EISSN 2667-6370

Turkish Journal of Anaesthesiology & Reanimation

Volume 53 • Issue 5 • October 2025

Official journal of the TURKISH SOCIETY OF ANAESTHESIOLOGY AND REANIMATION

galenos Publishing House

turkjanaesthesiolreanim.org

Turkish Journal of Anaesthesiology & Reanimation

Turkish Journal of Anaesthesiology & Reanimation

Turkish Journal of Anaesthesiology & Reanimation

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Publishing Date: October 2025
E-ISSN: 2667-6370
International scientific journal published bimonthly.

Turkish Journal of Anaesthesiology & Reanimation

Please refer to the journal's webpage (**https://turkjanaesthesiolreanim.org/**) for "Ethical Policy", "Instructions to Authors" and "Instructions to Reviewers".

The editorial and publication process of the Turkish Journal of Anaesthesiology and Reanimation are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing. Turkish Journal of Anaesthesiology and Reanimation is indexed in **PubMed Central, Web of Science - Emerging Sources Citation Index, Scopus, DOAJ, TUBITAK ULAKBIM TR Index, China National Knowledge Infrastructure (CNKI), EMBASE, EmCare, CINAHL, ProQuest** and **Gale**.

The journal is published online.

Owner: Prof. Jülide Ergil on behalf of the Turkish Anesthesiology and Reanimation Association

Responsible Manager: Zekeriyya Alanoğlu

Turkish Journal of Anaesthesiology & Reanimation

Contents

Turkish Journal of Anaesthesiology & Reanimation

DOI: 10.4274/TJAR.2025.252257

Editorial

Editorial Comment

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):185-186

The Present and Future of Regional Anaesthesia in Türkiye

Serkan Tulgar[1], Alper Kılıçaslan[2], Özlem Selvi Can[3], Zekeriyya Alanoğlu[4]

[1]Bahçeşehir University Faculty of Medicine, Göztepe Medical Park Hospital, Department of Anesthesiology and Reanimation, İstanbul, Türkiye
[2]Necmettin Erbakan University Faculty of Medicine, Department of Anesthesiology and Reanimation, Konya, Türkiye
[3]Ankara University Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Türkiye
[4]Washington University in St. Louis, School of Medicine, Department of Anesthesiology St. Louis, United States

Cite this article as: Tulgar S, Kılıçaslan A, Selvi Can Ö, Alanoğlu Z. The present and future of regional anaesthesia in Türkiye. *Turk J Anaesthesiol Reanim.* 2025;53(5):185-186.

Editorial

In examining the current position of regional anaesthesia in Türkiye, this comprehensive study provides insights on several distinct levels: from the practitioners' perspective, it delineates the preferences of colleagues across different age groups and the distribution of these choices within diverse institutions. From the vantage point of practice, it highlights the breadth of techniques and the nuances of case-based selection, and finally, from the patients' perspective, the study brings into focus the reasons for refusal, age-related patterns, and the spectrum of complications. This editorial draws on the paper by Kanat et al.1 published in this edition of the Turkish Journal of Anaesthesiology and Reanimation, to present these dynamics in greater depth and to contextualize them within the broader evolution of regional anaesthesia practice. In light of these findings, it is our endeavor to elevate the discourse on regional anaesthesia to a higher plane.

In the last decade, regional anaesthesia has undergone a global transition from neuraxial techniques to peripheral approaches, moving beyond plexus blocks toward the interfascial blockade of the most distal terminal branches. In Türkiye, this trend has gained exceptional momentum, driven by Turkish scholars whose unwavering focus on regional anaesthesia has propelled the field with remarkable force. Across every tier of our healthcare system, anesthesiologists of all generations have gained hands-on experience with fascial plane blocks, and many have subsequently contributed their insights to the academic reservoir, further enriching the collective knowledge of the discipline. It is, however, apparent that regional anaesthesia in pediatric patients and the use of catheters in regional anaesthesia remain underutilized. We particularly wish to encourage our colleagues to advance practice and research in these areas, always with the proviso that appropriate safeguards and a secure clinical environment are in place.

While reporting techniques and studies in regional anaesthesia that capture the current state of the art and at times even surpass the average, it is crucial for Turkish anesthesiologists, whether publishing in our journal or in other esteemed international outlets, to exercise meticulous attention to prospective clinical trial registration and proper sample size calculation. To minimize practices that may undermine scientific credibility and to avoid irreparable methodological errors, we strongly encourage colleagues to seek mentorship from seasoned academics who have already advanced along this path. For practicing anesthesiologists who may not be directly engaged in research, the significance of their daily clinical choices should not be underestimated. The cumulative expertise gained in routine practice, whether in the breadth of block applications or in the vigilance toward patient safety, constitutes

Corresponding author: Prof. Alper Kılıçaslan, e-mail: dralperkilicaslan@gmail.com

Received: October 03, 2025 Accepted: October 07, 2025
Published date: October 14, 2025

the very foundation upon which academic progress is built. We therefore encourage all colleagues, regardless of their academic involvement, to recognize the value of their practice and to share their insights whenever possible.

In this way, regional anaesthesia in Türkiye not only reflects global currents but also stands poised to shape its future trajectory.

Reference

1. Kanat E, Çağıran Z, Sertöz N. The Application of regional anaesthesia in Türkiye: national survey study. Turk J Anaesthesiol Reanim. 2025. [CrossRef]

DOI: 10.4274/TJAR.2025.241739

Review Article
Other

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):187-196

The Role of microRNA in Anaesthetics-induced Brain Injury: A Narrative Review

Elvan Öçmen[1], Bilge Karaçiçek[2], Burak İbrahim Arıöz[2], Hale Aksu[1], Şermin Genç[3]

[1]Dokuz Eylül University Faculty of Medicine, Department of Anaesthesiology and Reanimation, İzmir, Türkiye
[2]Dokuz Eylül University, İzmir Biomedicine and Genome Center, İzmir International Biomedicine and Genome Institute, İzmir, Türkiye
[3]Dokuz Eylül University Health Sciences Institute, İzmir Biomedicine and Genome Center, Department of Neuroscience, İzmir, Türkiye

Cite this article as: Öçmen E, Karaçiçek B, Arıöz Bİ, Aksu H, Genç Ş. The role of microRNA in anaesthetics-induced brain injury: a narrative review. *Turk J Anaesthesiol Reanim.* 2025;53(5):187-196.

Abstract

Anaesthetics are commonly used agents during medical interventions and surgeries. Exposure to anaesthetic agents in late intrauterine life or early childhood may cause neurodegeneration in developing brains. Neuroapoptosis and neural inhibition provided by several mechanisms and microRNAs (miRNAs) have crucial roles in this milieu. miRNAs have critical roles in response to anaesthetic exposure. Through this review, we performed a systematic search of the PubMed database for studies on the role of anaesthetics in the brain and their relation with miRNAs. The terms "anesthetic", "miRNA", and "brain" were searched. Here we summarized the roles and interactions of miRNAs under exposure to anaesthetics *in vivo* and *in vitro* studies. Anaesthetic agents studied included sevoflurane, isoflurane, ketamine, and propofol. Many microRNAs were identified to have regulatory roles in anaesthesia-induced neurotoxicity. The literature study supports the idea that miRNAs play crucial functions in neuroprotection and neurotoxicity in anaesthesia administration. The exact role and implication of miRNA in anaesthesia neurotoxicity needs to be elucidated to gain more knowledge about the area. Several gaps in knowledge should be filled by conducting basic, clinical, and translational analyses in the future to decipher the definite role of miRNAs and their functions in the context of anaesthesia-induced neurotoxicity.

Keywords: Anaesthesia, anaesthetic agents, miRNA, neurotoxicity

Main Points

- Anaesthetics cause microRNA (miRNA) expression changes in the brain.
- The exact mechanism of anaesthesia-induced neurotoxicity is still not certain. This review summarizes the miRNA expression changes that can be related to anaesthesia-induced neurotoxicity.
- miRNAs are not only related to neurotoxicity. Their expression changes can also result in the neuroprotection, addictive, and antidepressant properties of anaesthetics.
- It is too early to say which miRNA changes its expression after anaesthesia. But further studies and analysis may highlight one or a couple miRNAs related to anaesthesia-induced neurotoxicity. These could be the therapeutic candidates for neuroprotection.

Introduction

Globally, over 300 million surgical operations and diagnostic or interventional tests that require anaesthesia or sedation occur annually. Recent evidence suggests that anaesthetics may cause neurodegeneration in the brain. In this review, our primary goal was to search for articles related to the role of microRNAs (miRNAs) in anaesthesia-induced neurotoxicity (AIN) and our secondary goal was to summarize articles about anaesthesia and miRNA changes in the brain.

