in neonatal morbidity among infants receiving EENC. Neonatal infection rates were lower in the EENC group (4% vs. 12%, $p < 0.001$), as were rates of jaundice requiring treatment (6% vs. 15%, $p = 0.002$) and respiratory distress (3% vs. 10%, $p = 0.004$). These findings are consistent with those of Johansson et al. (2024) from Sweden, who reported that early skin-to-skin contact reduces the risk of neonatal infections by promoting breastfeeding, which enhances immune protection. [19] Additionally, another study conducted by Tran et al. (2021) from Vietnam found that early neonatal interventions significantly decrease the likelihood of post-delivery complications. [20] The study by Brimdyr K, et al. (2023) from the USA observed a reduction in respiratory distress in the EENC group that may be attributed to the physiological stabilization facilitated by immediate skin-to-skin contact. [21]

The mean length of hospital stay was significantly shorter in the EENC group (3.5 vs. 4.2 days, $p = 0.01$). This finding aligns with studies by Alsadaan N, et al. (2023) from Saudi Arabia, which suggest that improved neonatal health outcomes from early interventions contribute to shorter hospital stays and reduced healthcare costs.[22] Shorter hospitalization durations not only benefit healthcare systems by reducing resource utilization but also enhance maternal-infant bonding and decrease the risk of hospital-acquired infections.

Logistic regression analysis confirmed that the beneficial effects of EENC on neonatal health outcomes were independent of potential confounders such as maternal age and parity. Infants in the EENC group had significantly lower odds of neonatal infection (OR = 0.32, $p < 0.001$), respiratory distress (OR = 0.29, $p = 0.004$), and jaundice requiring treatment (OR = 0.42, $p = 0.002$). These findings are consistent with research by the World Health Organization (WHO) and UNICEF, emphasizing the effectiveness of immediate newborn care practices in improving survival rates and reducing neonatal complications.[23-25]

The findings of this study have significant implications for hospital policies and clinical guidelines. The evidence strongly supports the integration of EENC into standard neonatal care protocols in hospital settings. Training healthcare providers on the importance of early skin-to-skin contact, timely initiation of breastfeeding, and effective thermal care should be a priority in the hospital setting. Moreover, making EENC an established norm can help reduce rates of neonatal morbidity and length of hospital stay, which in turn improves neonatal survival and reduces the burden on healthcare services.

CONCLUSION

EENC offers significant improvements in health outcomes for newborns as compared to routine care. Newborns receiving EENC are more likely to maintain normal thermal stability; initiate breastfeeding within one hour of birth; and morbidity, including infections, jaundice, and respiratory distress, during their stay. These results support the importance of early care interventions in the first 90 minutes of life, which is consistent with global health recommendations for newborn care

Authors Contribution:
Sahiba Dost: Substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; Drafting the article & revising it critically for important intellectual content; Final approval of the version to be published.
Sadia Aftab: Acquisition of data, analysis and interpretation of data; Drafting the article, Final approval of the version to be published.
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Sobia Luqman: Drafting the article, Final approval of the version to be published
Qurrat-ul-Ain: Drafting the article, Final approval of the version to be published
Tahreem Sehar: Analysis and interpretation of data, Final approval of the version to be published

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Original Article **Open Access**

Antidepressant Effects of Imipramine and Ashwagandha: A Quasi Experimental Study

Ayesha Ramzan, Mashkoor Ahmed Ansari, Sadat Memon, Sawaira Hussain, Sophia Raza Laghari, Sumeira Naeem Khan

ABSTRACT:

Objective: Tocompares the antidepressant properties of Imipramine and Ashwagandha (Withaniasomnifera)

Study Design and Setting: Experimental Observational Study. Animal House of Agriculture University, Tando Jam, collaborated with the Department ofPharmacology and Therapeutics LUMHS Jamshoro

Methodology: Three groups of rats were used: Group A received normal saline (0.9% NaCl); Group B received 32 mg/kg of imipramine; and Group C received 100 mg/kg of Ashwagandha. To evaluate the antidepressant efficacy of the medications, Forced Swimming Test (FST) and the Tail Suspension Test (TST) were used. In the TST, the duration of immobility was recorded as an indicator of behavioral despair, while in the FST, the duration of immobility, climbing and swimming time were measured to evaluate the antidepressant effects. Data was analyzed by using SPSS v26. P-value <0.05 was considered significant.

Results: TST Test Results: Immobility duration was 201± 1.3 in the Ashwagandha Group (GroupB)and 198± 1.1 in the imipramine group (Group C), compared to 225 ± 1.8 in the Control group (Group A). FST Test Results: Immobility duration was 96 ± 1 in Group B and 102 ± 1 in Group C, compared to 206.2 ± 0.8 in Group A. The climbing times were 92 ± 0.2 and 90 ± 0.8 (Group C) vs 62.8 ± 0.9 (Group A). The swimming times were 172 ± 1.3 (Group B) and 168 ± 1 (Group C) vs 91 ± 1 (Group A).

Conclusion: Findings highlighted Ashwagandha as a promising natural alternative antidepressant agent, warranting further investigation into its mechanisms and clinical applications.

Keywords: Antidepressant effects, Ashwagandha, Imipramine, ForcedSwimming Test, Tail Suspension Test.

How to cite this Article:
Ramzan A, Ansari MA, Memon S, Hussain S, Laghari SR, Khan SN. Antidepressant Effects of Imipramine and Ashwagandha: A Quasi Experimental Study. J Bahria Uni Med Dental Coll. 2025;15(2):121-126 DOI: https://doi.org/10.51985/JBUMDC2025505

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Received: 07-01-25
Accepted: 25-03-25
1st Revision: 15-01-25
2nd Revision: 22-01-25
3rd Revision: 03-03-25

INTRODUCTION:

Depression is a diverse illness that impacts an individual's conduct, mental and physical wellbeing. In today's stressful culture, the prevalence of depressive mood disorders is on the rise, which raises the risk of suicide or self-harm as well as the death rate from associated general medical diseases.[1]Depression is a debilitating mental condition that is on the rise globally and contributes to morbidity and disability. Changes in structural synapses and protein composition are increasingly associated with mental disease. In the hippocampus's cornu ammonis 1 and dentate gyrus regions, for example, there is evidence of pyramidal neurone retraction, dendritic atrophy, and reduced gene expression of synaptic proteins such synapsin, microtubule-associated protein, and AMPA receptor subunits in the depressed brain.[2]One Up to 10–15% of people with this illness have suicidal thoughts at some point in their lives.According to the World Health Organisation, depression was the third most common cause of sickness worldwide in 2018. By 2030, it is predicted to overtake all other diseases.[3] According to studies, this lowers life satisfaction and raises the likelihood of divorce as well as major illnesses like cancer, heart disease, depression[4,5]. Tricyclic antidepressants (TCAs) are a class of psychotropic drugs that are mainly used to treat serious

depression, while they can also be used to treat a variety of other neurological and psychiatric conditions.[6]Depression treatment underwent a revolution in the middle of the 20th century thanks to this family of medications, which were the first to treat the condition. Although SSRIs are usually suggested as the main-stay of treatment for MDD (major depressive disorder), TCAs are endorsed for patients with chronic depression or as a backup for patients who don't respond to novel agents used for depression, according to the clinical practice guidelines for mood disorders published by the Royal Australian and New Zealand College of Psychiatrists and the National Institute for Health and Care Excellence (NICE). 7Impramine is a tricyclic antidepressant that is included in the WHO Model List of Essential Medicines. There are only two vital agents for the treatment of depression. [8] Imipramine acts primarily by inhibiting the reuptake of neurotransmitters such as serotonin and norepinephrine, which are crucial in mood regulation. It has been shown to reverse stress-induced changes in brain structures associated with depression, particularly in the amygdala and prefrontal cortex. Side effects of imipramine are notably higher compared to other antidepressants, with reports indicating that 86.7% of patients experience adverse reactions. Common side effects include: Dry mouth, Constipation, Urinary retention, Drowsiness, Weight gain, Cardiac issues, particularly in patients with pre-existing conditions.[9] The behavioral test for mouse called the tail-suspension test is significant for assessing many treatments that can influence behaviors linked to depression and for screening the agents used for depression. A Tape is used to hang mice by their tails so they are unable to flee or cling to adjacent items. This test, which typically lasts six minutes, measures the subsequent escape-oriented behaviours. An important method for high-throughput screening of possible antidepressant chemicals in drug discovery is the tail-suspension test. Another mouse behavioral test called the forced swim test is used to assess the effectiveness of antidepressant medications, novel substances, and experimental procedures intended to induce or avoid depressive-like conditions. Mice are kept in a transparent, unavoidable tank filled with water, and their movement behaviour in relation to escape is observed. The forced swim test requires little specialised equipment and is simple to perform consistently. Minimising unnecessary stress for the mice and following certain protocol guidelines are essential for a successful forced swim test.[6]

Ashwagandha is thought to have potential advantages in treating depression and anxiety, two issues that are becoming more and more prevalent in contemporary culture. Ashwagandha's bioactive ingredients, especially withanolides, may help lessen anxiety and depressive symptoms by influencing the nervous system through a number of biological processes. This may entail neurotransmitter control, anti-inflammatory properties, and assistance with stress management techniques. Ashwagandha's broad mode of action as a natural adaptogen and tendency to have less adverse effects than traditional antidepressants and anxiolytic medications offer a substantial advantage in terms of possible future treatment choices. Ashwagandha may be a natural complement in these areas, according to numerous research in the literature.

Ashwagandha, or Withaniasomnifera, is a well-known herb in India and a common ingredient in Ayurvedic medicines. Ashwagandha is also known as winter cherry, poison gooseberry, and others. The primary active ingredients of ashwagandha are withaferin and sitoindosides VII–x. Phytopharmacological research indicates that ashwagandha may have sedative, immunomodulatory, diuretic, anti-inflammatory, and cardioprotective effects.[10]Ashwagandha enhances the patients strength to manage with stress, potentially reducing anxiety and depressive symptoms. Ashwagandha modulates neurotransmitters and exhibits antioxidant properties, which may support mood regulation.[11] Many physiological effects of Withania somnifera (WS) have been extensively studied, with an emphasis on its possible application in the treatment of brain diseases, based on the close relationship between stress and neuropsychiatric diseases, the anti-stress characteristics of Withania somnifera WS are believed to play a crucial role in its potential benefits for depression, anxiety, and insomnia. Since GABA is the main inhibitory neurotransmitter in the central nervous system, GABAergic neurotransmission plays a major role in the mechanism of anxiety. GABA agonist medications are commonly given to treat anxiety disorders because they primarily act at GABA type A (GABAA) receptors, which improve GABAergic function. Substances in Withania somnifera WS actively engage and regulate GABAA receptors, according to extensive studies in non-human subjects. This could account for Withania somnifera WS's ability to reduce anxiety. The first proof that WS can imitate GABA was published in 1991 by Mehta et al. In the absence of GABA, the researchers found that a methanolic extract of WS root enhanced the flow of chloride ions in mammalian spinal cord neurones. In a way comparable to that of GABAA receptor agonists, the extract also prohibited GABA from binding to its receptor Ashwagandha has antioxidant and anti-inflammatory effects and modulates the effects of many neurotransmitters inside the brain, that may benefit mental illnesses such as anxiety, depression, obsessive-compulsive disorder, psychosis, attention deficit hyperactivity disorder, and addictive conditions.[12] Depressive disorders raise the risk of self-harm and suicide. While antidepressants have multiple side effects, herbal alternatives like ashwagandha offer better tolerance and compliance with fewer adverse effects.

METHODOLOGY:

The research study was officially approved by the Research Ethic Committee LUMHS Jamshoro. NO. LUMHS/REC/-

67. Dated: 11/05/2023. This was an Experimental Observational Study. It was conducted at Animal House of Agriculture University, Tando Jam, collaborated with the Department of Pharmacology and Therapeutics LUMHS Jamshoro. spanning a time of 6 months, i-e June 2023 to Nov 2023. A sum of 36 rats [13] (N=36) were employed as the sample size. Albino rats weighing between 200 and 250 grams. Rats were healthy, exhibiting typical conduct and activities. Rats weighing more than 250 grams and less than 200 grams, having any abnormalities in their bodies were excluded. Ashwagandha and Imipramine were purchased from local market and pharmacy respectively. Three groups of twelve albino rats each were created: In Group A's Rats received normal saline control (0.9%) 5 milliliters per kilogram. In Group B Rats received 32 mg/kg of imipramine. In Group C, Rats received 100 mg/kg Ashwagandha (WithaniaSomnifera). TST (Tail Suspension test) and FST (Force swim test) were used to assess rats' depression-like behavior. The animals were kept under particular standard settings of laboratory, through a 12-hour normal dark and light cycle, at a constant room temp: (23_+2oc), and with a 60% humidity level in accordance with CPCSEA norms. They were also given unrestricted access to food and drink as needed6. The behavioral tests were conducted between 9:00 a.m. and 11:00 p.m. after the animals had been acclimated for five days. We bought imipramine and ashwagandha from the market. All animals were housed in Sindh Agriculture University's animal home in Tando Jam in order to test for antidepressant effects.

Tail suspension test: A wooden chamber that is 70 cm high is used for the mechanical assembly of the tail suspension test (TST). A bar that was 60 cm from the ground or 10 cm from the top of the mechanical assembly was installed between the load-dividing side dividers. Sticky tape was used to hang the rats from the pole, one inch from the tip of their tails. Rats received a 15-minute pretest session for 12 days, and on day 13, they received a 5-minute test session following the administration of imipramine 32 mg/kg via nasogastric tube and normal saline (0.9% Nacl) 5 ml/kg orally to the control group. For the final 300-second test, each rat was suspended independently from the pole. Each animal's stability was recorded for a duration of 300 seconds.[6] Rats were thought to be stable when they hung motionless with bars and made an effort to escape.

Force Swim Test: Rats were forced to swim alone in a 45x40x30 cm vertical Plexiglass vessel with 20cm level of water above the surface and a temp: of 22+1UC. As a result, the rats' feet did not contact the vessel's floor and they did not climb out. Two sessions comprised the entire study.[14] PRETEST SESSION: For 12 days, rats were made to swim alone for 15mins in a vessel made of polypropylene. TEST SESSION: On day 13, each animal was once more compelled to swim. During a test session, swim for six minutes. During the first two minutes, each animal made a determined effort to leave the Plexiglas container. After that, they all became motionless and made sporadic attempts to do so, as shown by the head raising slightly above the water. Each test lasts two minutes, and the total time spent swimming, climbing, and immobility is recorded for a total of six minutes. The length of time spent swimming, climbing, and immobility was contrasted with that of the control group. All drugs were given oral by nasogastric tube.[13]

SPSS V.26 was used to analyze data. The mean and standard deviation were calculated for every numerical variable. The students's t-test were used & P-value < 0.05 regarded as statistically significant. Informed consent was not required as this study involved animals.

RESULTS:

The study evaluated the antidepressant effects of Ashwagandha (WithaniaSomnifera) and imipramine using tail suspension test (TST) and forced swim test (FST). Both treatments significantly reduced the immobility duration compared to the control group ($p<0.01$).

TST Test Results: The anti-depressant effect investigated by using Tail Suspension Test (TST) model suggested the statistically significant effect of Ashwagandha and imipramine when they are compared with the control group. There is statistically significant reduction of immobility duration in Group B & C which are treated with Ashwagandha and Imipramine respectively, as compared to Group A. Immobility duration was 201± 1.3 in the Ashwagandha Group (Group B) and 198± 1.1 in the imipramine group (Group C), compared to 225 ± 1.8 in the Control group (Group A) shown in Table 1 & Figure 1.

FST Test Results: The anti-depressant effect investigated by using Forced swim test (FST) model suggested the statistically significant effect of Ashwagandha and imipramine when they are compared with the control group. There is statistically significant reduction of immobility duration in Group B & C which are treated with Ashwagandha and Imipramine respectively, as compared to Group A. The climbing time and swimming time were increased statistically significant in Group B and C as compared to Group A. The climbing times were 92 ± 0.2 and 90 ± 0.8 (Group C) vs 62.8 ± 0.9 (Group A) shown in Table 2 & Figure 2. The swimming times were 172 ± 1.3 (Group B) and 168 ± 1 (Group C) vs 91 ± 1 (Group A) shown in Table 3 & Figure 3.

DISCUSSION:

In a preclinical context, the current study examined ashwagandha's potential as an antidepressant. According to our research, ashwagandha significantly decreased immobility time in the forced swim test (FST) and tail suspension test (TST), demonstrating antidepressant-like effects. A previous research by Jayshree Dawane et al concluded that Ashwagandha (Withania somnifera) exhibited significant

Table 1: Mean Duration of Immobility Time of Tail Suspension Test

Group	Dose (mg kg^{-1})	Mean Duration of Immobility	P-Value
Group A (Control)	Normal saline 5ml/kg	225 ± 1.8	<0.01
Group B (Ashwagandha)	Ashwagandha 100mg/kg	201 ± 1.3	
Group C (Imipramine)	32mg/kg	198 ± 1.1	

p < 0.05 is significantly different from control group

Table 2: Mean Climbing Time of Forced Swim Test

Group	Dose (mg kg^{-1})	Climbing Time (sec)	P-Value
Group A (Control)	Normal saline 5ml/kg	62.8 ± 0.9	<0.05
Group B (Ashwagandha)	Ashwagandha 100mg/kg	92 ± 0.2	
Group C (Imipramine)	32mg/kg	90± 0.8	

p < 0.05 is significantly different from control group

Table 3: Mean Swimming Time of Forced Swim Test.