In this study, we searched the PubMed database for studies on the role of anaesthetics in the brain and their relationship to miRNAs. The search was conducted in April 2022. The search terms were "anesthetic and miRNA and brain", "miRNA", and "brain". Articles were screened by the authors to exclude duplicates and those that

Corresponding author: Prdf. Elvan Öçmen, e-mail: elvan.sahin@gmail.com

Received: September 04, 2024 Accepted: January 14, 2025
Epub: May 08, 2025 Published date: October 14, 2025

did not meet the inclusion criteria. The inclusion criteria was the articles about anaesthetics and miRNAs in the brain. The exclusion criteria were abstracts, conference lectures, case reports, reviews, biographies, and editorials. In addition, articles not published in English, those for which full texts were not available, and those not related to the brain were excluded. Data regarding the miRNAs involved, their expression status, and their roles in AIN were retrieved (Figure 1). This study aimed to identify miRNAs and their pathways associated with AIN. This review highlights possible mechanisms and miRNAs involved in AIN. This will help researchers to design future studies on this topic and to study possible protective agents.

miRNA

miRNAs are small RNA molecules with a length of 19-25 nucleotides. Their main function is to regulate gene expression post-transcriptionally, and one miRNA can interact with hundreds of mRNAs.[1] The first miRNA was discovered in 1993 by Lee et al.[2] It has been shown that a smaller RNA product may bind to several sites of the 3′ untranslated region (UTR) of LIN-14 mRNA and mitigate LIN-14 protein expression without affecting its mRNA levels.[2]

miRNA Biogenesis

Canonical miRNA biogenesis begins with the transcription of miRNA genes into primary miRNAs (pri-miRNAs) by RNA polymerase II. Then, pri-miRNA is cleaved into a precursor RNA, 70-120 nucleotides in length, by microprocessor, a multiprotein complex containing the ribonuclease enzyme Drosha and the RNA-binding protein DiGeorge syndrome critical region 8 (DGCR8). Newly produced pre-miRNAs are transported into the cytoplasm by exportin 5, which is a Ran-dependent nuclear transport receptor protein. Pre-miRNAs mature into 19-25 nucleotide-long duplex miRNAs by removing the terminal loop with Dicer-1, an RNase III enzyme. Duplexes are then separated, and mature miRNAs may interact with Argonaute proteins to form an RNA-inducing silencing complex, which can bind to the 3′ UTR of mRNAs and exert a silencing effect.[1]

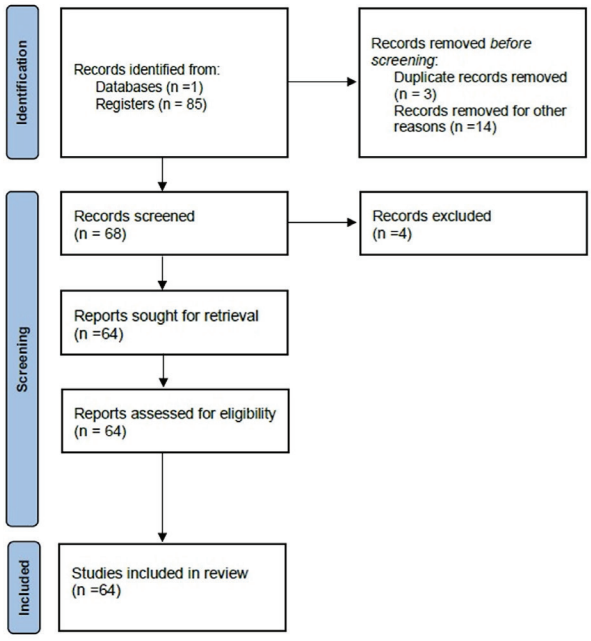

Figure 1. Study selection

Role of miRNAs in Brain

miRNAs are found in the human brain and have distinct functions. They contribute to development, physiological functions, and human cognition by regulating transcription in specific regions of the brain.[3] miR-124, one of the most abundant miRNAs in the brain, affects neural lineage differentiation by downregulating multiple mRNAs. Several studies have demonstrated that miRNAs show expression changes in many neurological diseases such as autism spectrum disorders, schizophrenia, frontotemporal dementia, Alzheimer's disease, Parkinson's disease, and neuropsychiatric diseases.[3] Discovering miRNA-mRNA interactions in the brain may shed light on drugs that affect the central nervous system, such as anaesthetics.

Sevoflurane

Sevoflurane is a commonly used inhalational anaesthetic, particularly during pediatric induction. Animal studies have widely reported sevoflurane-induced neuroapoptosis and cognitive dysfunction, especially during the brain growth spurt. The exact mechanism of sevoflurane-induced neurotoxicity (SIN) is unclear. In recent years, the roles of miRNAs and long non-coding RNAs (lncRNAs) in SIN have been studied. The hippocampus is the most studied part of the brain because it is closely associated with SIN.

Sevoflurane *in vitro* Studies

To investigate SIN and the role of miRNAs, E14 mESCs, primary neuron culture, SH-SY5Y neuroblastoma cells, NSC culture from neonatal rat hippocampus, and HN-h, HCN-2, and HEK293 cell lines were used. In these studies, let-7a, miR-27a-3p, miR-188-3p, miR-183, hsa-miR-302e, miR-34a, miR-19-3p, miR-101a-3p, miR-133a, miR-410-3p, miR-214, and miR-128-3p expression were investigated. Except for miR-410-3p, the expression of all miRNAs studied *in vitro* increased after sevoflurane exposure. Changes in miRNA expression inhibited self-renewal, proliferation, and differentiation and they induced apoptosis and neuroinflammation. *Lin-28, PPAR-δ, MDM2, Sox2, BDNF, OXR1, Wnt1, CCNA-2, CXCR5, Sox1, Peg13*, and *Sox13* were the target genes of miRNAs *in vitro* studies.[4-14] A decrease in the expression of lncRNAs Gm15621 and Rik-203 was found to be related to SIN.[11,15]

Sevoflurane *in vivo* Studies

Eight microarray studies investigated changes in miRNA expression after sevoflurane anaesthesia. Five of these studies used rats. Of these, three focused on the hazardous effects of sevoflurane on children. therefore, they involved 7-day-old (P7) rats in the study, while two studies included adult rats. Two studies included P7 mice, and the newest microarray study chose P5-6 Rhesus monkeys so the Rhesus monkeys can reflect the miRNA changes in the mammalian brain. Although the concentration of sevoflurane was similar between studies (1.9-2.5%), the duration of anaesthesia varied between two and eight hours. The exact duration of anaesthesia for SIN is not clear, but a longer anaesthesia time could be closely related to neurotoxicity. Therefore, the duration of anaesthesia may be associated with changes in the expression of different miRNAs. Brain sections that have been investigated for miRNA expression are essential for understanding miRNAs' role in brain function. Six of the eight microarray studies used the hippocampus, which is closely related to learning and memory disturbances, for miRNA expression. One study selected the left cortex, while another investigated the frontal cortex. The timing of analysis after anaesthesia can result in the detection of different miRNA expression changes. Lin et al.[16] showed this in their study. They found that the expression changes of only three miRNAs in the whole brain and four miRNAs in the hippocampus persisted for 2-4 months after sevoflurane anaesthesia. The exact time interval for the transient changes in miRNAs is unknown; therefore, after a few hours, some of the miRNA expression may return to normal. In addition to these methodological differences in microarray studies, changes in miR-125b-5p expression were observed in four studies.[17-20] Also, differential expression of miR-129-3p[16,17] and miR-448[18,21] has been detected in more than one study after sevoflurane anaesthesia.

Other studies on this topic chose miRNAs that are known to be related to brain function or neurodevelopment and analyzed their expression. Studies have shown that sevoflurane exerts differential effects on miRNAs. However, it can increase the expression of some miRNAs and decrease the expression of others. In a previous study, lncRNA Rik-203's target miR-4661-3p was investigated in P6 mice, but the researchers could find no change in the expression of miRNA after sevoflurane anaesthesia.[11] In contrast, Su et al.[12] showed that sevoflurane could decrease miR-410-3p expression and cause apoptosis. Another study chose the target miR-133a of lncRNA Gm15621 and found that its expression increased with increasing concentrations of sevoflurane.[15] LncRNA Rik-203 and its target miR-101a-3p were investigated. After sevoflurane anaesthesia, expression of miR-101a-3p was increased, while the expression of Rik-203 decreased.[11] Zhao et al.[10] investigated the miRNAs that bind to Cyclin A2 protein, which is downregulated after sevoflurane anaesthesia, showing that miR-19-3p was increased. Zhao et al.[9] investigated the role of miR-34a in cortical development and found that inhibition of the miRNA decreases SIN. Another study showed that an increase in miR-96 expression is related to apoptosis after sevoflurane anaesthesia.[22] A high concentration of sevoflurane (4.8%) was found to be related to increased expression of miR-183, resulting in SIN.[6] Wang et al.[6] reported that increased expression of miR-188-3p in the hippocampus is related to sevoflurane-induced apoptosis. Likewise, increased expression of miR-27a-3p[5] and miR-27b[23] induces SIN via different pathways. In addition, a recent study showed that increased expression of miR-214[13] plays a role in SIN. Unlike these studies, Shan et al.[24] showed that decreased expression of miR-30a, miR-31, miR-190a, and miR-190b is related to SIN in old rats.

SIN Related Pathways

Many pathways have been implicated in SIN; therefore, different pathways related to miRNAs have been investigated. One of the most investigated genes is brain-derived neurotrophic factor (BDNF), which plays an important role in neural differentiation.[7,10,11,13,18]

Another commonly studied gene family is the Sox family, which plays a crucial role in cell renewal and differentiation.[7,11,25] Neuroinflammation is one of the attributed reasons for SIN. miR-410-3p,[12] miR-101a-3p,[11] and miR-27a-3p[5] are the miRNAs found to be related to SIN through neuroinflammation. Other studied pathways include the WNT signaling pathway,[9,26] phosphatidylinositol 3-kinase (PI3K) and protein kinase B signaling pathway,[12] insulin-like growth factor 1,[22] KEGG pathway,[16] MDM2-p53 pathway,[6] and LIMK1.[23]

SIN Related Learning Memory and Function

Learning and memory tests are ways to observe the SIN's clinical expression and evaluate cognition. The Morris Water Maze (MWM) is the most common learning and memory test, in which an experimental animal learns to locate the swimming platform in a tank filled with water. Sun et al.[26] used MWM and showed that the WNT signaling pathway is the most strongly associated pathway to sevoflurane-induced cognitive dysfunction. Another study found a relationship between miR-410-3p and decreased latency time, and increased platform crossing in MWM after sevoflurane anaesthesia.[12] Similar to these studies, the link between miRNAs and sevoflurane-induced cognitive dysfunction has been investigated using MWM.[5,6,9,10,22,23] Zhao et al.[10] showed that the upregulation of miR-19-3p is associated with sevoflurane-induced learning and memory deficit, using the plus-maze discriminative avoidance task to demonstrate this association. Fujimoto et al.[18] reported that sevoflurane anaesthesia could cause subsequent behavioral disorders at open field tests and contextual and cued fear conditioning tests by increasing rno-miR-632.

SIN Related Concentrations in Neurotoxicity

The sevoflurane concentration used in these experiments is usually 1 MAC (2-3%), and the duration of anaesthesia varies between one-six hours.[12,13,16-21,24,26] These studies proved that even a relatively short duration of sevoflurane anaesthesia can cause SIN in an experimental setting. Studies that used repeated doses of sevoflurane anaesthesia (1 MAC for 2 hours over 3 consecutive days) also showed changes in the expression of miRNAs in the brain, resulting in SIN.[5,9,11,25,27] Only one study failed to show miRNA expression change with 0.5 and 1 MAC sevoflurane, while 4.8% sevoflurane increased miR-183 expression.[6]

miRNAs in Neuroprotective Role of Sevoflurane

In addition to its neurotoxic effects, sevoflurane exhibits neuroprotective properties under certain conditions. Shi et al.[28] showed that sevoflurane preconditioning decreases the injury of cerebral ischemia by attenuating the upregulation of miR-15b. Similarly, Zhong et al.[29] and Ding et al.[30] reported the protective effect of sevoflurane on cerebral ischemia by altering the expression of miR-203 and miRNA-490-5p, respectively. Studies in glioma cell cultures have found that sevoflurane can suppress the proliferation, migration, and metastasis of glioma through miR-637,[31] miR-124-3p,[32] miR-146b-5p,[33] miR-761,[34] miR-34a-5p,[35] and miR-7.[36]

Isoflurane

Isoflurane is an inhalational anaesthetic, many experimental studies demonstrated that it could cause apoptosis, neurotoxicity, and learning-memory deficits. Rapidly proliferating and aged neurons are particularly vulnerable to the neurotoxic effects of isoflurane. Since the hippocampus is closely related to learning and memory, it is one of the most studied brain regions.

Isoflurane *in vitro* Studies

Zhang et al.[37] showed that isoflurane treatment represses the self-renewal of E14 embryonic stem cells through the mechanism involving miR-9's direct target, E-cadherin. A study using hippocampal cell culture found that miR-448 increased after isoflurane anaesthesia, resulting in an increase in Bcl-x, a decrease in caspase-3, which causes neuronal apoptosis.[38] Yang et al.[39] reported that isoflurane can cause neuroapoptosis by decreasing miR-124 and BDNF in primary hippocampal neuron culture. Similarly, the increase in miR-142-5p expression after isoflurane was related to the inhibition of cell viability.[40] The PTEN/PI3K/Akt pathway was investigated in a human neuroblastoma cell line, and the authors found that the decrease in miR-214 resulted in neuroapoptosis through this pathway.[41]

Isoflurane *in vivo* Studies

In a miRNA microarray study, the hippocampus, was investigated after isoflurane anaesthesia. The authors found that 21 miRNAs increased in expression and 17 miRNAs decreased. They also showed that four miRNAs (miR-146a, miR-9, miR-143, and let-7d) are associated with learning memory deficits in the MWM. Additionally, they reported a relationship between downregulation of let-7d and increased amyloid-β expression.[42] Shan et al.[24] showed that a decrease in miR-30a, miR-31, miR-190a, and miR-190b expression in the hippocampus and mPFC is related to neuroapoptosis and impaired recognition and spatial memory. Similar to these two studies, it was shown that an increase in miR-448 expression in aged rats was related to learning and memory deficits and neurotoxicity.[38]

A study found that isoflurane decreased miR-124 expression in the hippocampus, increased EGR1, and caused learning-memory deficits and neuroapoptosis by increasing pro-apoptotic factors (cleaved-caspase-3 and Bax) and decreasing the anti-apoptotic factor Bcl-2 in neonatal rats.[39] Two other studies found an increase in miR-142-5p[40] and miR-191[43] expression in the hippocampus. Li et al.[43] showed that BDNF was the target gene of miR-191, whose increased expression results in neurotoxicity and learning-memory deficits.

Li et al.[44] showed that overexpression of miR-24 decreases oxidative stress-related molecules such as superoxide dismutase, glutathione peroxidase and catalase, and neuroapoptosis *in vivo* and *in vitro*.

Whitaker et al.[45] investigated the miRNA expression changes in female and male piglets' hippocampi after isoflurane anaesthesia. Although they did not find a relationship between miRNA levels and isoflurane-induced neurotoxicity, they reported that there was no significant difference in miRNA expression between sexes. In addition to other isoflurane-related neurotoxicity studies, Fan et al.[46] studied diabetic rats and found that miR-140-5p expression increased and caused neuroapoptosis through its target SNX12. In a study investigating the anaesthetic mechanism of isoflurane, the authors showed that among miRNAs, hsa-miR-17-5p had the highest expression level after isoflurane anaesthesia in the cortex. When they investigated sensory perception-related genes, they found that hsa-miR-16-5p, hsa-miR-424-5p, and hsa-miR-497-5p were the miRNAs with the highest expression changes after isoflurane exposure. The authors concluded that the mechanism of isoflurane anaesthesia could be related to the expression changes in miRNAs and related genes.[47]

Ketamine

Ketamine is commonly used in pediatric surgery. In long-term exposure, ketamine causes hippocampal apoptosis and damages learning memory functions.[48] Many studies have been conducted to understand the role of ketamine administration in neurotoxicity and miRNA interactions.