Group	Dose (mg kg^{-1})	Swimming Time (sec)	P-Value
Group A (Control)	Normal saline 5ml/kg	91 ± 1	<0.01
Group B (Ashwagandha)	Ashwagandha 100mg/kg	172 ± 1.3	
Group C (Imipramine)	32mg/kg	168± 1	

p < 0.05 is significantly different from control group

Figure 1: Mean Duration of Immobility Time of Tail Suspension Test

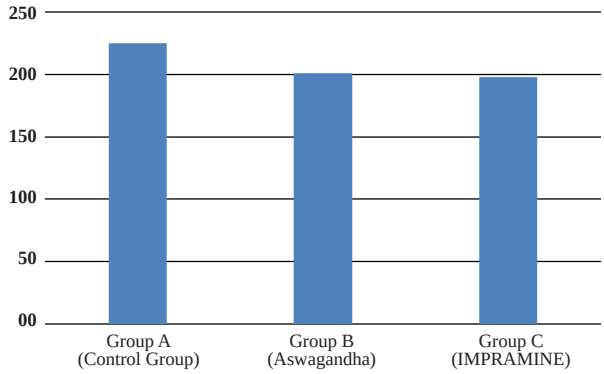


Figure 2: Mean Climbing Time of Forced Swim Test

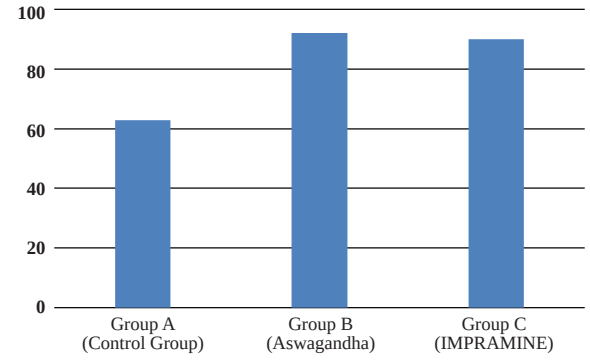
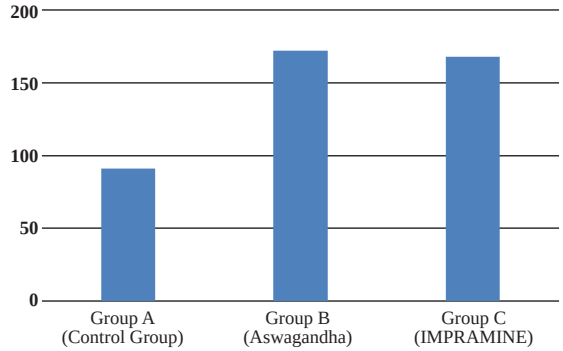


Figure 3: Mean Swimming Time 0f Forced Swim Test



anxiolytic and antidepressant effects in a rat model of chronic stress. Treatment with Ashwagandha root extract increased serotonin and BDNF levels while reducing CRH, ACTH, cortisol, IL-6, and TNF-á. These findings suggest its potential as a prophylactic and therapeutic agent for stress-related disorders.[15] A previous study by Shaista Yousuf et al. reported that Acorus calamus L. rhizome extract exhibits dose-dependent antidepressant activity in mice using the Tail Suspension Test (TST), which is consistent with our findings.[16] Likewise, Ridho Islamie et al. demonstrated that the ethanolic leaf extract of Ocimum sanctum L. has an antidepressant-like effect in the TST, further supporting our study.[17] However, Devesh D. Gosavi et al. found that the alcoholic extract of Withania coagulans fruits did not exhibit antidepressant properties; instead, it had a depressive effect in the TST, which contradicts the above studies.[18] Kosar Asadi et al. reported that components of Cuminum cyminum essential oil exhibited antidepressant-like activity similar to imipramine in both the Forced Swimming Test (FST) and Tail Suspension Test (TST), aligning with our findings.[19] In contrast, Hemant Tanwani et al. found that cinnamaldehyde

(CNM) at lower doses, alone or with escitalopram, showed antidepressant effects in both acute and chronic studies, while higher doses (200/400 mg/kg) did not. Additionally, CNM (200 mg/kg) combined with escitalopram reduced antidepressant effects upon chronic administration. Since their study used SSRIs while ours focused on TCAs, it does not align with our findings.[20] Another previous research stated that Ashwagandha had significant antidepressant effects., they have used Bramhi along with Ashwagandha. They stated that the Combination of these two indigenous drugs with Imipramine showed high efficacy in animal model. [21] a study by concluded that WS produced significant decrease in MIT (mobility time) in mice which could be mediated partly through á adrenoceptor as well as alteration in the level of central biogenic amines. [22]

An important and well-liked Indian medicinal herb, ashwagandha has strong anti-aging, immunomodulatory, anti-anxiety, and stress-relieving properties. Ashwagandha is a widely used Indian medicinal herb that has strong anti-aging, immunomodulatory, anti-anxiety, and stress-relieving properties. It works by boosting glutathione peroxidase activity and normalising elevated lipoxygenese (LPO) activity. According to our research, it has a noticeable antidepressant effect and enhances the effects of imipramine when taken in small doses. This outcome is consistent with Elhassaneen YA [23]findings. While this study is animal-based and employs behavioural tests like TST and FST, Majeed, M. et al[24]. previously showed that a 60-day passage of treatment with Withaniasomnifera root extract standardised for 2.5% of the withanolide compounds found in WS improved depression in normal grownups showing minor to modest symptoms of those endpoints. However, this study works on ashwagandha powder form rather than root extract.

Previously Lopresti AL et al [25] demonstated that Ashwagandha's impact on depression, anxiety reduction, and sleep quality whereas our research solely examines the impact of antidepressants They have also observed its manner of action, whereas our study has observed it as well. In contrast, they have used a number of medicines, whereas in our study we have just compared it with TCAs.

Our study does, however, have a number of limitations First, our findings may not be as broadly applicable as they may be due to the limited sample size. Second, because the study was preclinical in nature, more investigation is required to extrapolate these results to clinical populations. Third, we did not evaluate the possible interactions between ashwagandha and imipramine, which could be crucial for further research.

CONCLUSION:

Our research suggests that Ashwagandha is a safe and effective alternative for depression, potentially matching imipramine with fewer side effects. Its adaptogenic properties may enhance well-being and stress resilience, making it a promising stand-alone or adjunct treatment for mental health. Further studies are needed to confirm its long-term efficacy and safety.

Authors Contribution:
Ayesha Ramzan: conception, analyzed and interpreted the study data
Mashkoor Ahmed Ansari: conception, analyzed and interpreted the study data
Sadat Memon: conception, analyzed and interpreted the study data
Sawaira Hussain: contributor in writing the manuscript
Sophia Raza Laghari: contributor in writing the manuscript
SumeiraNaeem Khan: contributor in writing the manuscript

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Original Article **Open Access**

Gender Disparities in Postoperative Outcomes after Mechanical Heart Valve Replacement Surgery: An Investigative Analysis

Muhammad Waleed, Waqar Masud Malik, Kiran Jamal, Attiya Hameed Khan, Syed Shahkar Ahmed Shah, Muhammad Tariq

Objectives: To compare the pre- and post-operative factors among male and female patients of valvular heart surgery.

Study design and settings: This retrospective observational study was conducted in the department of Cardiac surgery at Peshawar institute of Cardiology from Dec 2020 to March 2022.

Methodology: This retrospective observational study included (n=165) adults, who underwent valvular surgery. Data was extracted from electronic medical record (EMR) and analyzed by using SPSS version 26.0. The study complied with ethical approval and the Helsinki Declaration.

Results: Majority of the patients who underwent valvular surgery were in younger age group (age<45) with predominantly female as compared to male (60.4% vs 38.09%, $p<0.05$). Similarly, the results showed that most of the men underwent aortic valve surgery as compared to females, who underwent mitral valve surgery with statistically significant difference among gender at ($p<0.05$). Comparison of post-operative complications with respect to gender showed that arrythmias along with wound infection and mortality showed statistically significant difference among gender at ($p<0.05$).

Conclusion: This study aimed to compare pre- and post-operative factors among male and female patients undergoing valvular surgery. The findings reveal significant gender-based differences in the distribution of age, types of valve surgery, and post-operative complications. However post operative and gender specific complications, hospital stay along with mortality associated with the type of valve procedure needs to be further explored. Detailed multicenter study and long-term follow up is needed to better analyze the long-term results and disease burden.

KEYWORDS: Atrial septal defect, Coronary artery bypass, heart valve diseases

How to cite this Article:
Waleed M, Malik WM, Jamal K, Khan AH, Shah SSA, Tariq M. Gender Disparities in Postoperative Outcomes after Mechanical Heart Valve Replacement Surgery: An Investigative Analysis. J Bahria Uni Med Dental Coll. 2025;15(2):127-133 DOI: https://doi.org/10.51985/JBUMDC2025506

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Received: 07-01-25
Accepted: 07-04-25
1st Revision: 09-01-25
2nd Revision: 13-03-25
3rd Revision: 28-03-25

INTRODUCTION:

Heart valve disease has been dubbed "the next cardiac epidemic," and as the population ages, its prevalence is predicted to double by 2040 and triple by 2060 .[1]However, it has gained increasing attention in the field of cardiovascular medicine due to significant changes in its presentation and management over the past 60 years. In industrialized nations, the prevalence of valve disease has evolved since the 1950s, transitioning from a predominant rheumatic etiology to a degenerative one. This shift has led to changes in patient demographics and the distribution of various types of valvular lesions.[2] Rheumatic heart disease (RHD), which affects more than 30 million people globally, accounts for 300,000 annual fatalities and 10 million annual disabilities, represents a major global burden, particularly in developing and low-income nations.[2] This growing burden of valvular heart disease highlights its importance as one of the most serious cardiovascular conditions worldwide, with its prevalence influenced by several factors, including age, gender, and socio-economic context.[3]

In particular, sex differentiation in VHD remains underexplored and poorly understood, contributing to disparities in treatment and outcomes.[4] Research indicates that women with VHD experience variations in the frequency

of disease, clinical presentations, symptom perception, and response to diagnostic procedures. For example, women may have different sensitivities and specificities to echocardiography and they often respond differently to medications, requiring distinct dosing strategies These gender-related differences also extend to the management strategies employed, which are frequently influenced by physician-related factors. This underscores the need for sex-specific approaches to diagnosis and therapy, as a one-size-fits-all model may not effectively address these differences.[5]

Despite the growing recognition of these gender disparities, current guidelines for diagnosing and treating valvular heart disease do not adequately incorporate sex-related variations. This gap in knowledge and practice is concerning, as personalized care for VHD, tailored to both sex and body size, has the potential to improve patient outcomes significantly.[6] The lack of concrete data on gender-specific recommendations for VHD treatment further complicates clinical decision-making. To address these issues, future research must focus on a more granular understanding of how gender influences VHD, which could lead to the development of more targeted and effective management strategies.

Surgical intervention plays a critical role in the treatment of VHD, resulting in reduced mortality and enhanced quality of life for many patients. Heart valve replacement, the second most common type of heart surgery after coronary artery bypass graft (CABG) surgery, is a key component of this therapeutic approach.[7] However, women are less likely than men to undergo surgical procedures, because of worse postoperative outcomes, including higher rates of complications and longer recovery times.[5] This disparity is likely influenced by a combination of biological, social, and healthcare system factors, further emphasizing the need for a sex-conscious approach to surgical management in VHD.

In many developing countries, where chronic rheumatic heart disease or rheumatic fever constitutes a significant portion of cardiac admissions, the demand for heart valve replacement surgeries is particularly high. Statistics indicate that these conditions account for between 10 and 35 percent of all cardiac admissions in low-income nations, where access to advanced care may be limited.[8]

The WHO Global Action Plan for the Prevention and Control of Non-Communicable Diseases (NCDs) includes a goal to achieve a 25% relative reduction in NCD mortality by 2025, which highlights the urgency of addressing VHD as a major contributor to global disease burden.[9] A key priority for achieving this goal should be the establishment of comprehensive rheumatic heart disease control programs in low- and middle-income countries, where the disease burden remains disproportionately high. Strengthening healthcare infrastructure, increasing access to early diagnosis, and improving surgical outcomes in these regions are crucial steps toward alleviating the global impact of valvular heart disease.[10]

In light of these challenges, this study aims to address the gap in knowledge regarding the predictors of valvular heart disease in the local population. By exploring demographic, clinical, procedural, sex-based differences and other surgical factors, the study seeks to provide valuable insights into the management of VHD at Peshawar Institute of Cardiology and identify strategies that could potentially reduce the risk of complications, including those related to surgical intervention.

METHODOLOGY:

The data for this retrospective study, conducted from December 2020 to March 2022 at Peshawar Institute of Cardiology, KPK, included male and female patients who underwent valvular surgery. The sample size of 165 patients was estimated through WHO sample size calculator based on a confidence level of 95% and a power of 80%, which are commonly used thresholds for ensuring statistical reliability. It was calculated to account for the potential differences in the prevalence of postoperative complications between male and female patients, with a significance level of $p < 0.05$ and a statistical power of 80%.

with data extracted retrospectively from the Electronic Medical Record (EMR). The study was approved by the hospital's Institutional Review Board committee (IRC/24/140), and informed consent was obtained from all participants. A team of researchers, statisticians, and physicians designed and critically evaluated the questionnaire used for data collection, ensuring that all relevant variables were included. The study adhered to the principles of the Helsinki Declaration and was conducted in accordance with ethical standards. Inclusion criteria encompassed adult patients (aged >18 years) undergoing valvular surgeries, ASD closure, and combined procedures. Exclusion criteria included patients aged <17 years, those with myxoma or renal failure, and those requiring re-opening. Data analysis was performed using SPSS 26.0 (IBM-SPSS Inc., Chicago, USA), with frequencies and percentages calculated for qualitative variables such as gender, etiology, complications, and valve types. Descriptive statistics (mean and ±SD) were used for continuous variables like cross-clamp time, bypass time, and ejection fraction. Chi- square test assessed relationships of gender with demographic variables, systolic function distribution and types of valvular surgery with statistical significance considered at $p < 0.05$. Additionally, a student t-test was applied to compare postoperative complications between males and females, with significance set at $p < 0.05$. The study further ensured the accuracy of the data through validation procedures, including cross-checking of medical records and verification of surgical outcomes. Ethical considerations were prioritized throughout the study to maintain patient confidentiality and data integrity.

To minimize bias, a detailed review process was implemented to ensure that all variables were accurately recorded and that all exclusions were appropriately made according to the predefined criteria. Furthermore, inter-rater reliability for data entry was confirmed by double-checking patient records, ensuring consistency in the interpretation of data.

RESULTS:

This study included a total of 165 patients who underwent valvular and combined surgical procedures. The demographic analysis revealed a nearly equal distribution of gender, with 50.9% males and 49% females (*p = 0.03*). Age distribution showed significant differences between genders, with males predominantly represented in the 45-65 age group and females in the 25-45 age group (*p = 0.02*). The 65-75 age group did not show any significant gender differences (*p = 0.98*).

In terms of systolic function, normal function was more common among males (89.3%) compared to females (81.5%). However, females had a higher percentage of moderate (12.34%) and severe (1.23%) systolic dysfunction compared to males (*p = 0.03* for moderate, *p = 0.00* for severe). Regarding valvular surgeries, males were more likely to undergo procedures like Aortic Valve Replacement (AVR) (*p = 0.04*). In contrast, females had a higher proportion of Mitral Valve Replacement (MVR), and there was a significant gender difference in the distribution of surgeries such as MVR and AVR combined (*p = 0.04*).

Post-operative complications were notably more common in males, with a higher incidence of arrhythmias (*p = 0.00*) and wound infections (*p = 0.01*). Males also had a slightly higher mortality rate (4.8%) compared to females (3.7%) (*p = 0.04*). Intra-operative data revealed a mean bypass time of 157.45 minutes and cross-clamp time of 119.73 minutes. Post-operatively, patients had a mean hospital stay of 6.61 days and an ICU stay of 34.11 hours. These findings emphasize the significant role of gender in shaping both clinical outcomes and post-operative recovery, highlighting the need for gender-specific considerations in surgical planning and care.

DISCUSSION:

The prevalence of heart valve disease is 0.7% in people aged 18 to 44 and 11.7% in people aged 75 and above. Heart valve disease (VHD) continues to present significant challenges in clinical practice, particularly as the

Table 1 presents the distribution of gender among the study participants at *p-value <0.05*

Characteristics	Total, n (%)	Male, n (%)	Female, n (%)	*P* value
Gender	165 (100%)	84 (50.9%)	81 (49%)	**0.03**

Table 2 illustrates age distribution of the patients included in the study at *p-value <0.05.*

Age (years)	Total, n (%)	Male, n (%)	Female, n (%)	*P* value
18-25	19 (11.51%)	11 (13%)	8 (9.9%)	0.00
25-45	81 (49%)	32 (38.09)	49 (60.4%)	0.05
45-65	56 (33.9%)	36 (42.9%)	20 (24.7%)	0.02
65-75	9 (5.4%)	5 (5.9%)	4 (4.9%)	0.98

Table 3 summarizes the systolic function distribution of the patients included in the study at *p-value <0.05*

Systolic Function	Male, n (%)	Female, n (%)	Total, n (%)	*P* value
Normal	75(89.3%)	66(81.5%)	141(85.5%)	0.089
Mild	4(4.76%)	4(4.9%)	8(4.8%)	0.459
Moderate	3(3.6%)	10(12.34%)	13(7.9%)	0.03
Severe	2(2.4%)	1(1.23%)	3(1.8%)	0.00

Table 4 illustrates the comparison of valvular surgeries by gender, showing significant differences in the distribution of surgeries for certain procedures at *p-value <0.05.*

Valve surgeries	Male, n (%)	Female, n (%)	Total, n (%)	*P* value
AVR	30(35.7%)	10(12.34%)	40(24.24%)	0.03
AVR+ Root Enlargement	2(2.38%)	2(2.47%)	4(92.4%)	0.987
MVR	23(27.4%)	45(55.5%)	68(41.2%)	0.00
AVR+CABG	2(2.4%)	2(2.5%)	4(24.24%)	0.84
MVR+CABG	6(7.14%)	1(1.23)	7(4.2%)	0.785
CABG+AVR+MVR	2(2.4%)	---	2(1.2%)	---
MVR+AVR	8(9.3%)	20(20.47%)	28(16.9%)	0.04
MVR+ TV repair	3(3.6%)	---	3(1.8%)	---
MVR+ASD	1(1.2%)	---	1(0.6%)	---
AVR+VSA	1(1.2%)	1(1.23%)	2(1.2%)	---
AVR+MVR+TV repair	3(3.6%)	---	3(1.8%)	---

Table 5 Illustrates the comparison of post-operative complications with respect to gender shows a significant result at *p-value <0.05*

Complications	Male, n (%)	Female, n (%)	Total, n (%)	*P* value
Arrhythmias	16 (19%)	14 (17%)	30 (18.1%)	0.00
Wound Infection	2 (2.3%)	1 (1.2%)	3 (1.8%)	0.01
Exploration for Bleeding	4(4.8%)	2 (2.5%)	6 (3.6%)	0.62
Acute renal failure	3 (3.6%)	1 (1.23%)	4 (2.4%)	0.56
Pericardial effusion	2 (2.3%)	1 (1.23%)	3 (1.8%)	0.95
Stroke	2 (2.3%)	2 (2.4%)	4 (2.4%)	0.48
No Complications	38 (45.2%)	70 (86.4%)	108 (65.5%)	0.67
Mortality	4 (4.8%)	3 (3.7%)	7 (4.2%)	0.04

Table 3.6 illustrates the Intra-Operative data mean By-pass time (157.45±53.713), and mean Cross-clamp time (119.73±43.911). Similarly post-operative outcomes show mean Hospital stay 6.61±1.079 and mean ICU-stay (34.11±11.84) respectively.

Intra-operative data		
Variables	**Mean**	**±SD**
By-pass time (mins)	157.45	±53.713
Cross clamp time (mins)	119.73	±43.911
post-operative outcomes		
Hospital-stay (Days)	6.61	±1.079
ICU-stay (Hrs.)	34.11	±11.84

epidemiology of this condition evolves with shifts in underlying causes, patient demographics, and surgical approaches.[11] Over recent decades, there has been a marked transformation in the prevalence and etiology of VHD. In industrialized nations, the predominant causes of valvular heart diseases have transitioned from rheumatic fever to degenerative conditions, such as aortic stenosis and mitral regurgitation. This shift has been accompanied by an increase in the overall burden of VHD, particularly among the aging population.[12] Understanding these changes is crucial for informing clinical management strategies and improving patient outcomes.

The present study provides valuable insights into the evolving landscape of VHD, especially with regard to gender-specific differences in disease prevalence, treatment patterns, and surgical outcomes. In the current study, a similar trend was observed, with a predominance of rheumatic valve disease in patients, especially in men. This finding aligns with previous research that identifies rheumatic conditions as the primary cause of VHD in both men and women in developing countries.[2]

In terms of age distribution, our study revealed that females in the 25-45 age group were more affected by VHD (60.4%) compared to males (38.09%), while males had a higher prevalence in the 45-65 age range. These findings are in contrast to some previous studies that suggested a relatively equal chance of developing VHD for both genders, but the type of valve lesion does show variations. A study by R Ocher et al. (2023) noted that while both men and women are equally susceptible to VHD, women tend to develop mitral valve disorders at an earlier age, which may explain the higher percentage of younger women in our cohort.[13] This could be attributed to factors such as hormonal changes and genetic predispositions, which may influence the age of onset of valvular diseases in women.