Ketamine *in vitro* Studies

The functions of miR-107, miR-375, and miR-206 were investigated *in vitro*. Ketamine upregulates the

aforementioned miRNAs, resulting in apoptosis, neurite degeneration, and neural death. Subsequently, the targeted miRNAs were downregulated via a lentiviral system, and the downregulation of miRNAs protected against ketamine-induced neural cell death and neural toxicity. In addition, BDNF was found to be a target gene for miRNAs.[48-51] In addition, ketamine downregulated the expression of miR-221-3p and attenuated IFN-α-stimulated NF-κB activation in human astrocytes (HA1800 cells).[52]

Ketamine *in vivo* Studies

In miRNA microarray studies, the expression profiles of the hippocampus and prefrontal cortex, have attracted interest under *in vivo* conditions. miR-331-5p, miR-496-5p, miR-206, miR-98-5p, miR-148a-3p, miR-128-3p, miR-448-3p, miR-764-5p, miR-1264-3p, miR-1298-5p, and miR-1912-3p were differentially expressed in the miRNA microarray profiles.[53,54]

Memory performance and cognitive function tests were performed for *in vivo* cognitive examination to understand the role of miRNAs in ketamine-induced neurotoxicity in the hippocampus. miRNAs overexpressed under ketamine exposure, which cause neuronal injury, were downregulated, or silenced to reverse neuronal injury. Inhibition of miR-124 enhances memory impairment in mice. In adolescent rats, the downregulation of miR-214 results in learning memory impairment. Downregulation of miR-34c improves memory in mice. Downregulation of miR-137 causes significant memory impairment, whereas overexpression of miR-137 rescues memory loss. miR-34a inhibition leads to enhanced memory impairment.[49,55-58]

The role of miRNA in Antidepresant Effect of Ketamine

Ketamine has a remarkable and persistent antidepressant effect . A study showed that miRNA-206 might be a therapeutic target for the antidepressant effects of ketamine.[59] Another study found that ketamine resulted in increased expression of miR-98-5p, and downregulation of miR-98-5p resulted in a decrease in the antidepressant effect of ketamine in a mouse model.[60] One study investigated the alteration of miR-29b-3p in rat brains. A significant increase in miR-29b-3p expression was observed in the prefrontal cortex of normal rats after ketamine exposure. Recombinant adeno-associated virus-mediated overexpression of miR-29b-3p resulted in recognizable relief of depressive behaviors in rats and lower expression of metabotropic glutamate receptor 4 (GRM4).[61] After administration of an antidepressant dose of ketamine, the miRNAs 448-3p, 764-5p, 1264-3p, 1298-5p, and 1912-3p clusters were upregulated.[62]

The role of miRNA in Ketamine Addiction

The hippocampus is a critical area in the brain involved in addiction. Li et al.[63] showed hippocampal miR-331-5p was significantly decreased in the ketamine group, and upregulated in the ketamine+rhynchophylline group. In conclusion, miR-331-5p was found to be an important regulator of Nurr1, and rhynchophylline is involved in ketamine addiction, via the miR-331-5p/Nurr1/BDNF pathway or the inhibition of CREB phosphorylation.

The role of BDNF Signaling in miRNA Alteration in the Brain by Ketamine

BDNF is a common target gene of miRNAs. Mir-107 inversely regulates BDNF. siRNA-mediated BDNF inhibition, reversed the protective effect of miR-107 downregulation on ketamine injury.[48] Similarly, ketamine upregulated hsa-miR-375 and downregulated BDNF. BDNF is inversely regulated by ketamine-induced neural cell death and toxicity in hESC-derived neurons.[51] miR-206 overexpression improved ketamine-induced upregulation of BDNF. This indicates that miRNA-206 may be a therapeutic target for the antidepressant effects of ketamine.[59] miR-206 is the target for KCNQ1OT1 and downregulates its expression level, indirectly increasing the expression level of BDNF, and thus has a protective role in neural injury.[50]

Propofol

Propofol (2,6-diisopropyl phenol) is a common sedative/anaesthetic.[64] Propofol acts rapidly and has antiemetic properties.[65] Aside from its sedative use, propofol is used in the management of refractory status epilepticus.[66] Both advantageous and harmful effects of propofol via miRNAs have been reported in this context.

Propofol *in vivo* Studies

An important miRNA that has caught the attention of researchers is miR-34a. Inhibition of miR-34a ameliorated propofol-induced impaired learning and memory function, as well as apoptosis, in Sprague-Dawley rats.[67] In another study, it was demonstrated that propofol increased neuronal injury in the hippocampus of rats via miR-34a expression, and dexmedetomidine mitigated injury by targeting SIRT1 and PI3K/Akt signaling.[68] Propofol injections in seven-day-old Sprague-Dawley rats resulted in miR-132 expression downregulation and a reduction in dendritic spine density in the hippocampus, and thus, impairment of learning and memory.[69] Wang et al.[70] verified that propofol caused elevated neurocyte damage by diminishing circRNA001372 levels while augmenting IL-1B, IL-6, IL-17, and IL-18. Subsequently, miR-148b-3p, an antagonist of circRNA001372, reversed the possible protective effects of circRNA001372. Propofol was shown to decrease inflammation through the miR-145-3p/NFATc2/NF-κB pathway.[71]

Propofol *in vitro* Studies

Several *in vitro* studies have demonstrated a highly intertwined relationship between propofol and Rno-

miR-665. After propofol treatment, Rno-miR-665 was upregulated in primary astrocyte cultures, and it represses BCL2L1; therefore, neuroprotection was decreased.[72-75] Li et al.,[67] proved that propofol enhanced miR-34a levels with subsequent neurotoxicity, and inhibition of miR-34a rescued negative effects through the MAPK/ERK pathway. A study stated a protective role of propofol. It inhibited pro-inflammatory factors such as NO, TNF-α, and IL-6 via mitigating miR-155 expression, which targets SOCS1.[76] In addition, propofol inhibited proinflammatory microglia activation via miR-221 and miR-222 downregulating IRF2 in BV2 microglia.[77] miRNA profile screening of primary microglia suggested that propofol inhibited LPS-induced pro-inflammatory responses through the miR-106/Pi3k/Akt pathway.[78] Propofol mitigated cerebral ischemia/reperfusion injury by downregulating MALAT1 and upregulating miR-182-5p.[79] Moreover, propofol alleviates cerebral ischemia/reperfusion injury via the SNHG14/miR-30b-5p axis.[80] Additionally, some screening studies show miRNA expression profiles, all miRNAs altered by propofol.[20,21,81] In two separate studies, miR-455-3p decreased neurotoxicity induced by propofol via HOTAIR/NLRP1[82] and EphA4.[83] Propofol also blocked apoptosis in hippocampal neurons via the miR-15a-5p/NR2B/ERK1/2 axis.[84]

Conclusion and Future Perspectives

Every year, many adults and infants are exposed to anaesthetics because of their medical needs. Herein, we compile comprehensive data on the role of miRNA in anaesthetics' effects (Figure 2). Animal studies demonstrated that anaesthesia induces neuroapoptosis and cognitive dysfunction during brain growth. According to studies on databases, sevoflurane, isoflurane, ketamine, and propofol are the most studied anaesthetic agents in relation to miRNA and neurotoxicity. In the light of the *in vivo* and *in vitro* studies, there is no doubt that substantial improvement has been made in understanding the role of miRNAs in anaesthesia neurotoxicity, but we are still in the early days, and so there is a lot of work to be done to fully resolve the neurobiology of miRNAs. Although we know that many miRNAs are related to neurotoxicity in the brain after anaesthesia exposure, the molecular mechanisms and degree of specific miRNAs involved in the onset and progression of these neurotoxicities are unknown.

A remarkable proportion of studies have stated that anaesthetics mostly affect the hippocampal region, where neurodegeneration and neuroapoptosis occur. Cognitive dysfunction and learning memory problems have also been observed.

Rodent studies have shown that sevoflurane anaesthesia can induce neurotoxicity and learning and memory deficits. The results of preclinical studies cannot be applied to clinical practice directly. The duration of anaesthesia, repeated exposure, the dose of the anaesthetic, the use of multiple agents, and the age of the animal are factors influencing cognitive dysfunction in preclinical studies. The results of clinical studies are contradictory.