An interesting finding from our study was the significant difference in systolic function between male and female patients. A higher proportion of males had normal systolic function, while females exhibited a greater prevalence of moderate and severe systolic dysfunction. This gender difference in systolic function outcomes is consistent with previous studies, which have suggested that gender-specific physiological factors, such as hormonal influences and vascular resistance, play a role in cardiac function. Moreover, moderate systolic dysfunction was notably more prevalent in females, which aligns with research indicating that women tend to present with more advanced cardiac dysfunction in the context of valvular disease. Severe systolic dysfunction, although less common, was more frequently observed in males in our cohort, highlighting a potential gender-based variation in the severity of cardiac conditions post-surgery.[14] These findings underscore the need for gender-specific management strategies in the treatment of valvular diseases.

The relationship between obesity and surgical outcomes remains a critical area of research. In particular, the impact of obesity on recovery time and post-operative complications continues to garner attention. A study by AR Vest et al. (2013) highlighted the importance of weight management pre-operatively, indicating that even modest weight loss before surgery could reduce complications such as wound infections and improve overall recovery. [15] This suggests that early intervention for obese patients, especially in cardiac surgery settings, could lead to better clinical outcomes.

Regarding the types of valve surgery, our study revealed that more males underwent aortic valve replacement (AVR), whereas more females underwent mitral valve replacement (MVR). This finding is consistent with existing literature, where it has been shown that men are more likely to suffer

from aortic valve disorders, such as aortic stenosis and regurgitation, while women predominantly suffer from mitral valve diseases, such as mitral valve prolapse or rheumatic mitral valve disease.[6] This gender-based difference may be influenced by anatomical, physiological, and hormonal factors that predispose each gender to different types of valvular conditions.

We also observed that the majority of patients who underwent combined procedures, such as AVR with coronary artery bypass grafting (CABG), were male. This finding is in line with previous studies indicating that men tend to undergo more complex surgeries, particularly those involving both valve replacement and coronary artery bypass. Concomitant CABG surgeries are associated with more complications, higher hospital costs, and longer recovery times, as noted in a study by Wong et al. (2021), which highlights the challenges of managing patients who require both valve replacement and coronary artery bypass surgery.[16]

Another notable finding from our study was the higher incidence of double-valve replacement (DVR) surgeries among females. Double-valve procedures, such as AVR and MVR combined, were more commonly performed in women, reflecting a tendency for women to seek medical intervention at later stages when multiple valves are affected. Previous research has shown that DVR procedures are associated with higher operative mortality compared to single-valve replacements, though advancements in surgical techniques and postoperative care have led to a significant reduction in mortality rates for these complex surgeries.[17] This is further supported by the study of A lio et al. (2019), which emphasized the role of modern myocardial preservation techniques and post-operative care in reducing the mortality risk associated with double-valve procedures.[18]

In terms of post-operative complications, our study observed a higher rate of arrhythmias among both male and female patients, which is consistent with the literature. Arrhythmias, particularly atrial fibrillation, are common following heart valve surgery, occurring in up to 65% of cases, and are associated with prolonged hospital stays, higher mortality, and long-term morbidity.[19] However, the underlying causes of post-operative arrhythmias remain poorly understood, and further research is needed to elucidate the mechanisms and risk factors associated with this complication in valvular heart surgery patients.

Wound infections were more common in male patients, a finding that aligns with the literature, which suggests that male patients are at a higher risk for surgical site infections. Wound infections in cardiac surgery patients can lead to serious complications, including prolonged hospital stays, the need for additional surgeries, and in some cases, sepsis or organ failure. The association between gender and wound infection rates may be related to differences in immune function, post-operative care, or even patient behavior regarding wound care. As noted by Y Song et al. (2023), surgical site infections remain a significant concern, and efforts to reduce infection rates are ongoing through better infection control practices and more stringent post-operative care protocols.[20]

Similarly, bleeding is also a major concern and complication after cardiac surgery. In the study male patients suffered more from this complication as compared to females. According to previous literature, bleeding increases hospital length of stay and critical care utilization, with affected patients requiring prolonged recovery, transfusions, and sometimes reoperations. This not only delays recovery but also puts additional strain on critical care resources, leading to higher healthcare costs.[21]

Another complication documented was the acute renal injury and male patients suffered more from the injury than females. Numerous studies indicate that between 1 and 10% of patients need RRT, while the prevalence of postoperative AKI varies between 28 and 94%. Acute kidney damage (AKI) following surgery is a recognized issue following heart surgery with cardiopulmonary bypass (CPB). Its appearance is caused by a number of reasons, including inflammatory response activation, hemolysis, embolic events, vascular redistribution, kidney damage from ischemia and loss of pulsatile flow. The likelihood of developing AKI is increased by patient risk factors, such as age and preexisting renal impairment.[22]

In the study, the stroke was found to be equal in both men and females. However, stroke is a rare but still a potentially crippling complication of heart valve replacement surgery with risk dependent on patient characteristics and concomitant procedures. Stroke rates after surgical valve replacement (SVR) have ranged widely from 1 to 10%. Several studies have evaluated risk factors and postoperative neurologic complications after heart valve surgery, though the results are conflicting or incomplete mainly due to a low number of interventions or a low number of variables.[23]

Regarding mortality, our study found a higher mortality rate in male patients, which contrasts with some studies that report higher mortality in females following cardiac surgery. However, our results support the notion that the complexity of the surgical procedure influences mortality, with more complex surgeries, such as those involving multiple valves, associated with higher risks of death. This is consistent with the findings of M Gupta et al. (2017), who found that combined surgeries, such as AVR and MVR, carry a higher risk of mortality, particularly when performed in older patients with multiple comorbidities.[24]

While this study provides valuable insights into gender differences in valvular heart surgery, several limitations should be considered. First, the study design was retrospective, and data were extracted from electronic medical records (EMRs), which may be prone to inaccuracies, missing

data, or inconsistencies. Such limitations in the quality of data can affect the robustness and reliability of the findings. Additionally, the sample size, although sufficient for preliminary analysis, may not fully represent the broader population of patients undergoing valvular heart surgery, limiting the generalizability of the results to other regions or healthcare settings. Furthermore, this study did not account for several confounding variables, such as socioeconomic status, lifestyle factors (e.g., smoking, alcohol use), and the presence of other comorbidities (e.g., diabetes, hypertension), all of which could potentially influence surgical outcomes. Finally, the study did not include long-term follow-up data, which would have provided a clearer understanding of the sustained impact of gender differences on patient recovery and quality of life post-surgery.

CONCLUSION:

In conclusion, this study highlights significant gender-based differences in the clinical presentation, treatment, and outcomes of valvular heart disease (VHD) patients undergoing surgical interventions. Key findings include gender disparities in the prevalence of specific valve disorders, surgical procedures, and post-operative complications, with males experiencing more complex surgeries and a higher incidence of complications such as arrhythmias, wound infections, and acute renal injury. Additionally, the study underscores the role of demographic factors like age and BMI in influencing patient outcomes. Although our findings contribute valuable insights into the evolving landscape of VHD and its surgical management, limitations such as the retrospective design, sample size, and lack of long-term follow-up must be considered. Further research, incorporating a broader cohort and exploring additional confounding variables, is necessary to enhance the understanding of gender-related differences in valvular heart surgery outcomes.

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Muhammad Waleed: Conception and Design
Waqar Masud Malik: Drafting
Kiran Jamal: Data Analysis
Attiya Hameed Khan: Data Analysis
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Original Article **Open Access**

Comparative Analysis of Intravenous Paracetamol and Tramadol for Labor Analgesia: Efficacy and Safety

Naila Mushtaq, Ayesha Arif, Shazia Iffet, Sadaf Moin, Tahira Parveen, Qosain Suriya

ABSTRACT

Objective: This study aims to compare the efficacy and safety of intravenous paracetamol and intramuscular tramadol for labor analgesia.

Study Design and Setting: This study was conducted for 1 year at PNS Shifa Hospital, Karachi (Sept 01, 2023 – Aug 31, 2024). Convenient sampling into two groups was done (Group A: IV Paracetamol n=50; and Group B: IM Tramadol n=50) of 100 laboring women. Visual Analogue Scale was used to assess pain intensity at baseline, 1 and 3 hours post administration.

Methodology: During the active phase of labor, participants were given either 1,000 mg IV paracetamol or 100 mg IM tramadol. Labor progression was monitored and the levels of pain were recorded on the VAS. Statistical tests were used to analyze maternal side effects and neonatal outcomes such as NICU admissions with a significance threshold of $p<0.05$.

Results: Superior pain relief was given by paracetamol with significantly lower VAS scores at 1 hour (4.44 vs. 5.55, p=0.0) and 3 hours (6.51 vs. 6.96, p= 0.0). In the paracetamol group, labor duration of paracetamol group was shorter in the first stage (10.16 vs. 11.44 hours, p=0). The number of frequent maternal side effects was higher in the tramadol group (24 vs 12%, p=0.118). Furthermore, there was no difference in NICU admissions or emergency cesarean rates (p=0.315).

Conclusion: Intravenous paracetamol is a safer and better alternative for labor analgesia as compared to intramuscular tramadol, having better pain control, shorter duration of labor and less maternal side effects and similar neonatal outcomes.

Keywords: Labor analgesia, maternal outcomes, Pain management, Paracetamol, Tramadol.

How to cite this Article:
Mushtaq N, Arif A, Iffet S, Moin S, Parveen T, Suriya Q. Comparative Analysis of Intravenous Paracetamol and Tramadol for Labor Analgesia: Efficacy and Safety. J Bahria Uni Med Dental Coll. 2025;15(2):134-139 DOI: https://doi.org/10.51985/JBUMDC2025535

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Received: 12-01-25
1st Revision: 12-02-25
Accepted: 07-04-25
2nd Revision: 27-03-25

INTRODUCTION:

Labor pain is considered one of the most intense forms of pain that women experience,[1] often compared to other severe physiologic causes of pain, such as complex regional pain syndromes (CRPS) or finger amputation.[2-5] For many women, labor pain is the most extreme discomfort they will face during their reproductive years, frequently accompanied by intense emotional responses such as anxiety, fear, and feelings of insecurity. These negative emotions can sometimes drive women to opt for a caesarean section in order to avoid the pain associated with labor.[5]

Labor pain, primarily due to uterine contractions,[6] is a natural part of childbirth. However, both anticipation and experience of this pain can cause concern, especially in first-time mothers (primiparous), who often feel heightened anxiety and fear. The pain's intensity is subjective, influenced by factors like contraction strength and frequency, cervical dilation rate, and parity, or number of prior births.[1] A woman's reaction to childbirth pain is shaped by her individual circumstances, including pain threshold, past delivery experiences, coping mechanisms, and pain intensity. Cultural factors also play a significant role, with some cultures favoring medical pain relief, like epidurals, while others view enduring

labor pain as a symbol of courage or a rite of passage. These personal, cultural, and medical influences significantly affect women's choices regarding pain management.[7]

As a result of the fact that the management of labor pain is dependent on the preferences of the individual, their prior experiences, and the cultural milieu in which they practice, medical professionals are required to take into consideration the aforementioned factors while providing opportunities for pain treatment and assistance during the delivery process.[7]

Labor analgesia can be broadly classified into non pharmacological and pharmacological methods. Non pharmacological approaches include transcutaneous electrical nerve stimulation (TENS), continuous labor support, touch and massage, water baths, intradermal sterile water injections, acupuncture, and hypnosis. These methods provide alternative pain relief without medication but may not always be sufficient for severe labor pain. On the other hand, pharmacological techniques include the use of parenteral opioids, opioid antagonists, inhalational agents, and regional analgesia.[8] Among these, regional analgesia is considered the gold standard for labor pain relief. However, it requires specialized equipment, continuous monitoring, and a 24-hour anesthetic service, which may not be feasible in resource-limited settings, especially in developing countries like Pakistan.

For labor analgesia, intramuscular (IM) tramadol and intravenous (IV) paracetamol are both viable options that may be used in situations when sophisticated aesthetic treatments might not be easily accessible. The fact that these drugs are widely available, require just a small amount of technical competence, and are reasonably affordable makes them ideal alternatives for controlling labor pain in circumstances like these.[8]

Tramadol is a synthetic opioid that functions similarly to pethidine, with a moderate affinity for mu-opioid receptors.[9] The analgesic action begins within 10 minutes after intramuscular injection and lasts for 2 to 3 hours. Prior evidence indicated that tramadol serves as an effective analgesic during labor, devoid of the maternal or newborn respiratory depression risks often linked to other opioids. Moreover, tramadol does not hinder stomach emptying, a common issue associated with opioid administration during childbirth.[10]

In contrast, paracetamol is a famous antipyretic and non-narcotic analgesic that has fewer adverse effects.[1] Its peripheral activities that prevent the production of pain impulses and its central nervous system inhibition of prostaglandin synthesis are what make it effective in relieving pain. Some researchers think that cannabinoid receptor agonism and serotonergic pathways contribute to its analgesic effects. Because of these effects, intravenous paracetamol is a promising substitute for opioids as a labor analgesic.[1]

In light of these considerations, we decided to carry out this research in order to evaluate the effectiveness and safety of intramuscular tramadol and intravenous paracetamol as they pertain to labor analgesics. In environments where there is a restricted availability of sophisticated anesthetic resources, our objective was to locate the most effective method for the treatment of labor pain.

METHODOLOGY:

The study was conducted over a period of one year from Sept 01, 2023 - Aug 31, 2024, at Gynae/Obs deptt of PNS Shifa hospital Karachi being a Quasi experimental study. The research stands under ERC # 132 and was approved by ethical review committee of the hospital. The objective of the study was to evaluate the analgesic efficacy and safety of intravenous (IV) paracetamol compared with intramuscular (IM) tramadol in the management of labor pain.

One hundred parturients meeting the inclusion criteria were enrolled and divided in two groups by convenient sampling technique. Group A (n = 50): Received 1,000 mg of IV paracetamol over a 15-minute infusion during the active phase of labor. Group B consisted of 50 women and received 0.1 g IM tramadol in a single dose at the same stage of labor.

Inclusion Criteria: Singleton pregnancy. The demo population was primigravida or multigravida women aged 18–40 years. Full-term pregnancy (37–42 weeks gestation). In active labor with cervical dilation =4 cm and regular contractions. No contraindications to vaginal delivery or analgesia.

Exclusion Criteria: History of hypersensitivity to paracetamol or tramadol. Ilnesses to the mother, such as preeclampsia, eclampsia, cardiovascular conditions. Multiple gestations or known fetal anomalies.

Other analgesics used within 24 hours before the study. Contradications on the labor analgesia (such as clotting disease, injection site infection). Outcome Measures: Primary Outcome: The pain severity was assessed by Visual Analogue Scale (VAS); (0 = no pain, 10 = worst pain).

Baseline (before drug administration). 1 hour after administration. 3 hours after administration Secondary Outcomes: Cervical dilation progression. Time duration of first and second stages of labor. Nauses, vomitus, drowsyess, allergic reactions. Apgar scores at 1 and 5 minutes and NICU admissions are neonatal outcomes.

Data Collection and Analysis: Labor and delivery doctors and nurses used standardized forms using convenient sampling to collect data. IBM SPSS (version 22.0) was used for statistical analysis.

VAS scores, duration of labour and cervical dilation were compared by use of independent t tests.

Categorical variables (maternal side effects, neonatal outcomes) were analyzed by means of Chi-square tests.

Statistical significance was defined as a p less than 0.05.

Institutional review board ethical approval and informed

written consent before enrollment was obtained for all participants.

Outcome Measures

Primary Outcome: Pain Severity was the primary outcome of this study, measured using the Visual Analogue Scale (VAS). The VAS is a 10-point scale, where 0 represents "no pain" and 10 represents the "worst possible pain." This scale was selected due to its widespread use in clinical pain assessments and its ability to quantify subjective pain intensity.

Pain intensity was measured at three key time points:

- Baseline (before drug administration): Pain levels were assessed to ensure that both groups had comparable pain intensity at the start of the intervention.
- 1 hour post-drug administration: This time point was selected to assess the short-term analgesic effect of both drugs.
- 3 hours post-drug administration: This time point was chosen to evaluate the sustained efficacy of each analgesic over time.
- All pain assessments were conducted by a designated doctor who was blinded to the treatment groups. The doctor/nurse recorded VAS scores for each participant, ensuring consistency in data collection.
- Secondary Outcomes In addition to pain relief, secondary outcomes included:
- Cervical Dilatation: The progression of labor was monitored by measuring cervical dilatation at baseline and every hour thereafter. Cervical dilatation was recorded in centimeters to assess whether analgesia had any impact on labor progression. It was hypothesized that effective pain relief could potentially shorten labor by reducing maternal stress and allowing for better cooperation during the labor process.
- Duration of Labor: The total duration of labor was recorded for each participant, from the active phase until delivery. Labor duration was divided into two stages:
- First stage of labor: Defined as the time from the onset of regular contractions with cervical dilatation of 4 cm to full dilatation (10 cm).
- Second stage of labor: Defined as the time from full cervical dilatation to the delivery of the neonate.
- Maternal Side Effects: Maternal safety was closely monitored, with adverse effects such as nausea, vomiting, disorientation, and allergic reactions recorded immediately after medication administration and during later labor stages. Side effects were categorized as mild, moderate, or severe, with prompt treatment provided as needed.
- Neonatal Outcomes: Neonatal well-being was assessed through 1- and 5-minute Apgar scores, evaluating heart rate, breathing, muscle tone, reflexes, and skin color. NICU admissions were documented to gauge the analgesics' safety for newborns, with any adverse neonatal outcomes carefully observed.

Data Collection and Management: Data was collected by qualified labor and delivery doctor and nurses who were unaware of the treatment groups to reduce bias. The drugs used were chosen because of their easy availability in abundance in the hospital. Pain ratings, cervical dilation, and maternal side effects were documented using standardized data collecting forms. Neonatal outcomes, like Apgar scores and NICU hospitalizations, were recorded immediately post-delivery. All gathered data were inputted into a secure, password-protected database to maintain confidentiality. Access to the data was restricted to authorized people, and each participant was granted a unique identity number to ensure anonymity. Data verification and cleansing were conducted before analysis to guarantee precision. Verification and cleansing were conducted prior to analysis to guarantee precision.

Data analysis was conducted using IBM SPSS version 22.0. Descriptive statistics, including means, standard deviations, and frequencies, summarized the demographic and clinical characteristics of the participants. For comparing continuous variables like VAS ratings, cervical dilation, and labor duration between the groups at specific time points, independent t-tests were used. Categorical variables such as maternal side effects, Apgar scores, and NICU admissions were analyzed with chi-square tests. A p-value of less than 0.05 was considered statistically significant in all analyses.

RESULTS:

The table 1 compares the effects of paracetamol and tramadol for labor analgesia. Both groups had similar baseline characteristics in age, gestational age, BMI, cervical dilation, and initial pain scores, with no significant differences observed. However, at 1 and 3 hours post-treatment, paracetamol provided significantly better pain relief (VAS scores of 4.44 and 6.51) compared to tramadol (VAS scores of 5.55 and 6.96). Paracetamol was also associated with shorter labor durations, including the first stage (10.16 vs. 11.44 hours), active phase of the first stage (4.18 vs. 5.06 hours), and second stage (34.04 vs. 37.66 minutes), all with significant p-values ($p = 0.0$), indicating its superior efficacy in both pain management and labor progression.

In Table 2, outcomes such as NICU admissions, maternal side effects, and emergency cesarean sections were also compared between the groups. NICU admissions were minimal, with only 1 admission from the Paracetamol group (2.0%) and none from the Tramadol group, resulting in a 1.0% NICU admission rate overall. The p-value of 0.315

indicates no statistically significant difference between the groups regarding NICU admissions. Maternal side effects were reported more frequently in the Tramadol group (24%) than in the Paracetamol group (12%), but this difference was not statistically significant (p = 0.118). Emergency cesarean sections were rare, with only 1 case in the Paracetamol group (2.0%) and none in the Tramadol group, with a p-value of 0.315 indicating no significant difference.