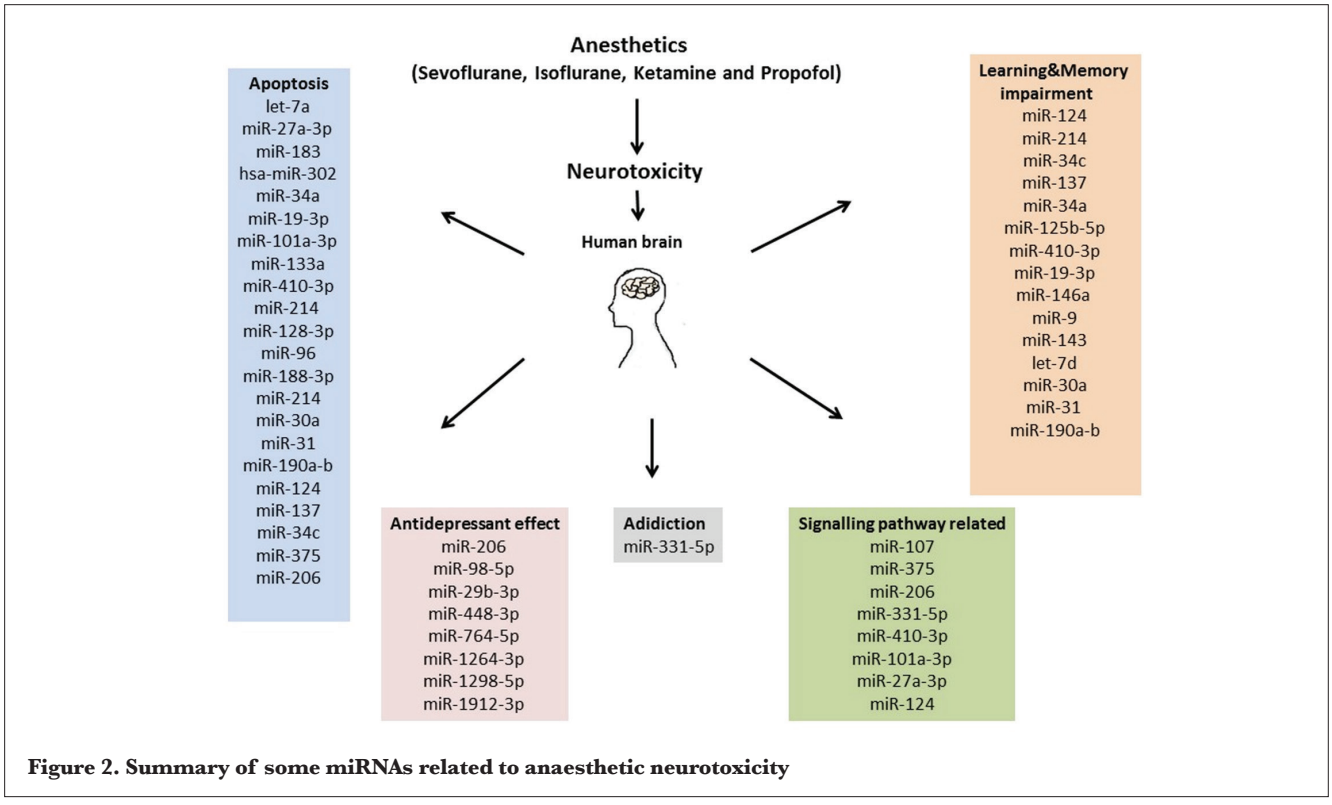

Figure 2. Summary of some miRNAs related to anaesthetic neurotoxicity

The altered miRNA expression in the brain after anaesthesia could be an underlying mechanism in the sevoflurane-induced cognitive dysfunction. The studies that investigated the effect of sevoflurane on cognitive dysfunction through miRNAs have varying results. Investigating the miRNA expression in response to sevoflurane anaesthesia has several challenges. First, different methods were used in different studies. Second, some studies investigated the whole miRNA expression in the hippocampus, while others investigated specific miRNA alterations. Third, the duration and concentration of sevoflurane anaesthesia were different in each study. Although additional consistency is needed for more meaningful results, these preclinical studies showed that sevoflurane-induced cognitive dysfunction is related to alterations in miRNA expression. Additionally, the use of miRNA-specific knockout animals in such studies should be considered. miRNAs are becoming biomarkers for the diagnosis and prognosis of other conditions; thus, they can be the targets of therapy for AIN and cognitive dysfunction.

Both *in vitro* and *in vivo* studies have investigated the effects of ketamine on neurotoxicity and miRNA interactions. *In vivo* studies have demonstrated that ketamine causes neurodegeneration in hippocampal neurons, which is followed by an increase in apoptosis and cognitive dysfunction.

One of the critical aspects of miRNAs is the diversity of technologies used for miRNA detection. In contrast to common methods like real-time fluorescent quantitative polymerase chain reaction (PCR) and digital PCR technology, *in situ* hybridization and new microarray methods have been successfully established and have started to be widely used. More recent advances for miRNA detection include electrochemical detection based on enzymatic signal amplification, rolling ring amplification, and nanoparticle technology.[85]

Due to scientific and technological achievements, some miRNAs can be used as candidate biomarkers, allowing earlier detection and possibly a higher rate of success for a neuroprotection strategy. Therefore, future work should focus on developing a non-invasive and effective method to deliver miRNA "drugs" into the injured brain to protect it from neurotoxicity.

A comprehensive functional characterization of miRNAs in the context of the interaction among themselves (miRNA/miRNA) with other non-coding RNA species, especially IncRNAs, has attracted attention. This is because carnici carried out an extensive analysis of the transcriptional landscape in mouse brains, and his colleagues demonstrated that a high number of lncRNAs are involved in the regulation of several target genes in the brain.[86] Therefore, miRNA-lncRNA interactions and their effect on the target gene are important for miRNA research, making it necessary to elucidate the cause/consequence relationship of their regulation in anaesthesia-related neuroprotection and neurotoxicity.

In conclusion, while the literature supports that miRNAs play crucial roles in neuroprotection and neurotoxicity during anaesthesia administration, the exact role of miRNAs in anaesthesia neurotoxicity needs to be elucidated. Moreover, whether a single miRNA or a combination of miRNAs should be considered the "ideal" therapeutic candidate for neuroprotection and treatment against neurotoxicity requires further studies and more in-depth analysis.

Footnotes

Author Contributions: Concept - E.Ö., Ş.G.; Design - Ş.G.; Data Collection and/or Processing - E.Ö., B.K., B.İ.A., H.A., Ş.G.; Analysis and/or/Interpretation - Ş.G.; Literature Review - E.Ö., B.K., B.İ.A., H.A., Ş.G.; Writing - E.Ö., B.K., B.İ.A.

Declaration of Interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. *Front Endocrinol (Lausanne)*. 2018;9:402. [CrossRef]
2. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell*. 1993;75(5):843-854. [CrossRef]
3. Prodromidou K, Matsas R. Species-specific miRNAs in human brain development and disease. *Front Cell Neurosci*. 2019;13:559. [CrossRef]
4. Cai Y, Liu J, Zhang L, et al. Grey matter volume abnormalities in patients with bipolar I depressive disorder and unipolar depressive disorder: a voxel-based morphometry study. *Neurosci Bull*. 2015;31(1):4-12. [CrossRef]
5. Lv X, Yan J, Jiang J, Zhou X, Lu Y, Jiang H. MicroRNA-27a-3p suppression of peroxisome proliferator-activated receptor-γ contributes to cognitive impairments resulting from sevoflurane treatment. *J Neurochem*. 2017;143(3):306-319. [CrossRef]
6. Wang L, Zheng M, Wu S, Niu Z. MicroRNA-188-3p is involved in sevoflurane anesthesia-induced neuroapoptosis by targeting MDM2. *Mol Med Rep*. 2018;17(3):4229-4236. [CrossRef]
7. Shao CZ, Xia KP. Sevoflurane anesthesia represses neurogenesis of hippocampus neural stem cells via regulating microRNA-183-mediated NR4A2 in newborn rats. *J Cell Physiol*. 2019;234(4):3864-3873. [CrossRef]
8. Yang L, Shen Q, Xia Y, Lei X, Peng J. Sevofluraneinduced neurotoxicity is driven by OXR1 posttranscriptional downregulation involving hsamiR302e. *Mol Med Rep*. 2018;18(5):4657-4665. [CrossRef]
9. Zhao X, Sun Y, Ding Y, Zhang J, Li K. miR-34a inhibitor may effectively protect against sevoflurane-induced hippocampal apoptosis through the Wnt/β-catenin pathway by targeting Wnt1. *Yonsei Med J*. 2018;59(10):1205-1213. [CrossRef]
10. Zhao X, Jin Y, Li H, Jia Y, Wang Y. Sevoflurane impairs learning and memory of the developing brain through post-transcriptional

inhibition of CCNA2 via microRNA-19-3p. *Aging (Albany NY)*. 2018;10(12):3794-3805. [CrossRef]

11. Zhang L, Yan J, Liu Q, Xie Z, Jiang H. LncRNA Rik-203 contributes to anesthesia neurotoxicity via microRNA-101a-3p and GSK-3β-mediated neural differentiation. *Sci Rep.* 2019;9(1):6822. [CrossRef]
12. Su R, Sun P, Zhang D, Xiao W, Feng C, Zhong L. Neuroprotective effect of miR-410-3p against sevoflurane anesthesia-induced cognitive dysfunction in rats through PI3K/Akt signaling pathway via targeting C-X-C motif chemokine receptor 5. *Genes Genomics*. 2019;41(10):1223-1231. [CrossRef]
13. Liu T, Wang B, Li G, et al. Disruption of microRNA-214 during general anaesthesia prevents brain injury and maintains mitochondrial fusion by promoting Mfn2 interaction with Pkm2. *J Cell Mol Med.* 2020;24(23):13589-13599. [CrossRef]
14. Jiang Y, Wang Y, Sun Y, Jiang H. Long non-coding RNA Peg13 attenuates the sevoflurane toxicity against neural stem cells by sponging microRNA-128-3p to preserve Sox13 expression. *PLoS One*. 2020;15(12):e0243644. [CrossRef]
15. Zhao Y, Ai Y. Overexpression of lncRNA Gm15621 alleviates apoptosis and inflammation response resulting from sevoflurane treatment through inhibiting miR-133a/Sox4. *J Cell Physiol*. 2020;235(2):957-965. [CrossRef]
16. Lin D, Liu J, Hu Z, Cottrell JE, Kass IS. Neonatal anesthesia exposure impacts brain microRNAs and their associated neurodevelopmental processes. *Sci Rep*. 2018;8(1):10656. [CrossRef]
17. Ye J, Zhang Z, Wang Y, et al. Altered hippocampal microRNA expression profiles in neonatal rats caused by sevoflurane anesthesia: microRNA profiling and bioinformatics target analysis. *Exp Ther Med.* 2016;12(3):1299-1310. [CrossRef]
18. Fujimoto S, Ishikawa M, Nagano M, Sakamoto A. Influence of neonatal sevoflurane exposure on nerve development-related microRNAs and behavior of rats. *Biomed Res*. 2015;36(6):347-355. [CrossRef]
19. Zhou X, Xian D, Xia J, et al. MicroRNA-34c is regulated by p53 and is involved in sevoflurane-induced apoptosis in the developing rat brain potentially via the mitochondrial pathway. *Mol Med Rep*. 2017;15(4):2204-2212. [CrossRef]
20. Goto G, Hori Y, Ishikawa M, Tanaka S, Sakamoto A. Changes in the gene expression levels of microRNAs in the rat hippocampus by sevoflurane and propofol anesthesia. *Mol Med Rep*. 2014;9(5):1715-1722. [CrossRef]
21. Lu Y, Jian MY, Ouyang YB, Han RQ. Changes in rat brain MicroRNA expression profiles following sevoflurane and propofol anesthesia. *Chin Med J (Engl)*. 2015;128(11):1510-1515. [CrossRef]
22. Xu C, Niu JJ, Zhou JF, Wei YS. MicroRNA-96 is responsible for sevoflurane-induced cognitive dysfunction in neonatal rats via inhibiting IGF1R. *Brain Res Bull*. 2019;144:140-148. [CrossRef]
23. Yu Y, Zhang P, Yan J, et al. Sevoflurane induces cognitive impairments via the MiR-27b/LIMK1-signaling pathway in developing rats. *Inhal Toxicol.* 2016;28(14):731-738. [CrossRef]
24. Shan L, Ma D, Zhang C, Xiong W, Zhang Y. miRNAs may regulate GABAergic transmission associated genes in aged rats with anesthetics-induced recognition and working memory dysfunction. *Brain Res.* 2017;1670:191-200. [CrossRef]
25. Yi X, Cai Y, Zhang N, Wang Q, Li W. Sevoflurane inhibits embryonic stem cell self-renewal and subsequent neural differentiation by modulating the let-7a-Lin28 signaling pathway. *Cell Tissue Res*. 2016;365(2):319-330. [CrossRef]
26. Sun H, Hu H, Xu X, Tao T, Liang Z. Key miRNAs associated with memory and learning disorder upon exposure to sevoflurane determined by RNA sequencing. *Mol Med Rep*. 2020;22(2):1567-1575. [CrossRef]
27. Zhang L, Xue Z, Yan J, Jiang H. LncRNA Rik-203 contributes to sevoflurane induced neurotoxicity? *Front Med (Lausanne)*. 2020;7:353. [CrossRef]
28. Shi H, Sun BL, Zhang J, et al. miR-15b suppression of Bcl-2 contributes to cerebral ischemic injury and is reversed by sevoflurane preconditioning. *CNS Neurol Disord Drug Targets.* 2013;12(3):381-391. [CrossRef]
29. Zhong H, Chen H, Gu C. Sevoflurane post-treatment upregulated miR-203 expression to attenuate cerebral ischemia-reperfusion-induced neuroinflammation by targeting MyD88. *Inflammation.* 2020;43(2):651-663. [CrossRef]
30. Ding L, Ning J, Wang Q, Lu B, Ke H. Retracted: sevoflurane improves nerve regeneration and repair of neurological deficit in brain damage rats via microRNA-490-5p/CDK1 axis. *Life Sci.* 2021;271:119111. [CrossRef]
31. Yi W, Li D, Guo Y, Zhang Y, Huang B, Li X. Sevoflurane inhibits the migration and invasion of glioma cells by upregulating microRNA-637. *Int J Mol Med.* 2016;38(6):1857-1863. [CrossRef]
32. Gao C, Shen J, Meng ZX, He XF. Sevoflurane inhibits glioma cells proliferation and metastasis through miRNA-124-3p/ROCK1 axis. *Pathol Oncol Res.* 2020;26(2):947-954. [CrossRef]
33. Zhang L, Wang J, Fu Z, et al. Sevoflurane suppresses migration and invasion of glioma cells by regulating miR-146b-5p and MMP16. *Artif Cells Nanomed Biotechnol.* 2019;47(1):3306-3314. [CrossRef]
34. Xu W, Xue R, Xia R, et al. Sevoflurane impedes the progression of glioma through modulating the circular RNA has_circ_0012129/miR-761/TGIF2 axis. *Eur Rev Med Pharmacol Sci.* 2020;24(10):5534-5548. [CrossRef]
35. Zhao H, Xing F, Yuan J, Li Z, Zhang W. Sevoflurane inhibits migration and invasion of glioma cells via regulating miR-34a-5p/MMP-2 axis. *Life Sci*. 2020;256:117897. [CrossRef]
36. Bao X, Peng Y, Shen J, Yang L. Sevoflurane inhibits progression of glioma via regulating the HMMR antisense RNA 1/microRNA-7/cyclin dependent kinase 4 axis. *Bioengineered*. 2021;12(1):7893-7906. [CrossRef]
37. Zhang L, Zhang Y, Hu R, et al. Isoflurane inhibits embryonic stem cell self-renewal and neural differentiation through miR-9/E-cadherin signaling. *Stem Cells Dev.* 2015;24(16):1912-1922. [CrossRef]
38. Wu Q, Dai Q, Jiang L, et al. Downregulation of microRNA-448 improves isoflurane-induced learning and memory impairment in rats. *Mol Med Rep*. 2017;16(2):1578-1583. [CrossRef]
39. Yang W, Guo Q, Li J, et al. microRNA-124 attenuates isoflurane-induced neurological deficits in neonatal rats via binding to EGR1. *J Cell Physiol*. 2019;234(12):23017-23032. [CrossRef]
40. Xie C, Wang H, Zhang Y, Wei Y. Neuroprotective effects of miR-142-5p downregulation against isoflurane-induced neurological impairment. *Diagn Pathol.* 2020;15(1):70. [CrossRef]
41. Wu Q, Shang Y, Shen T, Liu F, Xu Y, Wang H. Neuroprotection of miR-214 against isoflurane-induced neurotoxicity involves the PTEN/PI3K/Akt pathway in human neuroblastoma cell line SH-SY5Y. *Arch Biochem Biophys*. 2019;678:108181. [CrossRef]
42. Luo T, Yin S, Shi R, et al. miRNA expression profile and involvement of Let-7d-APP in aged rats with isoflurane-induced learning and memory impairment. *PLoS One*. 2015;10(3):e0119336. [CrossRef]
43. Li H, Du M, Xu W, Wang Z. MiR-191 downregulation protects against isoflurane-induced neurotoxicity through targeting *BDNF*. *Toxicol Mech Methods*. 2021;31(5):367-373. [CrossRef]
44. Li N, Yue L, Wang J, Wan Z, Bu W. MicroRNA-24 alleviates isoflurane-induced neurotoxicity in rat hippocampus via attenuation of oxidative stress. *Biochem Cell Biol*. 2020;98(2):208-218. [CrossRef]
45. Whitaker EE, Wiemann BZ, Xia JC, et al. Distinct, sex-dependent miRNA signatures in piglet hippocampus induced by a clinically relevant isoflurane exposure: a pilot study. *J Anesth.* 2019;33(6):670-679. [CrossRef]