Table 1: Continuous variables of the study

Variable	Group	Mean	Standard Deviation	p-value
Age(years)	Paracetamol	25.82	2.24	0.907
	Tramadol	25.22	2.25	
Gestational Age(weeks)	Paracetamol	39.07	0.26	0.342
	Tramadol	38.96	0.28	
Pre-pregnancy BMI	Paracetamol	23.28	0.44	0.191
	Tramadol	23.20	0.39	
Cervical Dilatation	Paracetamol	4.74	0.38	0.112
	Tramadol	4.87	0.42	
VAS Before Treatment	Paracetamol	8.54	0.54	0.708
	Tramadol	8.59	0.62	
VAS 1 hr After Treatment	Paracetamol	4.44	0.27	0.0
	Tramadol	5.55	0.30	
VAS 3 hr After Treatment	Paracetamol	6.51	0.33	0.0
	Tramadol	6.96	0.30	
Duration 1st stage (hours)	Paracetamol	10.16	0.95	0.0
	Tramadol	11.44	1.25	
Duration of active phase of first stage of labour(hours)	Paracetamol	4.18	0.85	0.0
	Tramadol	5.06	0.74	
Duration of 2nd stage (minutes)	Paracetamol	34.04	1.47	0.0
	Tramadol	37.66	1.73	

Table 2: Comparison of side effects of the drugs

Variables		Group			P value
		Paracetamol	Tramadol	Total	
NICU admission	Yes	1	0	1	0.315
		2.0%	0.0%	1.0%	
	No	49	50	99	
		98.0%	100.0%	99.0%	
Maternal side effects	Yes	6	12	18	0.118
		12%	24%	18%	
	No	44	38	82	
		88%	76%	82%	
Emergency cesarean section	Yes	1	0	1	0.315
		2.0%	0	2.0%	
	No	49	50	99	
		98.0%	1000%	99.0%	

DISCUSSION:

Pain management during labor remains a critical aspect of obstetric care, aiming to enhance maternal comfort while minimizing adverse effects on both the mother and neonate. As labor pain is often described as one of the most severe forms of pain, adequate analgesia can significantly improve the childbirth experience. Our study aimed to compare the analgesic efficacy and safety profiles of intravenous (IV) paracetamol and intramuscular (IM) tramadol during labor. These findings are supported by studies conducted by N Monisha et al,[11] Meenakshi Lallar,[12] and a comparative study involving primigravidae labor patients. Together, the evidence

strongly suggests that IV paracetamol is superior to IM tramadol in labor analgesia, offering prolonged pain relief, fewer maternal side effects, and improved labor progression.

In our study, the use of IV paracetamol demonstrated significantly better pain control compared to IM tramadol, as measured by the Visual Analog Scale (VAS) scores at 1 hour and 3 hours post-administration. The paracetamol group had a VAS score of 4.44 at 1 hour and 6.51 at 3 hours, compared to 5.55 and 6.96 for the tramadol group, with both differences being highly significant (p = 0.0). These findings align with the results of N Monisha et al.[11]

At 3 hours post-administration, Lallar[12] found that while 26% of women in the paracetamol group continued to experience "distressing" pain, 51% of women in the tramadol group still reported "horrible" pain. This marked difference emphasizes the longer duration of action and superior pain control offered by IV paracetamol compared to IM tramadol. Both our study and the referenced studies corroborate that IV paracetamol has a more sustained analgesic effect, significantly reducing the intensity of labor pain for a longer period compared to tramadol.

The ability of paracetamol to shorten labor duration can be particularly beneficial in reducing maternal exhaustion and improving overall labor outcomes. Tramadol, while effective to some extent, does not seem to offer the same advantages in labor progression. The longer duration of labor observed in the tramadol group across studies could be attributed to less effective pain relief, leading to heightened maternal discomfort and slower cervical dilation, which may contribute to prolonged labor stages.

Our results, together with those of N Monisha et a,l[11] Meenakshi Lallar[12] and the comparison analysis[5,7] all point to important directions for future research and patient care. It seems that intravenous paracetamol is a very efficient analgesic for labor, with advantages over intramuscular tramadol such as shorter labor length, less maternal adverse effects, and better pain alleviation.[15] The benefits listed above make intravenous paracetamol the drug of choice for labor analgesia, particularly when the mother's comfort and safety are paramount and long-term analgesia is necessary.

Further, our findings align with those of Sania Jindal[16] who compared intravenous paracetamol (1000 mg) and tramadol (1 mg/kg) for labor analgesia in parturients at 4-6cm cervical dilation. In her study, baseline pain scores were similar between groups, but at 1 hour, the Visual Analog Scale (VAS) score was significantly lower in the paracetamol group (4.60) than in the tramadol group (5.82), mirroring our results. By 3 hours, VAS scores were slightly lower for paracetamol (6.35) compared to tramadol (6.65), though the difference was not statistically significant. The incidence of side effects such as nausea, vomiting, and sedation was notably higher in the tramadol group (n=13) than in the paracetamol group (n=3), consistent with findings by Makkar et al[17] who observed more frequent sedation in tramadol-treated patients. Additionally, neonatal outcomes, assessed by 1- and 5-minute Apgar scores, were comparable between groups, suggesting both drugs are safe for neonatal health.

Similarly, Elbohoty et al[18] found paracetamol to be as effective as pethidine for labor analgesia, with only a brief period at 15 minutes where pethidine offered superior pain relief (p = 0.004). Beyond this time, there was no notable difference in analgesic effect. Regarding labor duration, Jindal observed no significant difference between paracetamol and tramadol, aligning with Aimakhu et al's[19] results comparing intramuscular paracetamol (600 mg) and tramadol (100 mg). Together, these studies indicate that intravenous paracetamol not only offers effective and prolonged pain relief but also maintains a favorable side effect profile, reinforcing its potential as a preferred labor analgesic.

Paracetamol administered intravenously has a positive safety profile and may be used during pregnancy to reduce the need for intense monitoring of both the mother and the fetus.[20] Its low effect on neonatal outcomes further supports this recommendation. Overall labor outcomes and the need for interventions like emergency cesarean sections may be improved if intravenous paracetamol were to be used more often, according to the data.[21]

In conclusion, our research, in conjunction with other studies indicates that intravenous paracetamol provides enhanced analgesia, a more advantageous safety profile, and reduced labor length relative to intramuscular tramadol. The uniform results from these trials underscore the efficacy and safety of IV paracetamol as an analgesic during labor. Additional extensive studies are necessary to further validate these findings and investigate further advantages of IV paracetamol in labor analgesia; nonetheless, the existing data robustly supports its use as a primary analgesic in obstetric care.

CONCLUSION

The results of this study indicate that intravenous (IV) paracetamol is more effective and less harmful as a labor analgesia than intramuscular (IM) tramadol. There was superior pain relief following IV paracetamol based on significantly lower Visual Analogue Scale (VAS) scores at one hour and three hours after administration. Also, labor duration was significantly shorter in newborns of the paracetamol group, indicating that efficient pain control could lead to faster labor progression.

Future research should consist of larger multi-center trials and comparisons with other analgesic options as well as long term maternal and neonatal outcomes. IV paracetamol is an attractive, non-opioid option to manage pain as it provides safe, effective, pain relief for labour without endangering neonatal safety.

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Original Article **Open Access**

Impact of Unilateral Amblyopia on Macular and Retinal Nerve Fiber Layer Thickness

Syed Amir Hamza, Maria Sultan, Maleeha Safdar Ali, Muhammad Tariq

ABSTRACT

Objective: To compare “retinal nerve fiber layer” (RNFL) and “macular thickness” in unilateral anisometropic and strabismic amblyopia using “optical coherence tomography” (OCT).

Study Design & Setting: Descriptive cross sectional study with purposive sampling technique. Department of Ophthalmology, Mardan Medical Complex, Mardan, July–December 2023.

Methodology: A total of 54 patients with anisometropic (n=27) or monocular strabismic (n=27) amblyopia with best-corrected visual acuity of 20/40 to 20/400 were included. Patients with refractive errors =5 diopters or axial length differences =1 mm were excluded. OCT was used to measure peripapillary RNFL and macular thickness in amblyopic and fellow eyes.

Results: The mean age of the patients was 10 ± 3.1 years 8.9 ± 3.7 years in the anisometropic group and in the strabismic group respevtively. Anisometropic amblyopic eyes had significantly increased macular thickness (224.5 ± 48.7ìm) compared to fellow eyes (207.5 ± 34.2ìm) (P=.002), with no significant RNFL difference (P=.55). Macular and RNFL thickness differences between amblyopic and the other eyes in the strabismic group were not statistically significant (P=.07 and .52). No significant differences were observed between anisometropic and strabismic amblyopic eyes.

Conclusion: Anisometropic amblyopia is associated with increased macular thickness, whereas strabismic amblyopia shows no significant change. Amblyopia does not appear to affect peripapillary RNFL thickness in either group.

Keywords: Amblyopia, anisometropia, strabismus, macular thickness, RNFL, optical coherence tomography.

How to cite this Article:
Hamza SA, Sultan M, Ali MS, Tariq M. Impact of Unilateral Amblyopia on Macular and Retinal Nerve Fiber Layer Thickness. J Bahria Uni Med Dental Coll. 2025;15(2):140-145 DOI: https://doi.org/10.51985/JBUMDC2025539

INTRODUCTION

“Reduced visual acuity” (VA) and contrast sensitivity in either one or both eyes are the hallmarks of amblyopia. It is a visual disorder brought on by either deprivation of vision or binocular interactions abnormally.

According to Malcol et al, reduced vision in one eye as a result of aberrant visual development during childhood is known colloquially as "lazy eye," or amblyopia.[1]

Amblyopia affects two or three out of every hundred children, making it the most prevalent cause of monocular visual acuity impairment in children. Normal visual development requires appropriate visual stimulation, such as clear retinal pictures in each eye and appropriate ocular alignment. Children under the age of seven are at risk for amblyopia due to frequent childhood eye problems such strabismus and anisometropia, which can disrupt visual stimulation throughout development. It is well known that the effectiveness of treating amblyopia decreases with age, and that if the condition is not identified and treated early, one eye's visual acuity may be permanently reduced.[2]

Many studies looking into the pathophysiology of amblyopia, like Hubel and Wiesel's animal experiments in the 1960s, have found anatomical and functional abnormalities in the lateral geniculate nucleus and visual cortex. Latest studies have identified abnormalities in the “visual cortex” (VC) and “lateral geniculate nucleus” (LGN) in human amblyopes[3,4,5]

According to Malcol et al, a disorder known as amblyopia occurs when an eye's visual pathways develop abnormally during childhood, resulting in impaired vision. The brain stops communicating with one eye when it receives inadequate information from that eye. This indicates that the brain depends on data from the "stronger" eye. A person

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Received: 14-01-25
Accepted: 28-03-25
1st Revision: 12-02-25
2nd Revision: 21-02-25
3rd Revision: 20-03-25

may develop amblyopia in both eyes.[1]

Visual acuity testing is the gold standard for amblyopia screening, and visual acuity charts continue to be the main screening tool used by the majority of vision screening programs. Instead of directly identifying amblyopia, automated technologies offer a simpler and more effective screening method that looks for refractive error and strabismus risk factors. However, the prevalence of amblyopia is 2.5%, whereas the prevalence of risk factors is 21%. This means that 8 or 9 out of 10 children who fail automated screening due to a risk factor are false positives and do not actually have amblyopia. [2]

Since amblyopia is common in youngsters and can cause severe visual impairment that lasts a lifetime if left untreated, it is a significant public health issue. The quality of life can be significantly impacted by amblyopia and its treatment. Prevalence estimates vary depending on the age, race, and ethnicity of the population studied; study methodology; and the definition of amblyopia used. For children aged 30 to 71 months, prevalence estimates from population-based studies range from 0.7% to 2.6%, while school-based studies of older children usually report higher rates (range, 1.0% to 5.5%).[6]

Ikeda, on the other hand, studied the neurophysiology of cats and found that amblyopia was associated with retinal ganglion cell defects. A functional impairment of the retina in human amblyopes was discovered through an electrical experiment. However, after a second evaluation, Hess was unable to confirm these retinal abnormalities. It hasn't been established, nevertheless, that amblyopes' retinas are completely normal.[5,7].

Human retinal anatomy can now be quickly and non-invasively assessed due to to the innovative use of “Optical Coherence Tomography” (OCT). Spectral-domain OCT (SD-OCT) has greatly improved scanning speed and spatial resolution, allowing for more thorough retinal research. According to a study by Yen et al, in eyes with refractive amblyopia, the circumpapillary retinal nerve fiber layer (cpRNFL) was found to be thicker than in their normal fellow eyes using time-domain OCT. Amblyopic eyes have thicker foveas than visually normal control eyes, according to OCT results reported by Li et al. However, it is still unclear why amblyopic eyes have thicker cpRNFL or foveal tissue than healthy eyes.[4,7] Amblyopia is characterized by a decrease in best corrected visual acuity (BCVA) in one or both eyes, without any associated anatomical abnormality of the globe. This unusual visual perception takes place as the visual system develops. Despite the fact that amblyopia is thought to have a structurally normal eye, it is well known that the VC (visual cortex) and LGN (lateral geniculate nucleus) are altered by deprivation of vision. [3,4] According according to certain authors, amblyopia is caused by abnormal variations in the RNFL, cells of ganglion and the optic nerve.[5]“Optical coherence tomography” (OCT) is an imaging technique which is simultaneously a noninvasive procedure that provides cross-sectional scans of the head of the optic nerve and the retina in a highly resolution form. OCT has been utilised to assess the RNFL and the thickness of macula in anisometropic and strabismic amblyopia; however, the results of the majority of earlier studies have been inconsistent and variable. [7,8,9] Therefore, in the current investigation, we utilized OCT to evaluate the thickness of peripapillary RNFL and macula in amblyopic eyes (both anisometropic and strabismic) and their normal contralateral eyes to identify any differences. Additionally, we aimed to explore the variations in the morphology or anatomy between these two amblyopia subgroups."

Since amblyopia's visual results are best when treated as soon as possible, risk factors for the condition must be detected in the pediatric population as early in life as possible and controlled appropriately. Newer ideas for binocular vision therapy are continually developing, despite the fact that monocular therapies like occlusion or penalization have proven to be quite helpful over time.

Amblyopia can be caused by strabismus, refractive error, or stimulus deprivation, all of which can be promptly detected with early and regular visual screening of newborns and toddlers. The prognosis is known to improve with early detection and treatment of these issues.[6]

METHODOLOGY

The research project was conducted for a total span of 6 months from July 2023 to December 2023 at Ophthalmology Department, Mardan Medical Complex, Mardan. This was a descriptive cross sectional study with a purposive sampling technique. Patients with presence of amblyopia unilaterally (BCVA ranging from 20/40 to 20/400) between the ages of 6 and 16 years were included in this study. Ethical approval was obtained from MTI BKMC Mardan ethical committee bearing NO.328 BKMC dated 02/06/2023.

Sample Size Calculation

G*Power software was used to calculate the appropriate sample size, assuming an appropriate size to authenticate the results. It is also based on past researches, a power of 80% , confidence interval 95% and an alpha level of 0.05.

Two groups of patients were identified:

One for strabismic amblyopia and the other for anisometropic amblyopia. There was no deviation on cover test when performed on patients in anisometropic group. Anisotropia was measured as difference of 1, 1.5, and 3 diopters in hyperopia, astigmatism, and myopia, respectively. According to the study's criteria, none of the patients in the strabismic group exhibited anisometropia. In the cover test, the smallest deviation angle that was visible was 10 prism diopters.

A thorough ophthalmic examination including slit-lamp including and fundus examination, visual acuity

assessment and cycloplegic refraction was performed. The subjects who were unable to keep a constant fixation behind the OCT camera, or who had any kind of neurologic or ocular disorder were removed from the study. To minimize the impact of refractive error on measurements, patients were excluded from the anisometropic group if the axial length difference between their eyes exceeded 1 mm or if either eye had myopia or hyperopia greater than 5 diopters.

Following complete pupil dilation, a single technician conducted all OCT measurements. Three consecutive 360-degree circular scans with a 3.4 mm diameter around the optic disc were employed as part of a rapid RNFL scan. Three samples were used to determine the average thickness using the OCT programmed. We performed a macular scan that comprised six radial scans in order to determine the macular thickness. The measurement was then carried out using a 6-mm diameter map.

Data Analysis

By applying software (SPSS) the statistical analysis was carried out. The paired sample t-test was used to compare the macular and RNFL thicknesses, and the Kolmogorov-Smirnov test was used to assess the distribution pattern. P-values less than or equal to 0.05 were taken as statistically significant.

RESULTS

Our study included 27 individuals with monocular strabismic amblyopia and 27 individuals with monocular anisometropic amblyopia**.** The average patient age in the strabismic group was 8.9 ± 3.7 years (range: 6 to 16 years), whereas the mean age in the anisometropic group was 10 ± 3.1 years (range: 6 to 16 years). There were 24 patients with esotropia and 3 patients with exotropia (16 males and 10 females) in the strabismic group. There were five anisomyopic patients and twenty-two anisohyperopic patients (9 females and 17males)in the anisometropic group.

The thickness of the macula in amblyopic eyes in the anisometropic group was significantly greater than the other contralateral normal eyes. But in this group, there was no significant change in thickness of the RNFL between amblyopic and fellow normal eyes as shown in Table 1. On the other hand, there was no statistically significant difference in thickness of peripapillary RNFL and macula between amblyopic and opposite normal eyes in the strabismic group as shown in Table 1. Also there was no significant difference between thickness of RNFL and macula between strabismic and anisometropic eyes with amblyopia as indicated in Table 2.

The possible reason of which could be that in anisometropic amblyopia, the increased macular thickness but unaltered RNFL thickness is probably due to selective alterations in the inner retinal layer, incomplete apoptosis, and aberrant retinal development rather than direct damage to the pathways of the optic nerve pathways.

The comparison of anisometropic and strabismic amblyopia reveals no statistically significant variations in macular or thickness of RNFL. The macular thickness in anisometropic amblyopia (224.5 ± 48.7 μm) is marginally lower than in strabismic amblyopia (232 ± 30.6 μm), although the difference is not statistically significant (p = 0.51). The thickness of RNFL in anisometropic amblyopia (89 ± 30.1 μm) is somewhat greater than that in strabismic amblyopia (85.7 ± 23.3 μm), although there is no noticeable significant difference statistically (p = 0.66). The findings indicate that both forms of amblyopia display comparable anatomical traits regarding macular and RNFL thickness, suggesting that abnormalities in the retina and nerve fiber layer may not be exclusive to a certain amblyopia subtype. The data reveal that in

Table-1: Average Thickness of Macula and RNFL (μm)

Parameter	Amblyopic Eyes	Fellow Eyes	p-value
Anisometropic Amblyopia			
Macular Thickness	224.5 ± 48.7	207.5 ± 34.2	.002
RNFL Thickness	89 ± 30.1	92 ± 28.7	.55
Strabismic Amblyopia			
Macular Thickness	232 ± 30.6	219.2 ± 33.4	.07
RNFL Thickness	85.7 ± 23.3	88.2 ± 31.1	.52
RNFL = Retinal Nerve Fiber Layer			

Table-2: Average Macular and RNFL Thicknesses (μm) in Strabismic and Anisometropic and Eyes

Parameter	Strabismic Amblyopia	Anisometropic Amblyopia	p-value
Anisometric Amblyopia			
Macular Thickness	232 ± 30.6	24.5 ± 48.7	0.51
RNFL Thickness	85.7 ± 23.3	89 ± 30.1	0.66
RNFL = Retinal Nerve Fiber Layer			

anisometropic amblyopia, macular thickness is markedly higher in amblyopic eyes (224.5 ± 48.7 µm) than in companion eyes (207.5 ± 34.2 µm, p = 0.002), indicating structural alterations in the macula. Nonetheless, RNFL thickness showed no noticeable difference between eyes with amblyopia (89 ± 30.1 µm) and fellow eyes (92 ± 28.7 µm, p = 0.55). In strabismic amblyopia, macular thickness is greater in amblyopic eyes (232 ± 30.6 µm) compared to companion eyes (219.2 ± 33.4 µm), although this difference lacks statistical significance (p = 0.07). Likewise, RNFL thickness showed no noticeable difference between eyes with amblyopia (85.7 ± 23.3 µm) and fellow eyes (88.2 ± 31.1 µm, p = 0.52). The data indicate that macular thickness may be influenced in anisometropic amblyopia, but RNFL thickness remains similar across amblyopic and fellow eyes throughout both forms of amblyopia.

DISCUSSION

In our study, we found that in anisometropic amblyopia, the difference in the thickness of macula between normal healthy eyes and contralateral with amblyopia is considered statistically significant.

Our results are consistent with a research by AlHaddad et al. In their study they reported significant increase in central macular thickness in anisometropic amblyopia patients by using OCT.[10]

We measured the anisometropic amblyopia in 27 eyes (four had myopic anisometropia and 22 had hyperopic anisometropia). According to research by Pang et al., children who are unilaterally high myopic and amblyopic typically have thicker foveas in their eyes with amblyopia than in their healthy eyes.[11] According to Huynh et al., individuals with hyperopic anisometropia amblyopia had thicker foveas.[12] On the other hand, some other previous studies show variable results. There was no difference in the thickness of macula between normal healthy eyes and eyes with amblyopia when Dickmann et al. assessed 20 eyes with mixed anisometropic amblyopia (10 with myopic and 10 with hyperopic anisometropia) [13]. Yoon et al. came to the same conclusion after examining 31 patients with hyperopic anisometropic amblyopia.[14]

Although it is reported by some authors that myopia—particularly more than 5 diopters—was linked to a shift in the thickness of macula [15], we were unable to find any evidence in the literature between hyperopia and macular thickness. In order to decrease the effect of refractive errors on macular thickness in our study, Patients having myopia or hyperopia of more than 5 diopters in either eye or with a difference in the axial length between two eyes of more than 1 mm were not included.In our study most of patients in anisometropic group had hyperopic anisometropia(22 patients).

According to Leone et al the increase in macular thickness in amblyopia may result from inadvertent measurement of parafoveal eccentric point.[16]In our study, the patients with unsteady fixation were excluded and to examine off-center scans in patients with steady fixations, the scan placement was adjusted. So in our study difference in macular thickness is not result of off-centered scans.

According to Al-Haddad et al., in nonamblyopic anisometropia control group, the interocular difference is not significance.[10] Therefore, the change in macular thickness may be primarily because of amblyopia and not because of anisometropia and refractive error alone.The increase in the thickness of macula in amblyopic eyes was not statistically significant in amblyopia with strabismus, according to our findings as well. This result is in line with previous research.[7,14] Patients with strabismic amblyopia did not exhibit any change in macular thickness, according to Altintas et al. [7] Quoc et al. found the similar results in patients with amblyopia having strabismus.[14] In contrast, one research conducted by Dickmann et al. found that the only significant difference in thickness between their normal contralateral healthy eyes and eyes with strabismic amblyopia in the macular region only[13] According to a research by Huynh et al. also stated increase in foveal thickness in strabismic amblyopia patients.[12]

Our results confirm the theory of Huynh et al. that increase in macular thickness is seen only in amblyopic patients having inisometropicamblyopia. The reason of which suggested that disruption in the typical postnatal development of amblyopic eyes may hinder the maturation of normal macula. This could cause Henle's fibers to migrate away from the foveola, potentially resulting in increased thickness of fovea as observed on OCT.[12] Nevertheless, future research has to decide how to interpret our findings.

Children with ametropic and anisometropic amblyopia who did not regain normal visual acuity after treatment had a thicker macula on OCT examination, according to Liu et al.[15] Thus, macular involvement in anisometropic amblyopia seems to be a potential source of treatment resistance. Our patient's medical history and records about the treatment of amblyopia were inadequate. More investigation is needed to confirm the impact of amblyopia treatment on macular thickness.

According to our research findings, neither strabismic nor anisometropic amblyopia was associated with a statistically significant difference in the thickness of the macular or peripapillary RNFL between normal healthy eyes and opposite eyes with amblyopia.

Also reported in earlier researches, majority of writers have presented findings that are comparable to our study.[16–18] Patients with hyperopic anisometropic amblyopia showed a considerably higher RNFL thickness according to Yoon et al.'s report on OCT examination.[14] Kee et al. found that in comparison to strabismic amblyopia, anisometropic amblyopia had a much thicker RNFL.[18] In our study we

found that in anisometropic amblyopia group, the average thickness of the peripapillary RNFL was more as compared to strabismic amblyopia group but this difference in thickness was not statistically significant.

It has been noted that refractive error influences RNFL thickness measurement by OCT.[19] RNFL thickness has positive correlation with refractive error.[20] To lessen the influence of refractive errors on thickness of RNFL thickness, we excluded the individuals with myopia and hypermetropia of 5 diopters or more in each eye from our study.

In comparison to the control group, the Parkinsons disease (PD) group's mean for the average, superior, and inferior RNFL thickness was noticeably smaller. In comparison to the control group, the PD group's mean for the average, central, outer superior, outer inferior, and outer nasal macular thickness was noticeably smaller.[21] However we didn't evaluate parkinson's disease which may be a confounding factor in our research. Hence it is advisable to consider this factor to eradicate the maximum number of confounding factors which may hider your effective results.

According to a study[22], alcohol is a possible risk factor influencing RNFL and macular thickness, as evidenced by the substantial correlation between increased alcohol consumption and thinner RNFL and macular thickness.

In our study, we were unable to do subgroup analysis based on anisometropia type and deviationas there were less number of individuals involved, which is limitation of our study. The absence of a control group comprising patients with anisometropia or strabismus with absence of amblyopia was another limitation in our research.

Our findings indicate that the maculae of anisometropic amblyopic eyes were significantly thicker than those of the corresponding normal fellow eyes. On the other hand, there was no statistically significant increase in the macular thickness of eyes with amblyopia having strabismus. Moreover, it was discovered that amblyopia had no effect on the thickness of the peripapillary RNFL in both groups. A contentious and disputed issue is retinal involvement in amblyopia. Further research is required to identify changes in retina in amblyopia and determine whether involvement of retina influences the responsiveness to amblyopia therapy.

CONCLUSION

According to our research, compared to other normal eyes, the anisometropic amblyopic eyes were thicker in the macular region, and this difference in macular thickness was statistically significant. Eyes with amblyopia having strabismus did not exhibit a noticeable significant increase in macular thickness statistically. Furthermore, it was found that neither group's peripapillary RNFL thickness was impacted by amblyopia.

Authors Contribution:
Syed Amir Hamza: Concept & design of study, final approval of version
Maria Sultan: Drafting, critical review, final approval of version
Maleeha Safdar Ali: Data analysis, final approval of version
Muhammad Tariq: Data analysis final approval of version

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Medical Education - Review Article **Open Access**

In-Class Active Engagement Strategies to Enhance Student Participation During Lectures : A Systematic Review

Zubia Waqar, Shafaq Sultana, Madiha Ata

ABSTRACT

Improving students' engagement in lectures has been a challenge in higher education. This systematic review aims to synthesize evidence on active engagement strategies, including technology-enhanced tools, interactive pedagogies, and classroom modifications alongside an evaluation of their effectiveness and determinants. Following the PRISMA 2020 guidelines, 36 peer-reviewed articles were identified through systematic searching in PubMed, ERIC, and Google Scholar (2014–2024). The quality of studies was evaluated using validated appraisal tools, with high interrater reliability (Cohen's Kappa = 0.82) and methodological rigor. The evidence shows that technology-enhanced tools like polling systems, Socrative, and Kahoot support real-time interaction and feedback but are challenging to use in resource-limited environments. Interactive strategies like Think-Pair-Share and Buzz Groups enhance collaboration and critical thinking but are more effective in smaller class sizes. Classroom modifications like flexible seating improve inclusivity. The effectiveness of these strategies depends on instructor preparation, class size, and the infrastructure of the institution. Future studies should investigate multimodal strategies, low-tech options, and long-term effects to promote sustainability and wider applicability.

Keywords: Education, Engagement, Interaction, Instruction/Teaching Methods, Student Participation, Lectures

How to cite this Article:
Waqar Z, Sultana S, Ata M. In-Class Active Engagement Strategies to Enhance Student Participation during Lectures: A Systematic Review. J Bahria Uni Med Dental Coll. 2025;15(2):146-158 DOI: https://doi.org/10.51985/JBUMDC2024486

INTRODUCTION

Student engagement is the force that drives the academic success of students, and it is often described as "a student's intellectual commitment and effort to learn, understand or become an expert in the skills, information, or trades that academic activities need to foster."[1] This definition highlights the complex construct of engagement as it has behavioral, emotional, and cognitive dimensions. The behavioral aspect of engagement reflects one's active participation in academic activities, and the emotional aspect relates to the learner's motivation and interests. Lastly, the cognitive aspect concerns one's intellectual or psychological investment in learning.[2] These three separate yet interconnected dimensions indicate the importance of fostering environments and strategies that actively encourage student participation in the educational process. Since engagement is reported to be associated with improved learning outcomes, student retention, and overall academic achievement, educators and institutions should focus on strategies that improve engagement across these three dimensions.

Following the critique over lectures, several other pedagogical approaches have been introduced, but lectures are still regarded as fundamental instructional methods. Although few perceive lectures as an outdated instruction method, there are still many reasons for which the lectures are valued: these include their ability to convey complex information efficiently to large audiences, having a good alignment with curriculum, their structured & consistent format, and the ability to set clear learning objectives, making them indispensable in the academic setting.[3,4]

Moreover, it is evident that in STEM fields, including education, science, and clinical studies, lectures provide a structured platform for disseminating foundational and advanced knowledge.[5] Nevertheless, engagement during lectures is another important aspect of their effectiveness. An engaging lecture enables educators to capture students' attention, stimulate curiosity, and maintain interest through dynamic and well-organized presentations.[6] Similarly, few interactive elements have been reported to help educators transform passive listening into an active learning experience by promoting a deeper connection between students and the material being taught.[7] Despite these advantages, lectures are not without their challenges. The traditional lecture

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Received: 09-12-24
1st Revision: 24-12-24
Accepted: 26-03-25
2nd Revision: 20-03-25

format often limits opportunities for student participation, resulting in passive learning.[8,9] Research suggests that students who passively listen to lectures may struggle with information retention and application, particularly when the content is dense or abstract.[3,4] Furthermore, students with diverse learning styles may find lectures less effective compared to other interactive or discussion-based methods. Therefore, the passive nature of traditional lectures demands educators to integrate strategies that encourage active engagement, leading to an improved retention of information.

The research exploring the teachers' and students' perceptions emphasized the importance of strategies or tools used to engage students.[8,9] However, engaging students during large sessions remains a challenge for the teaching faculty. This challenge has been reported to have maximized effects in large classroom settings, where it is not convenient for educators to assess the engagement level of individual students.[10] In 2019, Bond & Bedenlier presented a student engagement framework that emphasized three main aspects: behavior, emotions, and thinking. Based on this framework, behavioral engagement describes participation, effort, and persistence in academic and social activities. Emotional engagement reflects affective reactions, a sense of belonging, and overall attitudes toward learning, and cognitive engagement focuses on deep learning strategies, self-regulation, and metacognition.

Moreover, this framework provides educators and institutions a holistic understanding of engagement by taking account of the broader context, including the institutional environment, teaching practices, social environment, and technological environment, all influencing student engagement.

The foundations of this review, built on Bonds & Bedenlier's framework, aim to provide a comprehensive understanding of the various methods, their effectiveness, and the perceptions of both students and faculty regarding these strategies. It explores different engagement strategies used in lecture settings and the impact of these strategies on student participation and learning outcomes.

Research Methodology

The study selection process was conducted systematically following the PRISMA 2020 guidelines to ensure transparency and reproducibility.[11] A comprehensive search including PubMed, ERIC, and Google Scholar was performed to identify relevant studies on active engagement strategies in lecture-based learning. Search terms with a combination of keywords such as "classroom interaction," "student engagement," "active learning," and "higher education" alongside Boolean operators (AND, OR, NOT) were constructed to explore the literature. The initial database search yielded a total of 2000 publication records. These records were imported into the Mendeley reference manager to facilitate the organization and removal of duplicates. Out of 2000 publications, 199 studies remained after duplicate removal. Two independent reviewers screened titles and abstracts for relevance based on predefined inclusion and exclusion criteria. The decision to include studies was based on whether the studies were published in English between 2014 and 2024 in peer-reviewed journals, focused on educators employing active engagement strategies in lecture settings, reported impacts on student participation or learning outcomes, and explored the perspectives of both students and faculty. In contrast, studies were excluded if they were focused on flipped classrooms, blended learning, or the provision of pre-class materials, opinion pieces, editorials, or non-peer-reviewed articles and were not available in full-text format. A total of 36 studies were selected for full-text review. Each excluded study was tagged with specific reasons (e.g., "focus on blended learning," "not peer-reviewed," or "non-English article") to enhance the transparency of the process. The PRISMA flow diagram (Figure 2) visually represents the study selection process, detailing the number of records identified, screened, excluded, and included at each stage.

The appraisal of included studies was conducted with the help of validated tools tailored to respective study designs to ensure methodological rigor and reliability. Two independent reviewers evaluated the selected studies, maintaining a Cohen's Kappa statistic (=0.80), which indicates strong agreement. The discrepancies were resolved through discussion and consultation with a third reviewer. For observational and quasi-experimental studies, the Newcastle-Ottawa Scale (NOS) and the ROBINS-I Tool were employed to evaluate the risk of bias. These tools have

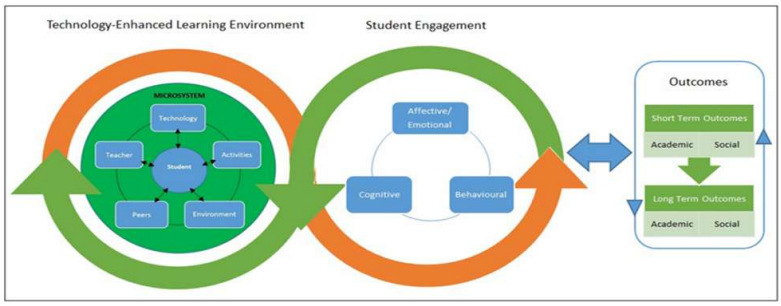

Figure 1: Student Engagement Framework adopted by Bond & Bedenlier 2019

a strong focus on selection methods, group comparability, and outcome measurement.[12,13]. discrepancies were resolved through discussion or consultation with a third reviewer.

The tools selected to appraise studies helped to compare strengths such as randomization in sampling while also identifying limitations like selection bias and confounding variables. Mixed methods studies were assessed using the Mixed Methods Appraisal Tool (MMAT), which ensured a balanced appraisal of qualitative and quantitative integration, particularly in studies evaluating polling systems like Kahoot and Socrative.[14] Qualitative studies, including those exploring storytelling techniques, were appraised using the Critical Appraisal Skills Program (CASP) Checklist, which evaluated the credibility, transferability, and dependability of findings.[15]

Additionally, educational tools and techniques, such as Learning Catalytic, Clickers, and polling systems, were critically reviewed for validation of instruments and statistical analyses, with studies using validated tools (e.g., Dvoroková & Kulhánek, 2017) demonstrating higher credibility compared to those relying on unvalidated self-reported data.

Framework for Appraisal of Diverse Studies

To ensure methodological rigor and consistency, a standardized scoring framework was applied to all included studies. Studies were evaluated across five criteria: study design, sampling method, validity of instruments, data analysis, and relevance to review objectives. Studies were appraised for quality using a scoring framework across five criteria: study design, sampling method, validity of instruments, data analysis, and relevance to review objectives. Each study was rated on a 10-point scale and categorized as Excellent (9–10), Good (7–8.9), or Fair (5–6.9) based on total scores. All studies were included in the review, with quality ratings noted to contextualize the findings. This approach enabled us to systematically appraise diverse methodologies, including experimental, quasi-experimental, mixed methods, and qualitative studies. To ensure methodological rigor, a comprehensive appraisal framework (Table 1) is tailored based on the above-mentioned tools to appraise the selected studies.

Findings:

A total of 36 studies were included, classified into four engagement strategies. The extracted data covered study details such as author, engagement techniques, study design, sampling, data type, analysis, conclusions, and limitations. Table 2 represents the distribution of the student engagement strategies identified through a systematic literature search. Out of these 36 studies, 7 studies were rated "Excellent" for their robust methodologies, validated tools, and high relevance, 26 studies were rated "Good" having minor limitations like convenience sampling or partial validation whereas, 3 studies were rated "Fair" because of weaker designs or analyses but provided insights.

This interrater reliability analysis Cohen's Kappa = 0.82 further confirmed the rigor and reliability of the appraisal process. Table 3 represents the details of the information appraised during the process.