46. Fan D, Yang S, Han Y, Zhang R, Yang L. Isoflurane-induced expression of miR-140-5p aggravates neurotoxicity in diabetic rats by targeting SNX12. *J Toxicol Sci*. 2020;45(2):69-76. [CrossRef]
47. Chen Y, Zhou ZF, Wang Y. Prediction and analysis of weighted genes in isoflurane induced general anesthesia based on network analysis. *Int J Neurosci*. 2020;130(6):610-620. [CrossRef]
48. Jiang JD, Zheng XC, Huang FY, Gao F, You MZ, Zheng T. MicroRNA-107 regulates anesthesia-induced neural injury in embryonic stem cell derived neurons. *IUBMB Life*. 2019;71(1):20-27. [CrossRef]
49. Xu H, Zhang J, Zhou W, Feng Y, Teng S, Song X. The role of miR-124 in modulating hippocampal neurotoxicity induced by ketamine anesthesia. *Int J Neurosci*. 2015;125(3):213-220. [CrossRef]
50. Yao Y, Wang X, Gao J. LncRNA KCNQ1OT1 sponges miR-206 to ameliorate neural injury induced by anesthesia via up-regulating BDNF. *Drug Des Devel Ther.* 2020;14:4789-4800. [CrossRef]
51. Zhao X, Shu F, Wang X, et al. Inhibition of microRNA-375 ameliorated ketamine-induced neurotoxicity in human embryonic stem cell derived neurons. *Eur J Pharmacol*. 2019;844:56-64. [CrossRef]
52. Feng J, Wang M, Li M, et al. Serum miR-221-3p as a new potential biomarker for depressed mood in perioperative patients. *Brain Res.* 2019;1720:146296. [CrossRef]
53. Arqué JM, Sans-Coma V, Durán AC, Cardo M. Origen anómalo de la arteria coronaria izquierda en el tronco pulmonar y su relación con otras anomalías coronarias primarias: estudio experimental [Anomalous origin of the left coronary artery at the pulmonary trunk and its relationship with other primary coronary anomalies: experimental study]. *Rev Esp Cardiol*. 1989;42(6):399-409. [CrossRef]
54. Choi Y, Kim B, Ham S, et al. Subanesthetic ketamine rapidly alters medial prefrontal miRNAs involved in ubiquitin-mediated proteolysis. *PLoS One.* 2021;16(8):e0256390. [CrossRef]
55. Cao SE, Tian J, Chen S, Zhang X, Zhang Y. Role of miR-34c in ketamine-induced neurotoxicity in neonatal mice hippocampus. *Cell Biol Int*. 2015;39(2):164-168. [CrossRef]
56. Huang C, Zhang X, Zheng J, Chen C, Chen Y, Yi J. Upregulation of miR-137 protects anesthesia-induced hippocampal neurodegeneration. *Int J Clin Exp Pathol*. 2014;7(8):5000-5007. [CrossRef]
57. Jiang XL, Du BX, Chen J, Liu L, Shao WB, Song J. MicroRNA-34a negatively regulates anesthesia-induced hippocampal apoptosis and memory impairment through FGFR1. *Int J Clin Exp Pathol.* 2014;7(10):6760-6767. [CrossRef]
58. Wang J, Zhou M, Wang X, et al. Impact of ketamine on learning and memory function, neuronal apoptosis and its potential association with miR-214 and PTEN in adolescent rats. *PLoS One.* 2014;9(6):e99855. [CrossRef]
59. Yang X, Yang Q, Wang X, et al. MicroRNA expression profile and functional analysis reveal that miR-206 is a critical novel gene for the expression of BDNF induced by ketamine. *Neuromolecular Med*. 2014;16(3):594-605. [CrossRef]
60. Huang C, Wang Y, Wu Z, et al. miR-98-5p plays a critical role in depression and antidepressant effect of ketamine. *Transl Psychiatry*. 2021;11(1):454. [CrossRef]
61. Wan YQ, Feng JG, Li M, et al. Correction: prefrontal cortex miR-29b-3p plays a key role in the antidepressant-like effect of ketamine in rats. *Exp Mol Med.* 2022;54(11):2104-2105. [CrossRef]
62. Grieco SF, Velmeshev D, Magistri M, et al. Ketamine up-regulates a cluster of intronic miRNAs within the serotonin receptor 2C gene by inhibiting glycogen synthase kinase-3. *World J Biol Psychiatry*. 2017;18(6):445-456. [CrossRef]
63. Li C, Tu G, Luo C, et al. Effects of rhynchophylline on the hippocampal miRNA expression profile in ketamine-addicted rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;86:379-389. [CrossRef]
64. Stogiannou D, Protopapas A, Protopapas A, Tziomalos K. Is propofol the optimal sedative in gastrointestinal endoscopy? *Acta Gastroenterol Belg*. 2018;81(4):520-524. [CrossRef]
65. Lundström S, Twycross R, Mihalyo M, Wilcock A. Propofol. *J Pain Symptom Manage*. 2010;40(3):466-470. [CrossRef]
66. Brown LA, Levin GM. Role of propofol in refractory status epilepticus. *Ann Pharmacother*. 1998;32(10):1053-1059. [CrossRef]
67. Li GF, Li ZB, Zhuang SJ, Li GC. Inhibition of microRNA-34a protects against propofol anesthesia-induced neurotoxicity and cognitive dysfunction via the MAPK/ERK signaling pathway. *Neurosci Lett.* 2018;675:152-159. [CrossRef]
68. Xing N, Xing F, Li Y, et al. Dexmedetomidine improves propofol-induced neuronal injury in rat hippocampus with the involvement of miR-34a and the PI3K/Akt signaling pathway. *Life Sci.* 2020;247:117359. [CrossRef]
69. Zhang S, Liang Z, Sun W, Pei L. Repeated propofol anesthesia induced downregulation of hippocampal miR-132 and learning and memory impairment of rats. *Brain Res.* 2017;1670:156-164. [CrossRef]
70. Wang M, Suo L, Yang S, Zhang W. CircRNA 001372 reduces inflammation in propofol-induced neuroinflammation and neural apoptosis through PIK3CA/Akt/NF-κB by miRNA-148b-3p. *J Invest Surg*. 2021;34(11):1167-1177. [CrossRef]
71. Cui C, Zhang D, Sun K, et al. Propofol maintains Th17/Treg cell balance and reduces inflammation in rats with traumatic brain injury via the miR1453p/NFATc2/NFκB axis. *Int J Mol Med*. 2021;48(1):135. [CrossRef]
72. Sun WC, Pei L. rno-miR-665 targets BCL2L1 (Bcl-xl) and increases vulnerability to propofol in developing astrocytes. *J Neurochem*. 2016;138(2):233-242. [CrossRef]
73. Sun WC, Liang ZD, Pei L. Propofol-induced rno-miR-665 targets BCL2L1 and influences apoptosis in rodent developing hippocampal astrocytes. *Neurotoxicology*. 2015;51:87-95. [CrossRef]
74. Sun W, Pei L. microRNA expression profiling of propofol-treated developing rat hippocampal astrocytes. *DNA Cell Biol*. 2015;34(8):511-523. [CrossRef]
75. Sun WC, Pei L. Dexmedetomidine attenuates propofol-induced apoptosis of neonatal hippocampal astrocytes by inhibiting the Bcl2l1 signalling pathway. *Eur J Neurosci*. 2021;54(11):7775-7789. [CrossRef]
76. Zheng X, Huang H, Liu J, Li M, Liu M, Luo T. Propofol attenuates inflammatory response in LPS-activated microglia by regulating the miR-155/SOCS1 pathway. *Inflammation*. 2018;41(1):11-19. [CrossRef]
77. Xiao X, Hou Y, Yu W, Qi S. Propofol ameliorates microglia activation by targeting microRNA-221/222-IRF2 axis. *J Immunol Res*. 2021;2021:3101146. [CrossRef]
78. Liu J, Ai P, Sun Y, et al. Propofol inhibits microglial activation *via* miR-106b/Pi3k/Akt axis. *Front Cell Neurosci*. 2021;15:768364. [CrossRef]
79. Hu Y, Ye C, Cheng S, Chen J. Propofol downregulates lncRNA MALAT1 to alleviate cerebral ischemia-reperfusion injury. *Inflammation*. 2021;44(6):2580-2591. [CrossRef]
80. Sun B, Ou H, Ren F, Guan Y, Huan Y, Cai H. Propofol protects against cerebral ischemia/reperfusion injury by down-regulating long noncoding RNA SNHG14. *ACS Chem Neurosci*. 2021;12(16):3002-3014. [CrossRef]
81. Jiang C, Logan S, Yan Y, et al. Signaling network between the dysregulated expression of microRNAs and mRNAs in propofol-induced developmental neurotoxicity in mice. *Sci Rep*. 2018;8(1):14172. [CrossRef]
82. Gong H, Wan X, Zhang Y, Liang S. Downregulation of HOTAIR reduces neuronal pyroptosis by targeting miR-455-3p/NLRP1 axis in propofol-treated neurons in vitro. *Neurochem Res*. 2021;46(5):1141-1150. [CrossRef]

83. Zhu X, Li H, Tian M, Zhou S, He Y, Zhou M. miR-455-3p alleviates propofol-induced neurotoxicity by reducing EphA4 expression in developing neurons. *Biomarkers*. 2020;25(8):685-692. [CrossRef]

84. Liu X, Geng J, Guo H, Zhao H, Ai Y. Propofol inhibited apoptosis of hippocampal neurons in status epilepticus through miR-15a-5p/NR2B/ERK1/2 pathway. *Cell Cycle*. 2020;19(9):1000-1011. [CrossRef]