1- **Technology-Enhanced Learning Tools:** Technology-enhanced learning Tools, also known as student or classroom response systems, work through handheld devices, including platforms and apps designed to promote more interaction and engagement through instant feedback. These technology-enhanced learning

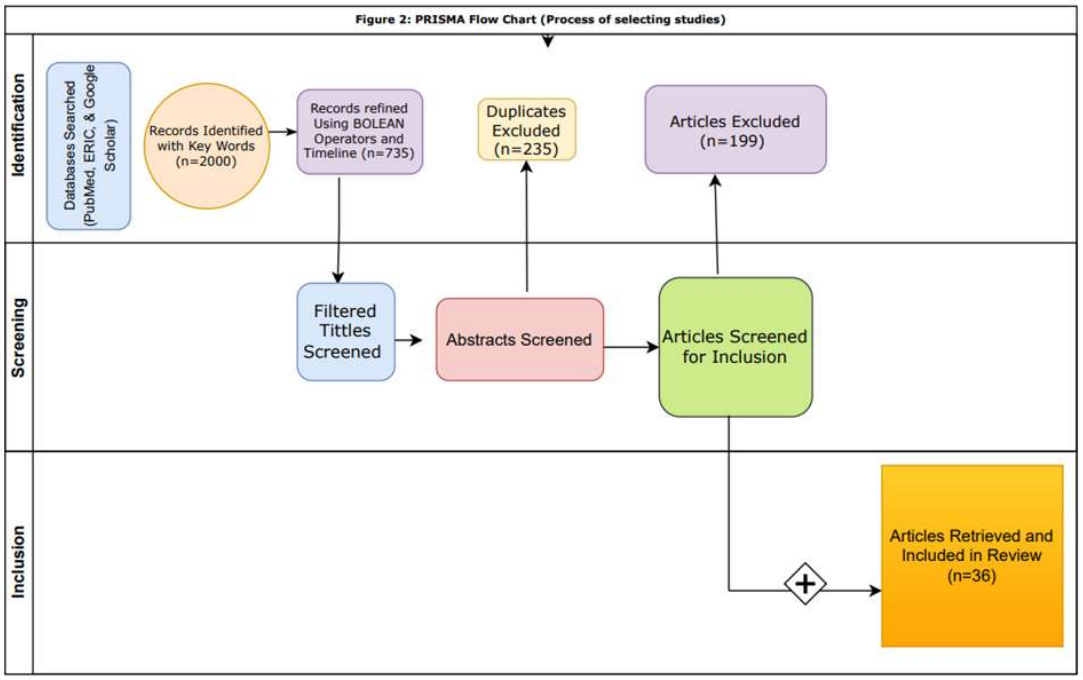

Table 1: Comprehensive Appraisal Framework

Criterion	Description	Experimental / Quasi-Experimental Studies	Mixed Methods Studies	Qualitative Studies
Study Design (2 Points)	Appropriateness and rigor of the study design	2: Randomized or well-defined quasi-experiment	2: Clear integration of qualitative & quantitative approaches	2: Robust and clearly described design (e.g., case study, ethnography)
		1.5: Partial control (e.g., quasi-experiment without randomization)	1.5: Partial integration of methods or unclear rationale	1.5: Design described but lacks sufficient detail
		1: Poorly described design or significant flaws	1: Weak integration of methods, poor rationale	1: Unclear or weak design
Sampling Method (2 Points)	Appropriateness and justification of sampling strategy	2: Random or stratified sampling	2: Justified purposive sampling and integration of sampling strategies	2: Purposive sampling with a clear rationale
		1.5: Convenience sampling with justification	1.5: Partial justification of sampling methods	1.5: Convenience sampling with some rationale
		1: Unjustified sampling or unclear method	1: Poorly justified or inconsistent sampling	1: Unclear or unjustified sampling
Validity of Instruments (2 Points)	Use of validated tools and measures	2: Fully validated and reliable tools	2: Validated tools for both quantitative and qualitative components	2: Piloted tools, and validated frameworks (e.g., interview protocols)
		1.5: Partial validation or some unclear details	1.5: Partial validation in one component	1.5: Limited description of validation
		1: Non-validated or unclear instrument validity	1: No evidence of validation in either method	1: No validation mentioned
Data Analysis (2 Points)	Appropriateness and rigor of the analysis	2: Advanced and appropriate statistical methods (e.g., ANOVA, regression)	2: Thorough integration of qualitative and quantitative findings	2: Robust analysis (e.g., thematic coding, grounded theory)
		1.5: Basic statistical methods or unclear reporting	1.5: Partial integration or basic analysis in one method	1.5: Thematic analysis with limited depth
		1: Inappropriate or missing analysis	1: Weak analysis or lack of integration	1: Limited or unclear analysis
Relevance to Review Objectives (2 Points)	Alignment with review focus	2: Highly aligned with engagement strategies	2: Both components address engagement strategies	2: Highly relevant to engagement strategies
		1.5: Moderately aligned, some gaps	1.5: Partial alignment between methods and engagement focus	1.5: Moderately relevant findings
		1: Limited or tangential relevance	1: One component relevant, overall weak relevance	1: Weak or limited relevance to review objectives

tools include learning catalytic, clickers, polling, Socrative, and Kahoot. Learning Catalytic is defined as a tool that can be used for real-time polling and assessment.[16,17,18] Another technology-based tool that can be employed to engage students and provide instant feedback in a lecture is Clickers, which are believed to provide instant feedback.[19,20,21] General Polling Systems are another example of real-time questioning and feedback.[22,23,24] Over the years, Socrative and Kahoot, which rely on game-based approaches to facilitate engagement and learning through quizzes and other interactive endeavors, have emerged as the dominant trend in educational technology.[25,26,27,28,29]

2- **Interactive Teaching Strategies**: The Interactive Teaching Strategies aiming to increase students' interaction through collaborative methods include activities such as Buzz Groups; a technique where the students all engage in a group discussion[30,31,32], and Think-Pair-Share; where the students first think independently and then discuss with their partner afterward followed by sharing in the big class to gain further understanding.[33,34,35,36]

3- **Educational Methodologies:** Educational Methodologies use innovative approaches to ensure the inculcation of interest, including Storytelling, in which the use of narratives makes learning more relational and memorable.[37,38,39,40] Concept and Mind Mapping helped the students organize information visually[41,42,43,44]; the Minute Paper Review was a quick assessment of student understanding.[45,46,47]

4- **Classroom Environment & Seating Arrangement:** Lastly, the studies also examine optimizing the classroom environment and seating arrangement, especially with proper seating arrangements for better interaction and engagement among students.[48,49,50]

DISCUSSION

Student engagement during lectures is an essential component of effective learning. This review critically examines strategies such as technology-enhanced tools, interactive teaching methodologies, storytelling, concept mapping, and classroom environmental changes, drawing on the studies summarized in the table. A comparative yet critical analysis of these strategies reveals their effectiveness and limitations, providing an advanced understanding of their applications in different educational contexts.

Evidence indicates that student participation increased by employing technology-enhanced tools, including Learning Catalytic, Clickers, and polling systems like Socrative and Kahoot. For example, Rogerson and Chomicz (2014) observed that Learning Catalytic fosters student learning experiences through real-time feedback. Similarly, Dvoroková and Kulhánek (2017) determined that learning catalytic improved course delivery. However, individual institution-focused findings and the educator's ability to employ these tools vary across these studies.

Subsequently, Heaslip et al. (2014) found Clickers to facilitate engagement in large classes by encouraging interaction through anonymous responses. Furthermore, Walklet et al. (2016), while extending these findings to psychology lectures, emphasized peer learning and engagement without fear of judgment. However, the small sample sizes and discipline-specific applications of these tools limit the generalizability of their outcomes.[19,20]

An in-depth analysis across the methodologies employed reflects differences that ultimately influence the external validity of these research studies. To include this, Rogerson and Chomicz (2014) adopted a qualitative case study approach, providing rich contextual insights but lacking statistical generalizability. In contrast, Dvoroková and Kulhánek (2017) used a quasi-experimental design, combining objective pre- and post-test scores with subjective survey data, adding depth to their analysis but raising questions about replicability across different institutions. Meanwhile, some of these researchers incorporated mixed methods, strengthening their ability to triangulate data but introducing complexity in data synthesis.[19,20] However, most of the studies relied heavily on convenience sampling, a consistent limitation, leading to a reduced external validity.

Subsequently, the outcomes of the studies employing different technology-enhanced tools vary from one study to another. For example, the studies incorporating polling systems, such as Poll Everywhere, Socrative, and Kahoot, enhance interaction in large classes[22], while Sedghi et al. (2021) observed high overall engagement levels among large cohorts. A study conducted by Arjomandi et al. (2023) established a positive correlation between polling and academic performance in statistics students, using controlled trials to support causal inferences.

Evidence indicates that the use of validated tools significantly enhances the credibility and reliability of studies by ensuring consistent, accurate, and reproducible results.[51] For example, studies employing validated questionnaires or systems, such as Rinaldi et al. (2017) and Dervan (2014), provide robust evidence of student engagement and academic performance improvements. In contrast, studies lacking tool validation, such as Sedghi et al. (2021), raise reliability concerns, with findings possibly skewed by biases inherent in unvalidated instruments. Additionally, the infrastructure requirements for these tools highlight the challenges of implementing technology in resource-constrained environments.[29] However, there certainly is variability from employing a wide range of methodologies, choice of validated questionnaires[22] to a reliance on self-reported data, which may lead to bias.[23]

Similarly, interactive teaching strategies, including Buzz Groups and Think-Pair-Share, seemed to help students shift the focus to active and collaborative learning. The studies conducted by Ihsan (2019) illustrate an improved vocabulary among secondary school students through Buzz Groups, whilst Romeike and Fischer (2019) observed that these teaching strategies help in enhancing histopathological competencies in medical students. Considering the choice of study design, the use of quasi-experimental designs across these studies provides a controlled yet flexible framework for intervention assessment. However, on the other hand, the absence of randomization, as seen in Afifah (2019), carries potential selection bias.

Likewise, Think-Pair-Share, as highlighted by Vázquez-García (2018), showed improved knowledge retention in

Table 2: No. Of Studies Included in this Review

Student Engagement Strategies:	**No. of Studies**
Technology-Enhanced Learning Tools	
Learning Catalytic	3
Clickers	3
Polling	3
Socrative	3
Kahoot	3
Interactive Teaching Strategies	
Buzz Groups	3
Think-Pair-Share Activities	4
Educational Methodologies	
Storytelling	4
Concept & Mind Mapping	4
One Minute Paper Review	3
Classroom Environment & Seating Arrangements	**3**
Total Number of Studies Included in Review:	**36**

Table- 3 Summary of Studies on Student Engagement Strategies during Lectures

Specific Engagement Strategy	Study Reference	Study Design	Sampling Population	Sampling Technique	Type of Data	Validity of Instruments	Data Analysis	Outcomes	Study Limitations	Score & Ratings
Learning Catalytic	Rogerson C, Chomicz G. (2014)	Case study	One institution	Not Specified	Qualitative	Not Applicable	Thematic analysis	Enhanced student learning experience	Limited to one setting; lacks broader applicability.	6.0 Fair
	Dvoroková K, Kulhánek L. (2017).	Quasi-experimental	University students, varied class sizes	Unclear	Objective (test scores), subjective (surveys)	Pearson's interactive response system	Quantitative (pre/post-test scores)	Improved course delivery	Limited to one institution; results may not be replicable	9.5 Excellent
	Abdulla MH. (2018).	Quasi-experimental	Medical students	Convenience Sampling	Quantitative	Validated questionnaire	Descriptive statistics	Improved understanding of physiology	Limited to physiology; may not generalize to other subjects.	8.0 Good
Clickers	Heaslip G, et al. (2014).	Mixed methods	Large classes	Convenience Sampling	Mixed	Self-reported	Qualitative & Quantitative	Increased engagement in large classes	Small sample size; limited to specific courses.	7.5 Good
	Walklet et al. (2016)	Quasi-experimental (Clickers in psychology lectures)	Undergraduate psychology students	Convenience Sampling	Objective (MCQ responses), subjective (feedback)	Validated clicker system	Quantitative (MCQ performance, feedback surveys)	Fostered peer learning, and enhanced engagement without fear of judgment	Small sample size, limited to psychology students, potential over-reliance on clicker technology.	8.5 Good
	Rinaldi VD, et al. (2017).	Quasi-experimental	Histology students	Convenience	Quantitative	Validated instrument	Inferential statistics	Improved student performance	Laboratory settings may affect engagement outcomes.	7.5 Good

Specific Engagement Strategy	Study Reference	Study Design	Sampling Population	Sampling Technique	Type of Data	Validity of Instruments	Data Analysis	Outcomes	Study Limitations	Score & Ratings
Polling	Voelkel S, Bennett D. (2014).	Experimental	Large classes	Convenience	Quantitative	Validated questionnaire	Descriptive statistics	Enhanced interaction in lectures	Potential bias in self-reported data	8.0 Good
	Sedghi N, et al. (2021).	Experimental	Large cohorts	Purposive	Quantitative	Not specified	Descriptive statistics	High levels of student engagement	Same cohort; longitudinal effects not assessed.	7.5 Good
	Arjomandi A, Paloyo AR, Suardi S. (2023).	Experimental	Statistics students	Controlled Trial but Convenienc e Sampling	Quantitative	Not specified	ANOVA	Positive correlation with academic performance	Focused on statistics; may not represent all disciplines	8.5 Good
Socrative	Dervan P. (2014).	Quasi-experimental	Nursing students	Convenience	Quantitative	Validated tool	Descriptive statistics	Increased engagement and participation	Limited to specific student population; narrow focus.	7.0 Good
	Guarascio AJ, et al. (2017).	Comparative study	Pharmacy students	Convenience	Quantitative	Validated instrument	Descriptive statistics	Enhanced classroom engagement	Focused on pharmacy students; may not generalize.	7.5 Good
	Amoia-Watters L. (2023).	Experimental	Nursing students	Convenience	Quantitative	Validated instrument	ANOVA	Positive impact on student engagement	Focus on the nursing program; limited to a specific discipline.	8.5 Good
Kahoot	Martínez-Fernández T, et al. (2017).	Comparative study	Business students	Convenience	Quantitative	Not specified	ANOVA	Comparison of engagement levels	Focused on business subjects; results may vary in other fields.	6.5 Fair
	Kim KJ. (2019).	Experimental	Medical students	Convenience	Quantitative	Not specified	ANOVA	Increased self-efficacy and active learning	Limited to medical English; potential bias in self-reporting.	8.5 Good
	Muir S, et al. (2020).	Mixed methods	University students	Convenience	Mixed	Self-reported	Mixed methods analysis	Increased classroom engagement	Small Sample Size, Context-specific results	7.0 Good
2- Interactive Teaching Strategies										
Buzz Group	Ihsan D. (2019)	Quasi-experimental	Secondary school students	Random sampling	Quantitative	Not specified	Descriptive statistics	Improved vocabulary mastery among students using buzz groups.	Limited to one institution, may not be generalized.	7.0 Good

Specific Engagement Strategy	Study Reference	Study Design	Sampling Population	Sampling Technique	Type of Data	Validity of Instruments	Data Analysis	Outcomes	Study Limitations	Score & Ratings
	Afifah N. (2019)	Quasi-experimental	University students	Random sampling	Quantitative	Not specified	Descriptive statistics	Enhanced reading comprehension skills through buzz group discussions.	Specific to reading comprehension, may not apply to other areas.	7.0 Good
	Romeike BF, Fischer M. (2019)	Quasi-experimental	Medical students	Convenience sampling	Quantitative	Not specified	ANOVA	Improved histopathological competencies through collaborative learning.	Focused on histopathology, may not generalize to other disciplines.	9.0 Excellent
Think-Pair Share or Collaborative Learning	Fernandez-Rio J, Sanz N, Fernandez-Cando J, Santos L. (2017)	Quasi-experimental	Secondary education students	Random sampling	Quantitative	Not specified	ANOVA	Increased student motivation following the intervention.	Limited to physical education; results may not be generalized.	7.5 Good
	Vázquez-García M. (2018)	Experimental	Second-year medical students	Random sampling	Quantitative	Validated tool	Descriptive statistics	Improved knowledge retention in human physiology topics.	Focused on medical students; may not apply to other disciplines.	9.0 Excellent
	Harahap RR, Makhroji M, Zulida E, Fadlia F, Chairuddin C. (2021)	Quasi-experimental	English as a Foreign Language (EFL) students	Random sampling	Quantitative	Not specified	Descriptive statistics	Enhanced learning outcomes in the EFL classroom through cooperative models.	Limited to EFL context; may not generalize to other educational settings.	7.5 Good
	Fernández MA, Quintana J, Dominic W, Darius L, Alexandra W. (2023)	Quasi-experimental	University students	Convenience sampling	Quantitative	Not specified	Descriptive statistics	Increased student interest and improved learning outcomes	Focused on a specific population; may not generalize to all disciplines.	7.0 Good
3- Educational Methodologies										
Story Telling	Lal S, Donnelly C, Shin J. (2015)	Mixed methods	Occupational therapy students	Purposive Sampling	Mixed (qualitative and quantitative)	Not specified	Mixed analysis	Positive outcomes in education and practice via digital storytelling.	Limited focus on one discipline.	8.0 Excellent
	Choi GY. (2018)	Qualitative	Lecture attendees	Convenience Sampling	Quantitative	Not specified	Thematic analysis	Enhanced learning experience through digital storytelling techniques.	Focused on a specific educational context.	7.0 Good

Specific Engagement Strategy	Study Reference	Study Design	Sampling Population	Sampling Technique	Type of Data	Validity of Instruments	Data Analysis	Outcomes	Study Limitations	Score & Ratings
Story Telling	Demirci T, Okur S. (2021)	Experimental	Science students	Random sampling	Quantitative	Validated tool	ANOVA	Improved academic achievement, writing skills, and positive opinions.	Limited to a specific student population.	9.0 Excellent
	Maharaj-Sharma R. (2024)	Experimental	Physics students	Purposive sampling	Quantitative	Not specified	Thematic analysis	Positive impact of storytelling on learning physics topics.	Limited to one topic within physics.	7.0 Good
Concept or Mind Mapping	Kotze SH, Mole CG. (2015)	Case study	Histology students	Convenience sampling	Qualitative and quantitative	Not specified	Thematic analysis & descriptive statistics	Enhanced engagement and learning in large classes.	Limited to histology, lacks broad applicability.	7.5 Good
	Mathew S. (2018)	Randomized Control Study	Medical students (first year)	Random sampling	Quantitative	Not specified	ANOVA	Mind mapping was more effective than didactic lectures for knowledge gain.	Focused on anatomy students, potential for bias in self-reporting.	9.0 Excellent
	Astriani D, Herawati S, Suwono H, et al. (2020)	Quasi-experimental	University students	Random sampling	Quantitative	Not specified	Descriptive statistics	Improved metacognitive skills through mind mapping	Limited to one learning context.	7.5 Good
	Silva H, Lopes J, Dominguez C, Morais E. (2022)	Quasi-experimental	University students	Convenience sampling	Quantitative	Validated Instrument	ANOVA	Concept mapping improved both critical and creative thinking.	Single institution, limited subject areas.	8.5 Good
One-Minute Paper Review	SrivaSTava TK, Mishra V, Waghmare LS. (2018)	Controlled trial	Pre-clinical medical students	Random sampling	Quantitative	Validated tool	ANOVA	FACTs resulted in improved understanding and retention of course material.	Limited to pre-clinical education, small sample size.	9.0 Excellent
	Darnell DK, Krieg PA. (2019)	Experimental	College students	Random sampling	Quantitative	Validated heart rate monitors	Inferential statistics (t-tests)	No significant change in engagement levels during active learning.	Heart rate may not be the best indicator of engagement in, a small sample size.	6.5 Fair
	Solamo FSD. (2022)	Quasi-experimental	Undergraduate students	Convenience sampling	Quantitative	Not specified	Descriptive statistics	OMP improved formative assessment and student reflection.	Limited to a specific context, may not generalize to other settings.	7.0 Good

4- Classroom Environment & Seating Arrangement										
Specific Engagement Strategy	**Study Reference**	**Study Design**	**Sampling Population**	**Sampling Technique**	**Type of Data**	**Validity of Instruments**	**Data Analysis**	**Outcomes**	**Study Limitations**	**Score & Ratings**
Seating Arrangement	Haghighi MM, Jusan MB. (2015)	Quasi-experimental	University students	Random sampling	Quantitative	Validated questionnaire	ANOVA	Identified correlation between seat selection and academic performance.	Focused on specific classroom settings; may not generalize to other contexts.	8.0 Good
	Shekhar P, Borrego M. (2018)	Case study	Engineering students in large classes	Convenience sampling	Qualitative and quantitative	Not specified	Thematic analysis and descriptive statistics	Insights into factors affecting student engagement in large classes.	Limited sample; findings may not apply to all engineering classes.	7.5 Good
	Seet HA, Tan E, Rajalingam P. (2022)	Quasi-experimental	Medical students	Random sampling	Quantitative	Not specified	Descriptive statistics	Increased class engagement associated with specific seating arrangements.	Limited to one institution; results may not be generalized.	7.0 Good

physiology, with randomized sampling enhancing the reliability of findings. Harahap et al. (2021) further linked these benefits to English as a Foreign Language (EFL) classrooms, showcasing the adaptability of collaborative models. Nevertheless, there is a lack of longitudinal studies to evaluate sustained impact, which remains a notable gap. Subsequently, another study by Fernandez-Rio et al. (2017) addressed challenges, suggesting that smaller class sizes may be better suited for these strategies.

Similar to the choice of the study design, statistical analysis also plays a pivotal role in determining the strength and applicability of study findings.[52] The reviewed studies employed a range of statistical methods, including descriptive statistics, inferential statistics, and mixed methods analysis. Descriptive statistics, as widely used in studies such as Voelkel and Bennett (2014) and Amoia-Watters (2023), provide foundational insights but are limited to summarizing data without assessing relationships or causality. Inferential statistics, including t-tests and ANOVA, were employed in controlled or quasi-experimental studies like those of Arjomandi et al. (2023) and Mathew (2018), enhancing study quality by enabling causal inferences. However, their applicability is contingent on assumptions like normality and variance homogeneity, which require careful consideration. Mixed methods analysis, as utilized by studies such as Heaslip et al. (2014), enabled a holistic understanding of engagement strategies but complicated the synthesis of findings.

Studies utilizing advanced statistical techniques, particularly inferential methods, exhibit greater rigor by addressing causal relationships and controlling for confounding variables. Conversely, reliance solely on descriptive statistics or subjective data without rigorous validation limits the generalizability and robustness of findings. A comprehensive approach integrating robust statistical methods with validated tools is critical for advancing research quality and applicability. [52]

Storytelling, as an instructional methodology, bridges cognitive and emotional engagement. Lal et al. (2015) demonstrated its effectiveness in fostering reflective thinking in occupational therapy students, employing a mixed-methods approach to capture both quantitative outcomes and qualitative nuances. Demirci and Okur (2021) validated the role of storytelling in improving academic achievement and writing skills among science students, utilizing controlled experiments to establish causal links. Choi (2018), through qualitative thematic analysis, explored the subjective impact of digital storytelling on lecture attendees. However, the heavy reliance on instructor creativity and the novelty effect, as noted by Maharaj-Sharma (2024), limits its scalability and long-term efficacy. Comparing these methodologies, Lal et al.'s mixed-methods design offers a more comprehensive evaluation, while Choi's qualitative focus highlights contextual richness but lacks broader applicability. Future research could benefit from integrating experimental controls to assess the comparative impact of storytelling against other engagement strategies.

Concept and mind-mapping techniques structure information to promote critical thinking and comprehension. Kotze and Mole (2015) demonstrated significantly improved

engagement in histology classes through draw-along mapping, utilizing case studies to contextualize their findings. Silva et al. (2022), while extending these benefits to university students, reported enhanced critical and creative thinking through concept mapping. Astriani et al. (2020) explored the effect of digital adaptations in concept mapping and revealed that these innovations help foster metacognitive skills and collaborative learning. Methodologically, these studies predominantly employed quasi-experimental designs with varying levels of rigor. For example, Mathew (2018) adopted a randomized controlled approach, providing robust evidence for mind mapping's effectiveness in anatomy education. However, the common reliance on single-institution samples limits the external validity of these findings. Expanding sample diversity and incorporating cross-disciplinary comparisons would strengthen the generalizability of future research.

The classroom environment and seating arrangements also significantly influence engagement outcomes. Seet et al. (2022) observed that flexible seating arrangements foster inclusivity and active participation, particularly in medical education. Another study by Haghighi and Jusan (2015) observed a positive correlation between seat selection and academic performance. However, the traditional seating arrangement of lecture halls often restricts these benefits, particularly in large class settings. A comparative analysis reveals that while Seet et al. highlighted interaction benefits, Haghighi and Jusan emphasized individual academic outcomes. Despite a difference between outcomes, both studies underline the need for modular seating designs to facilitate collaborative activities. Nevertheless, the methodological limitations, such as small sample sizes and single-institution settings, remain consistent challenges across this research domain.

Future Directions

Based on the findings of this systematic review, several recommendations are proposed to enhance student engagement in lecture-based settings.

- Educators should be trained and facilitated to develop structured and integrated multimodal engagement strategies by combining storytelling, polling, and collaborative learning techniques within a single group.
- The institutions need to have reconfigurable seating arrangements that facilitate seamless transitions between lectures, group discussions, and individual reflection.
- Future research should assess the long-term impact of engagement strategies on student learning, knowledge retention, and professional readiness to evaluate the effectiveness.
- There is a need to implement structured training programs to equip educators with the skills needed to integrate and adapt engagement strategies effectively

CONCLUSION

This critical exploration of research reveals that lectures are a foundation of higher education, valued for their efficiency and ability to convey complex information to large groups. However, to remain relevant and impactful, lectures must evolve by addressing their limitations and incorporating active learning techniques. By fostering student engagement through interactive strategies, leveraging technology, and tailoring content to meet diverse learning needs, lecturers can continue to play a vital role in promoting academic success. Engagement, in all its dimensions, remains the key to unlocking the full potential of this timeless instructional method.

By addressing the above-mentioned future directions, educational institutions can refine and adapt engagement strategies to diverse environments, ensuring broader applicability and improved learning experiences.

Authors Contribution:
Zubia Waqar: Conducted a detailed review of the literature, contributed to the synthesis of the findings, and helped in writing and revising sections related to methodology and critical discussions.
Shafaq Sultana: Conceived the initial idea, designed the structure of the review, and was responsible for drafting the manuscript, including the literature search and analysis of key studies.
Madiha Ata: Assisted with the data analysis, contributed to the interpretation of results, and was involved in editing and revising the manuscript for clarity and consistency.

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Case Report **Open Access**

Scleral Perforation following Transscleral Diode Laser Cycloablation:

Afshan Ali

ABSTRACT

Transscleral Diode laser cycloablation (DLCA) is one of the cycloablative procedures usually used for treating cases of refractory glaucoma. We report here a case of 80 years old man, who underwent transscleral diode laser cycloablation in his left painful blind eye. The main aim of this treatment was to lower down the intraocular pressure so that his pain could be relieved. On regular follow up visit, just two weeks after the procedure, he presented with scleral perforation on inferior 180 degrees of eye exactly where laser was applied. His intraocular pressure was 12mmHg. Patient had to undergo tectonic and conjunctival grafting on emergency basis to save the integrity of the globe and to avoid phthisis, pain and infection. His post op intraocular pressure (IOP) was 10mmHg with graft in place. This is a very rare complication and to the authors knowledge, this is first reported case of scleral perforation following transscleral diode laser cycloablation in Pakistan.

Key Words: Glaucoma, Intraocular pressure, diode laser

How to cite this Article:
Ali A. Scleral Perforation following Transscleral Diode Laser Cycloablation. J Bahria Uni Med Dental Coll. 2025;15(2):159-161 DOI: https://doi.org/10.51985/JBUMDC2025518

INTRODUCTION

The aim of cyclodestructive procedures is to reduce intraocular pressure in glaucomatous patients. It is achieved by causing coagulative effect on ciliary body, which produces aqueous humor. [1] It is mostly used in cases of painful blind eye but it is also being used in glaucoma cases with good visual potential.[2] Complications such as uveitis, conjunctival burns, hyphema, hypotony, cystoid macular edema, retinal detachment, and phthisis bulbi are possible after this procedure.[3] But scleral perforation is a very rare complication.[4] Spread of thermal energy to the surrounding area causes the main damage resulting in these complications.[5] Here, we describe a case of scleral perforation seen two weeks following transscleral diode laser cycloablation which was done in painful blind eye to control intraocular pressure.

Case Report

This 80 years old male, presented to our glaucoma outdoor department with complaint of pain in his left eye for last six months. Pain was severe, gradually getting worse in intensity and radiating to left side of his head. There was history of trauma in the same eye with fist eight years ago. At the time of injury, patient was given symptomatic treatment and no invasive procedure was performed. Medical history included multiple antiglaucoma drugs for last three years in the same eye. He was currently on maximum topical antiglaucoma therapy which included alpha agonists, beta blockers and prostaglandins. He was also on oral carbonic anhydrase inhibitors for last three months due to severe pain. There was history of frequent use of oral pain killers for pain relief. Surgical history included uneventful bilateral cataract surgery 10 years ago. There was no significant systemic or family history.

Examination of left eye showed no perception of light. Intraocular pressure was 42mmHg. There was conjunctival congestion, corneal edema, shallow anterior chamber (AC) of grade 1 with van Herrick method and peripheral anterior synechiae. The eye was pseudophakic. Optic disc showed cup of 1 but view was hazy due to corneal edema, foveal reflex was not visible for the same reason. Gonioscopy was not possible due to hazy view.

Examination of right eye showed Visual acuity of 6/9. Intraocular pressure was 14mmHg. Anterior chamber depth was grade 3 by van herrick method. Eye was pseudo phakic. Gonioscopy showed grade 4 open angle. Cup disc ratio was 0.3 with healthy neuroretinal rim, fovea was normal.

We made a clinical diagnosis of left painful blind eye secondary to uncontrolled glaucoma with very high intraocular pressure. B Scan left eye was carried out to rule out any other posterior segment pathology, which turned out to be normal. Other investigations for glaucoma were not possible due to corneal edema hence the hazy view.

To relieve his pain and to control his Intraocular pressure, it was decided to do transscleral diode laser cycloablation on inferior 180 degrees of left eye. After the patient's consent, he was given peribulbar anesthesia. The left eye was draped. 5% povidone iodine solution was applied to conjunctival sac. Procedure was performed with total 18 burns applied to said area with contact G probe. Power used was 2000

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Received: 22-01-25
1st Revision: 25-01-25
Accepted: 22-03-25
2nd Revision: 10-02-25

mW, adjusted according to barely audible popping sound and duration of each shot was 2 seconds. Total energy delivered to inferior 180 degrees of eye, was 70 Joules. At the end, subconjunctival injection of steroid and antibtioic was given in inferior fornix. After the procedure patient was prescribed oral Nonsteroidal anti inflammatory drug to manage post operative pain and topical steroid antibiotic combination drops four times day to manage post op ocular inflammation.

On first post op day, Intraocular pressure of left eye was down to 10mmHg with corneal edema and pain was relieved. Patient was asked to continue steroid antibiotic drops four times a day and he was called back after two weeks for follow up. On two weeks follow up, examination of the same eye showed scleral thinning and perforation on inferior 180 degree of eye exactly where diode laser was applied [Figure 1]

Intraocular pressure was 12 mmHg. To manage this perforation, patient was admitted as an emergency case. After the patients consent, tectonic and conjunctival grafting was performed on perforated site to safe integrity of his eye, pain and infection. On one month follow up, graft is in place with intraocular pressure of 12mmHg and patient is pain free [figure 2]

Figure 1: inferior 180 degrees of left eye showing scleral perforation

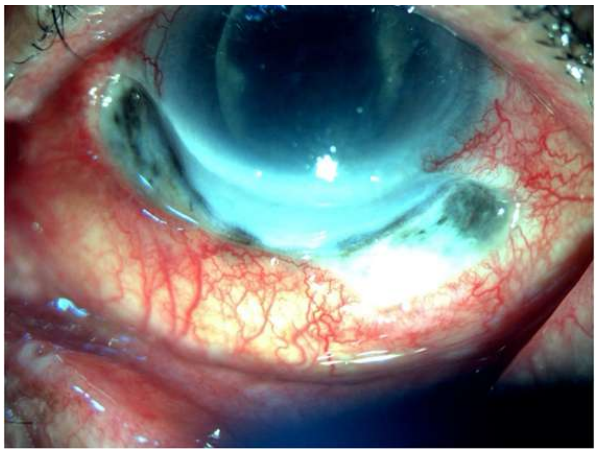
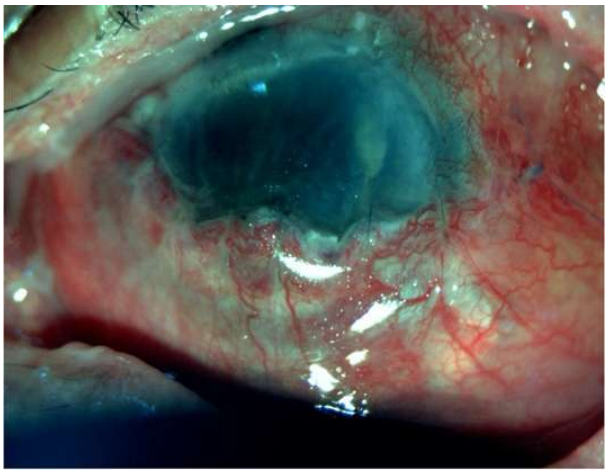


Figure 2: inferior 180 degrees of left eye showing conjunctival graft in place



DISCUSSION

Transscleral diode laser cycloablation is usually a mode of treatment for refractory glaucoma, term used for glaucoma cases not responding to conventional medical or surgical therapy.[6] These patients usually have poor visual prognosis.

Destruction of ciliary body has been used to treat glaucoma since 1930s.[7] Diode laser reduces Intraocular pressure by destroying pigmented and non pigmented ciliary epithelium and capillaries in ciliary processes. It also causes coagulative necrosis, muscle damage and reduced vascularity.[8]

There is wide variety of complications. Most common are iritis, corneal edema, hyphema. Less common include scleral perforation, malignant glaucoma, sympathetic ophthalmitis and hypotony.[9]

In this particular case, patient was alright on the table and on first post op day. Scleral perforation was observed two weeks after the procedure. All the local risk factors that could cause it, were absent in this case like pre op scleral thinning or staphyloma. Use of high power of laser, mechanical pressure on the eyeball with the probe could also be the potential causes of this complication. But Power used during the procedure was according to conjunctival reaction seen accompanied by barely audible popping sound. No mechanical pressure was applied on the globe during laser application. There were no conjunctival burns seen during the process. New probe was used, its tip was clean and carbonization of tissue was prevented by making sure that the tip remained clean in between the shots.

A few reported cases on complications of transscleral diode laser are those in which scleral perforation happened on table during application of laser.[10,11] In these cases, there was a full thickness hole through conjunctiva, sclera and choroid. That area had to be closed with two 10.0 vicryl suture on table. There was pre op scleral thinning as pre disposing factor. However, in our case scleral perforation appeared two weeks after the procedure which had to be managed, on emergency basis so aim of presenting this case is to emphasize on the importance of regular follow up after the procedure to look for potential complications and their timely management even when there are no risk factors involved.

CONCLUSION

Transscleral diode laser cycloablation is a very effective treatment for the control of intraocular pressure in cases of refractory glaucoma. It can be used in cases of painful blind eye and also in eyes with good visual potential. Like any other procedure diode laser application has its own set of complications, of which scleral perforation is one of the most serious, but a rare complication.

They were apparently no predisposing risk factors in this case. We had previously used the same G probe and power settings on large number of patients, but no complications were seen so scleral perforation in this case was an unexpected finding. Due to this, we recommend regular follow up of the patient in all cases of transscleral diode laser cycloablation, even if there are no pre-op warning signs like thinned out sclera so that complications can be managed timely.

Authors Contribution:
Afshan Ali: Conception/ Study design, Acquisition of data, Manuscript drafting, Given final approval of version to be published

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Case Report **Open Access**

A Rare Renal Twist in Sjögren Syndrome: Type I RTA

Mujeeb ur Rehman, Muhammad Irfan, Shahneela Tabassum, Muhammad Nasir

ABSTRACT

Sjögren's syndrome (SS) is an autoimmune condition that causes chronic inflammatory and degenerative changes in exocrine glands and systemic organs. Rare in adolescents, it often goes undiagnosed due to absent xerostomia, xerophthalmia, or sicca symptoms. Adolescents may initially present with parotitis or systemic organ involvement. We report a 36-year-old woman with recurrent severe hypokalemic episodes since age 21, ultimately diagnosed with type I (distal) renal tubular acidosis (RTA) due to SS. Despite significant hypokalemic paralysis in her background, the diagnosis was delayed as distal RTA is rare in this age group. The diagnosis was confirmed following severe hypokalemia, non-anion gap metabolic acidosis, raised urine anion gap and pH, supported by autoimmune workup. She was successfully managed with potassium and alkali replacement therapy, which stabilized her condition. This case highlights diagnostic challenges of SS when initial symptoms deviate from typical exocrine manifestations.

Key words: Hypokalemia, Renal Tubular Acidosis, Sjögren Syndrome.

How to cite this Article:

Rehman MU, Irfan M, Tabassum S, Nasir M. A Rare Renal Twist in Sjögren Syndrome: Type I RTA. J Bahria Uni Med Dental Coll. 2025;15(2):162-165 DOI: https://doi.org/10.51985/JBUMDC2025509

INTRODUCTION

The inability of the renal tubules to maintain the proper balance of physiologic acid-base is the hallmark of renal tubular acidosis (RTA). It frequently arises from a malfunction in tubular transporters which are involved in the secretion or absorption of certain ions as a result of autoimmune diseases, nephrotoxic medication exposure, diuretic usage, congenital conditions or malignancy (e.g. multiple myeloma). The three primary types of RTA are hyperkalemic or type 4, proximal or type 2 and distal or type 1. All three types of RTA are characterized by anomalies in serum potassium levels (hypo- or hyperkalemia), an alkalotic or acidotic urine pH, a positive urine anion gap, and hyperchloremic non-anion gap metabolic acidosis.

This case report focuses on distal RTA (also known as type 1 or classic RTA), which is further characterized by significant hypokalemia (<3 mmol/L) and an alkalotic urine pH (>5.5). It is frequently brought on by a malfunction in the distal renal alpha-intercalated cells' ability to secrete hydrogen ions. Thus, ionic wasting results from a compromised luminal gradient, which may cause rickets/ osteomalacia, nephrocalcinosis, nephrolithiasis, respiratory failure and muscle weakness. Adolescents with SS may experience distal RTA infrequently, but research has shown that tubulointerstitial nephritis causes abnormalities in distal tubular acidification in a larger percentage of adult patients.[1] The case being reported is of a middle aged lady who came up with hypokalemic periodic paralysis, actually was suffering disease since adolescence, ultimately diagnosed with distal RTA as a cause of hypokalemia and subsequently revealed its association with SS. The patient was successfully treated with potassium and alkali replenishment that led to complete resolution of symptoms and improvement in investigational findings.

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Received: 11-01-25
1st Revision: 19-02-25
Accepted: 03-03-25
1st Revision: 27-02-25

Case Presentation

36 years of age, female, known case of well controlled hypothyroidism, having very significant history of hospitalizations on various occasions in last fifteen years for hypokalemic periodic paralysis, was admitted in hospital for video-assisted thoracoscopy for Empyema thoracis. After few hours of procedure completed, she developed sudden-onset weakness of all four limbs. The patient stated that her symptoms resembled those of her earlier/ previous attacks. Systemic review revealed no signs of syncope, gastrointestinal distress, urinary complaints, joint discomfort and rash, overuse of diuretics or laxatives, suicidal or homicidal thoughts. Family history revealed no ongoing autoimmune

disorders. She denied drinking or smoking. For her probable tuberculosis, the woman was receiving anti-tuberculous medication in addition to her potassium chloride regimen.

Her neurological examination revealed normal bulk, lower limb power of 2/5, upper limb power of 3/5, decreased reflexes, and downgoing plantars. Rest of clinical examination were unremarkable. Her serum sodium was138 mmol / L, potassium 1.8 mmol / L, chloride 112 mmol / L, bicarbonate 14.6 mmol / L and blood pH was 7.26, urine sodium 104 mmol / L, urine potassium 25.12 mmol / L, and urine chloride 99 mmol / L. Urinalysis showed pH of 7.0 without blood or protein (Table 1). Ultrasound KUB revealed bilateral nephrolithiasis. On the ECG, U waves, delayed intraventricular conduction, and sinus bradycardia were observed. She was diagnosed with distal RTA due to hyperchloremic non-anion gap metabolic acidosis and a positive urine anion gap of 30.12. In addition to receiving potassium citrate and sodium bicarbonate, she was hydrated with intravenous normal saline, which resolved her hyperchloremic non-anion gap metabolic acidosis and hypokalemia. Upon her discharge from hospital, she was prescribed with oral potassium citrate and sodium bicarbonate. After three months of treatment, she remained asymptomatic with normal potassium and no acidosis.Before this presentation, she had episodes of acute paralysis on low serum potassium and was treated by general practitioner with IV and oral potassium but was not worked-up. No history of sicca symptoms in past and at present.

Antinuclear antibodies (ANA) (1:388) and anti-Ro / SSA antibodies (SSA - 52: 17.45 U / mL and SSA - 60: 16.28 U / mL) were positive in her autoimmune profile and she was borderline positive for anti-La / SSB. Anti-double-stranded DNA (dsDNA), anti-Smith, and anti-U1-ribonucleoprotein (RNP) antibodies were negative (Table 1). Fanconi syndrome, Bartter syndrome, and Gitelman syndrome were excluded from list of causes for renal tubulopathies. Patient could not be investigated for genetic/ molecular parameters because of financial constraints. A preliminary diagnosis of Sjögren's syndrome (SS) was made in light of a positive autoimmune panel. She now sees a rheumatologist and a nephrologist on a regular basis.

DISCUSSION

Type 1 renal tubular acidosis affects the distal nephron making it unable to lower the pH of urine. It is possibly to inherit or acquire type 1 RTA. Autoimmune conditions such as systemic lupus erythematosus, sarcoidosis and SS are linked to type I RTA.[2] Possible pathophysiological mechanism described to the occurrence of hypokalemic paralysis due to primary SS is based on proposed assumption for presence

Table 1: Laboratory Results of Patient

Laboratory markers	Results	Reference ranges	Values after treatment
Serum Markers			
Sodium	138.0	135 – 145 mmo l /L	
Potassium	1.8	3.5 – 5.0 mmol / L	4.5
Chloride	112.0	95 – 105 mmol / L	98
Bicarbonate	14.6	22.0–26.0 mmol/L	23.6
Urine electrolytes			
pH	7.0	4.5 – 7.8	5.2
Sodium	104.0	< 20 mmol / L	38
Potassium	25.12	< 15 mmol / L	12
Chloride	99.0	14 – 50 mmol / L	64
Anion gap	30.12	< 10 mEq / L	
Venous blood gas			
pH	7.26	7.31 – 7.41	7.37
Autoimmune panel			
ANA	1:388	< 1:80	
Anti-dsDNA	Negative	< 20.0 AU / mL	
Anti-Smith	Negative	< 10 U / mL	
Anti-Ro/SSA-52	17.45	< 10 U / mL	
Anti-Ro/SSA-60	16.28	< 10 U / mL	
Anti-La/SSB	Borderline positive	< 10 U / mL	
Anti-U1-RNP	Negative	< 10 U / mL	

ANA: antinuclear antibody; anti-ds DNA: anti-double-stranded DNA antibody; anti-SSA: anti-Sjögren's syndrome-related antigen A; anti-SSB: anti-Sjögren's syndrome-related antigen B; anti-U1-RNP: anti-U1 ribonucleoprotein antibody

of antibodies against H+-ATPase and carbonic anhydrase enzymatic pumps that lead to a positive urinary anion gap and a urine pH > 5.5.[3] Typically, distal RTA manifests as normal anion gap acidosis and mild hypokalemia. However, the literature has only reported a few number of cases of severe hypokalemia in distal RTA that led to muscle paralysis.[4] Numerous extra-glandular symptoms can accompany SS; two typical renal manifestations are renal tubular dysfunction and tubulointerstitial nephritis resulting in distal renal tubular acidosis.[5] In literature, the rare presentations of distal RTA due to SS has been reported in different ways. Some patients have reported with sicca symptoms while many remain asymptomatic and presents with unusual symptomatology like hypokalemia which is considered most prevalent electrolyte imbalance in distal RTA patients. Chinmaye S et al reported a case that was challenging to be diagnosed as a case of distal RTA due to SS as the hypernatremia masked usual clinical presentation though the reported patient was having hypokalemia and acidosis as well.[6] Therefore, diagnosis SS is challenging particularly when it initially presents with renal rather than exocrine manifestation.

Our patient had recurrent hypokalemic paralysis since adolescence, but the rare distal RTA remained undiagnosed. Hypokalemia rarely results in quadriplegia with imminent respiratory failure, however it can present with polyuria and polydipsia.[7] Hypokalemia may be initial presentation of distal RTA complicated with SS. Meena DS et al also intimated a case with same presentation of hypokalemic paralysis but patient was suffering from dryness of eyes and mouth and further diagnosis was confirmed with positive Schirmer test. [8] In this case severe hypokalemia, non-anion gap metabolic acidosis, raised urine anion gap and pH led to the diagnosis of SS confirmed by autoimmune workup. Diagnosing such cases is challenging, as they often don't meet criteria; our patient lacked sicca symptoms and other diagnostic features.

Despite the fact that muscle weakness has occasionally been reported as an SS presenting characteristic, clinicians rarely initially link muscle weakness with SS because the other factors are taken into consideration when evaluating patients who exhibit muscle weakness. In order to assess the clinical phenotype of primary Sjögren's syndrome (PSS) patients who presented with hypokalemic paralysis, Nahar N et al. performed a retrospective cross-sectional study. They discovered that 61.5% of patients experienced multiple episodes of hypokalemic paralysis, 69% experienced dry eyes, and 23% had inflammatory arthritis and 1 patient had Raynaud's phenomenon, myopathy.[9] Boro H et al described a case series and highlighted that how severe forms of distal RTA have bone mineral disorders that leads to deforming joints and easily breakable bones with minimal traumatic injuries. This results from exaggerated osteoclastic bone resorption due to untreated acidosis in RTA.[10] Our patient had developed hypocalcemia, hypercalciuria and subsequent nephrolithiasis but before bone mineral disorder may have emerged, diagnosis of disease has been made and successfully treated that led to reversal of these parameters.

CONCLUSION

With the current diagnostic criteria, it may be challenging to detect and diagnose SS early, increasing the risk of a missed/ delayed diagnosis. Patients may present with a range of symptoms that differ from the typical presentation of the condition. Most of the times, unusual presentations are overlooked but whenever recurrence of same presentation of symptoms is observed then it is deemed necessary to investigate those thoroughly to reach at exact root cause. Association of presenting symptoms coupled with laboratory and imaging parameters may surface exact pathological disturbance that may guide to ascertain exact cause like in current case. Therefore, to prevent potentially deadly results, patients who develop persistent or recurrent hypokalemia should receive prompt therapy for metabolic abnormalities using potassium and alkali medications and undergo further investigations to rule out SS.

Authors Contribution:
Mujeeb ur Rehman: Conception/ Study design, Acquisition of data, Manuscript drafting, Given final approval of version to be published
Muhammad Irfan: Conception/ Study design, Acquisition of data, Manuscript drafting, Given final approval of version to be published
Shahneela Tabassum: Conception/ Study design, Acquisition of data, Manuscript drafting, Given final approval of version to be published
Muhammad Nasir: Conception/ Study design, Acquisition of data, Manuscript drafting, Given final approval of version to be published

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Case Report **Open Access**

Iatrogenic Calcinosis Cutis

Muhammad Danish, Asma Afzal Kiyani, Sana Sharif, Sarah Khan, Sana Mehmood, Huma Hameed

ABSTRACT

Calcinosis cutis is a condition which occurs due to deposition of calcium salts in the skin and subcutaneous tissue. Various etiologies include dystrophic, metastatic, idiopathic, calciphylaxis, or iatrogenic calcinosis cutis. The type related to our case is iatrogenic calcinosis cutis, and one its possible causes is intravenous calcium infusion.

Case presentation:

First case of 01-month-old baby boy, who was treated with IV calcium gluconate for hypocalcemia and vitamin D deficiency. Later on, he developed treatment-related complication of intravenous(IV) calcium, and was diagnosed with iatrogenic calcinosis cutis.

Second case was of 02 months old baby boy, who was treated with surfactant replacement therapy and IV calcium for respiratory distress syndrome and hypocalcemia. He developed swelling at IV inj site and diagnosed with iatrogenic calcinosis cutis.

Conclusion: Calcinosis cutis has wide differential diagnosis. Treating doctors should be aware of this benign condition when giving IV calcium infusion.

Keywords: Calcinosis cutis, Extra osseous calcification, IV Calcium gluconate

How to cite this Article:
Danish M, Kiyani AA, Sharif S, Khan S, Mehmood S, Hameed H. Iatrogenic Calcinosis Cutis. J Bahria Uni Med Dental Coll. 2025;15(2):167-169 DOI: https://doi.org/10.51985/JBUMDC2025503

INTRODUCTION:

Calcinosis cutis typically arises in individuals due to the abnormal accumulation of calcium salts within the subcutaneous tissues. One contributing factor is the administration of intravenous calcium gluconate or calcium chloride for conditions linked to hypocalcemia. The development of lesions and nodules in calcinosis cutis can occur either slowly and gradually or may progress rapidly and severely[1]. The clinical manifestations can range from localized areas to extensive lesions affecting larger regions. In instances of calcinosis cutis resulting from intravenous calcium treatment, lesions commonly emerge at the site of intravenous access. Calcinosis cutis can be difficult to diagnose and treat because it mimics a lot of other conditions. In addition, calcinosis cutis can also be idiopathic, dystrophic, metastatic, or calciphylaxis[2].

Here, we report two cases iatrogenic calcinosis cutis.

Case 01: A baby boy was admitted on 1st day of life in NICU as baby was observed to have hypoglycemia, hypocalcemic seizures and respiratory distress and was kept in incubator care on low flow nasal oxygen. All essential labs were sent and appropriate antibiotics were started. Baby was monitored for hypoglycemic episode and low calcium levels for which he was placed on inj Calcium gluconate. First CRP was raised and Beta D glucan was also raised, so baby was treated accordingly for sepsis and thrombocytopenia. Oxygen was gradually tapered off. 2D ECHO was done which showed small ASD and closing PDA for which brufen was given. Baby was shifted to cot care and mother handling was done. A swelling was observed in medial aspect of left leg with overlying reddish discoloration of skin with no itchiness, pus discharge. The area exhibited tenderness and felt warm to the touch(Figure-

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Received: 08-01-25 1st Revision: 23-01-25
Accepted: 18-03-25 1st Revision: 26-02-25

1). The patient was afebrile, and all other joints remained unaffected. There was no family history of a similar condition, no consanguinity between the parents, and no prior occurrences of congenital or metabolic diseases within the family. X-ray showed extra osseous calcification in subcutaneous tissues of medial side of left leg. (Figure-2). Repeat X-ray after 04 months showed complete resolution of swelling and calcification in aforementioned area of left leg. (Figure-3).

Figure-1 shows swelling and redness of at medial aspect of the leg

Figure-2 shows subcutaneous extra osseous ossification in left leg

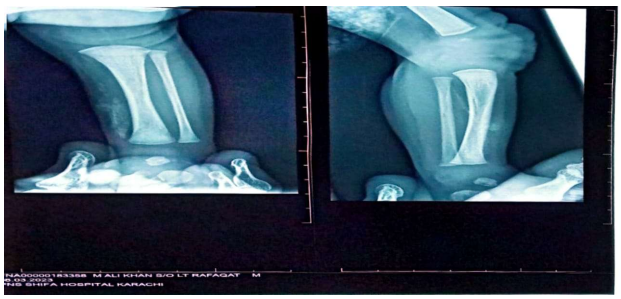
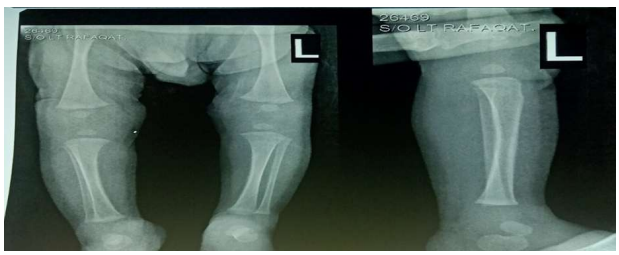


Figure-3 of repeat X-ray after 04 Months shows complete resolution of soft tissue calcification



Case 02: Another patient admitted in NICU for neonatal respiratory distress. He was admitted for 4 weeks. Vascular access was done at right leg for IV fluids and IV injections. He developed swelling, redness over lateral aspect of right leg. On X-ray, there was soft tissue swelling and calcification of right lower lateral aspect of leg without intra osseous extension (Figure-4). Repeat x-ray was done which showed complete resolution of soft tissue swelling and calcification (Figure-5).

DISCUSSION:

Iatrogenic calcinosis cutis refers to an illness which occurs due to deposition of calcium in soft tissues following the

Figure-4 shows subcutaneous soft tissue extra osseous calcification of lateral aspect of leg

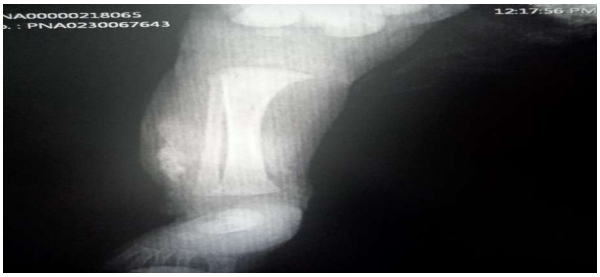
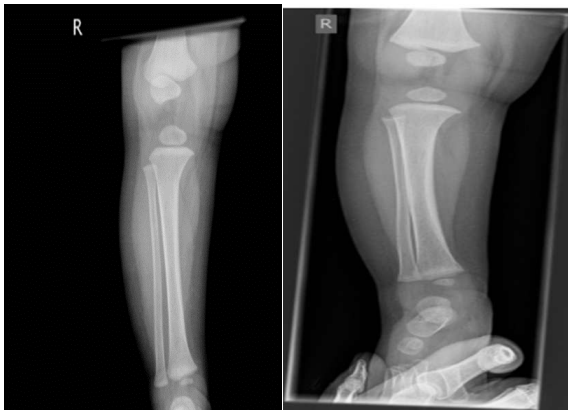


Figure-5 Repeat X-ray after 3.5 Months-Complete disappearance of soft tissue calcification



IV administration of calcium. It occurs due to extravasation of calcium in soft tissues and associated tissue damage leading to localized skin thickening, erythema, pain and tenderness[3]. Broadly, Calcinosis cutis refers to deposition of calcium in soft tissues of the skin and iatrogenic (therapy related) calcinosis cutis is one of the other etiologies, which include certain connective tissue disorder, soft tissue injury, malignancy, and elevated Ca++ and phosphate levels. Initial symptoms include swelling at IV inj access site with overlying reddish discoloration of skin, associated tenderness and warm sensation. Generally, there is no associated itchiness or pus discharge. These findings initially seem to be soft tissue infection; however, afebrile and focal area of involvement at IV inj site help in making a diagnosis and treatment of this benign therapy related complication while excluding other etiologies. Most of the patients of iatrogenic calcinosis cutis usually have fresh history of hospitalization. Other causes of iatrogenic calcinosis include tumour lysis syndrome or numerous heel sticks in infants[4].

Autoimmune connective tissue disorders lead to dystrophic calcinosis cutis, which represents the most prevalent form of calcinosis cutis, accounting for 70% of all the cases[5]. Additionally, a severe variant of calcification, known as calciphylaxis, arises in patients with end-stage kidney disease. It causes arteriolar calcification and ischemic skin necrosis due to luminal narrowing and thrombosis[6]. Certain skin disorders such as scleroderma and dermatomyositis can also cause calcinosis cutis may be due to delay in starting the

treatment or the severity of the disease itself[7,8]. Imaging or fine-needle aspiration cytology (FNAC) can aid in diagnosis. X-ray findings include subcutaneous soft tissue swelling and calcific foci at IV inj site. Bone scan will show increased tracer uptake at affected site[9]. The differential diagnosis should encompass infection, thrombophlebitis, arthritis, periostitis. Multidisciplinary team approach to diagnosis and management is essential for achieving improved outcomes[10]. A case of neonatal calcinosis cutis who developed swelling at IV inj site with calcium gluconate infusion. The symptoms resolved with conservative management, as in our reported cases, with wound care only[11]. A patient with chronic kidney disease(CKD) undergoing long-term dialysis, experienced iatrogenic calcinosis cutis as result of low molecular weight heparin administration. Symptoms were resolved following successful medical treatment[12]. Diagnosis in CKD patients can be aided by laboratory tests of parathyroid hormone, vitamin D, phosphate, calcium, and renal function. A case of 23 years old female with subcutaneous calcification[13] and another case is of an infant[14], developed multiple subcutaneous tender nodules (of calcinosis cutis) in subcutaneous tissues at different sites after IV calcium gluconate for hypocalcemia. Wound care, discontinuation of IV calcium gluconate and short term follow up lead to complete resolution of subcutaneous nodules. Iatrogenic calcinosis cutis is a benign condition and most of the patients are managed conservatively with proper wound care and follow up (radiography at each visit, laboratory investigation of calcium, parathyroid hormone, phosphate, and vitamin D levels)[14]. Other treatment options include medical and surgical treatment depending upon the size of the lesion (smaller lesions are managed surgically and larger lesions are managed medically) and treatment of specific etiology[15].

CONCLUSION:

The disorder known as iatrogenic calcinosis cutis is benign. In order to rule out other potential etiologies and make a diagnosis, a thorough history and clinical examination are crucial. Regular and thorough examination of the intravenous line site and intravenous calcium dilution lower the risk of extravasation, enable early diagnosis, and avoid needless testing and treatment.

Authors Contribution:
Muhammad Danish: Substantial contributions to conception and design along with acquisition of data.
Asma Afzal Kiyani: Acquisition, analysis and interpretation of data
Sana Sharif: Revising it critically for important intellectual content
Sarah Khan: Drafting the article, contributions to analysis and interpretation of data
Sana Mehmood: Acquisition, analysis and interpretation of data
Huma Hameed: Acquisition, analysis and interpretation of data

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1. Abstract:

It should have no more than 150 words for unstructured abstracts or 250 words for structured abstracts. The structured abstract should include:

1) Objective, 2) Study design and setting, 3) Methodology, 4) Result and 5) Conclusion.

[state the purpose of the study (objective), basic procedures (methodology with study design, subjects/animals, place & duration of study, drug/chemical/equipment, procedure or protocol), main findings (results) and conclusion (It should emphasize new and important aspects of the study.)]

Below the abstract provide, 3-10 key words that will assist indexers in cross-indexing the article. The key words should be in alphabetical order.

2. Introduction:

State the purpose of the article and summarize the rationale for the study. Give only strictly pertinent references and do not include data or conclusions from the work being reported. At least 10 to 12 references should be included in the introduction. International and national literature review indicating the rational and objective of the study.

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This section should include a statement indicating that the research was approved by independent local or regional or national review body(eg. Ethics committee, institutional review board) with ERC number. Clearly describe the type of study, selection of observational or experimental participants, including eligibility and exclusion criteria and a description of source population. Identify the age, gender and other characteristics of subjects. Mention the sample size and how it is calculated and the sample technique. Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. For randomized clinical trials provide information on all major study elements, including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization, concealment of allocation to treatment groups), and the method of masking (blinding). Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract. Describe statistical methods with enough detail to enable a knowledgeable person with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Define statistical terms, abbreviations, and most

symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

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Present your results in logical sequence in the text, tables, and illustrations according to the objective of the study. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Describe appropriate indicators of measurement error or uncertainty such as confidence intervals, P values. Report complications of treatment and dropouts from a clinical trial. Specify any general-use computer programs employed for analysis.

5. Discussion and Conclusion:

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6. Acknowledgment:

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The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4

c) No author given:

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d) Chapter in a book:

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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),
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