85. Jet T, Gines G, Rondelez Y, Taly V. Advances in multiplexed techniques for the detection and quantification of microRNAs. *Chem Soc Rev.* 2021;50(6):4141-4161. [CrossRef]

86. Forero DA, van der Ven K, Callaerts P, Del-Favero J. miRNA genes and the brain: implications for psychiatric disorders. *Hum Mutat.* 2010;31(11):1195-1204. [CrossRef]

DOI: 10.4274/TJAR.2025.251926

Review Article
Perioperative Care

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):197-207

Foundations and Advancements in Hemodynamic Monitoring: Part II - Advanced Parameters and Tools

Muhammed Enes Aydın[1], Aslıhan Aykut[2], Ümit Karadeniz[2], Emre Sertaç Bingül[3], Zeliha Aslı Demir[2], Gamze Talih[4], Başak Akça[5], Burhan Dost[6]

[1]Atatürk University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Erzurum, Türkiye
[2]University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Clinic of Anaesthesiology and Reanimation, Ankara, Türkiye
[3]İstanbul University, İstanbul Faculty of Medicine, Department of Anaesthesiology and Intensive Care, İstanbul, Türkiye
[4]Erciyes University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Kayseri, Türkiye
[5]Hacettepe University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Ankara, Türkiye
[6]Ondokuz Mayıs University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Samsun, Türkiye

Cite this article as: Aydın ME, Aykut A, Karadeniz Ü, et al. Foundations and advancements in hemodynamic monitoring: part II - advanced parameters and tools. *Turk J Anaesthesiol Reanim.* 2025;53(5):197-207

Abstract

Advanced hemodynamic monitoring has revolutionized perioperative medicine and critical care by providing comprehensive insights into cardiovascular physiology and facilitating precise assessment and management of complex parameters such as cardiac output, systemic vascular resistance, fluid responsiveness, and tissue perfusion. These technologies enhance the capacity of clinicians to detect subtle physiological alterations, enabling timely interventions and individualized therapeutic strategies, particularly for critically ill patients and those undergoing major surgical procedures. This two-part review offers a comprehensive analysis of hemodynamic monitoring. Part I examined the fundamental principles of macrohemodynamics and microhemodynamics. Part II focuses on advanced hemodynamic monitoring tools, tracing the evolution of cardiac output measurement techniques from Fick's oxygen consumption method in 1870 to contemporary innovations, such as pulse contour analysis, bioimpedance/bioreactance, and real-time non-invasive modalities like advanced echocardiography. By examining the underlying principles, devices, invasiveness, clinical applications, advantages, and limitations of various monitoring techniques, this review elucidates the clinical utility of advanced tools in addressing the limitations of standard monitoring and optimizing patient outcomes in modern anaesthesia and critical care practices.

Keywords: Anaesthesia monitoring, hemodynamics, intensive care, patient outcomes, perioperative care

Main Points

- Advanced hemodynamic monitoring tools provide precise, real-time assessment of cardiovascular parameters, improving clinical decision-making in perioperative and critical care settings.
- The evolution of cardiac output measurement techniques—from thermodilution and pulse contour analysis to less invasive modalities like echocardiography and bioimpedance—has significantly enhanced the accuracy, practicality, and safety of hemodynamic monitoring.
- Dynamic parameters such as stroke volume variation, pulse pressure variation, and pleth variability index offer superior reliability in predicting fluid responsiveness compared to static parameters, reducing complications from unnecessary fluid administration.
- The integration of advanced hemodynamic parameters, including ventriculo-arterial coupling, arterial elastance, and cardiac power output, facilitates a more comprehensive understanding of cardiovascular dynamics, enabling individualized therapeutic strategies.
- Echocardiography serves as a cornerstone for hemodynamic assessment, offering valuable insights into preload, contractility, and valve function.

Corresponding author: Assoc. Prof. Burhan Dost, e-mail: burhandost@hotmail.com

Received: February 05, 2025 Accepted: April 29, 2025
Epub: June 17, 2025 Published date: October 14, 2025

Introduction

Advanced hemodynamic monitoring tools have revolutionized the field of perioperative medicine and critical care by providing detailed insights into the cardiovascular status of patients. These tools enable clinicians to assess and manage complex hemodynamic parameters such as cardiac output (CO), systemic vascular resistance, fluid responsiveness, and tissue perfusion with greater precision. The clinical significance of these monitoring techniques lies in their ability to detect subtle physiological changes that may indicate impending complications, allowing for timely interventions. By interpreting these advanced data, clinicians can tailor therapeutic strategies to optimize patient outcomes, particularly in critically ill patients and those undergoing major surgeries.

CO measurement has evolved significantly over time. In 1870, Adolf Eugen Fick used oxygen consumption and arterial-venous oxygen differences for the calculation of CO. The mid-20th century introduced indicator dilution methods, including thermodilution with pulmonary artery catheters. The 1980s saw the rise of pulse contour analysis (e.g., PiCCO) and esophageal Doppler, enabling continuous monitoring; and, in the early 21st century, lithium dilution (LiDCO) and bioimpedance/bioreactance (e.g., NICOM) emerged as less invasive options. By the 2010s, devices like MostCare Pressure Recording Analytical Method (PRAM) and advanced echocardiography provided real-time and non-invasive solutions.[1] These innovations have continually enhanced the precision and practicality of CO measurement.

In Part I of this series, we examined the fundamental principles of hemodynamics, emphasizing that macrohemodynamic and microhemodynamic parameters are crucial for ensuring adequate tissue perfusion and guiding clinical decision-making in perioperative settings. Building on this foundation, Part II investigates advanced hemodynamic monitoring tools that have transformed perioperative medicine and critical care. These technologies provide more comprehensive insights into cardiovascular physiology, enabling clinicians to assess and manage complex parameters, such as CO, systemic vascular resistance, fluid responsiveness, and tissue perfusion, with enhanced precision. Table 1 organizes the various CO measurement techniques based on their underlying principles, devices, invasiveness, clinical applications, advantages, and limitations.

Determinants of Blood Volume

Predicting fluid status and fluid responsiveness in critically ill patients is essential for identifying those who will benefit from volume expansion and more importantly, for avoiding fluid administration in patients who would not respond. Preload refers to the end-diastolic blood volume in the ventricles, reflecting the patient's blood volume. The Frank-Starling law explains the relationship between preload and ventricular performance. In a healthy individual, located on the ascending portion of the Frank-Starling curve, fluid therapy increases stroke volume (SV) and consequently CO. However, as the myocardial fiber length continues to increase, tension and force begin to decrease beyond a certain point.[2] Therefore, fluid replacement when the actual status is close to the "flat" part of the curve has little effect on CO and may result in overload, tissue edema, and ventricular dysfunction. The shape of the Frank-Starling curve depends on the patient's cardiac contractility and afterload.[3] In cases of systolic heart failure where left ventricular contractility is impaired, cardiac performance decreases for a given preload, shown by a downward shift of the normal curve. In contrast, an increase in left ventricular contractility due to vasopressor, and/or inotropic medication results in greater cardiac performance for a given preload, represented by an upward shift in the normal curve. Changes in afterload, the resistance the ventricle must overcome to initiate systole, will also shift the Frank-Starling curve. A reduction in afterload, similar to an increase in inotropy, causes the ventricular performance curve to shift upwards, while an increase in afterload shifts the curve downward, resembling a decrease in inotropy.

Preload Assessment

Various pressure and volumetric parameters are used to assess preload. Central venous pressure (CVP) has been traditionally used for evaluating right ventricular preload and volume status. Transmural CVP (measured by subtracting end-expiratory intrathoracic pressure from the end-expiratory CVP) is assumed to reflect right ventricular filling pressure. Elevated transmural CVP may indicate right heart failure, necessitating echocardiographic evaluation for a definite diagnosis.[4] Pulmonary artery occlusion pressure (PAOP), which reflects pressures in the pulmonary vasculature and left atrium, is an estimate of left ventricular end-diastolic pressure. Elevated PAOP may indicate severe left heart failure or significant mitral stenosis. Although both PAOP and CVP reflect the filling pressures of the left and right ventricles, they are static parameters with poor correlation to fluid responsiveness and have limited utility in goal-directed fluid therapy.[5] Another pressure parameter, mean systemic filling pressure (Pmsf), refers to the "theoretical" pressure when blood is evenly distributed throughout the systemic circulation once the heart stops pumping. Pmsf values lie between the mean arterial pressure (MAP) and CVP, and Pmsf is more closely related to stressed blood volume. While Pmsf can be used to assess volume status accurately, it is difficult to measure and has limited clinical use.[6] Volumetric parameters such as global end-diastolic volume (GEDV) and extravascular lung water (EVLW), provide more accurate assessments of ventricular preload when compared to filling pressures. GEDV, the volume of blood in all cardiac chambers at the end of

Table 1. Comparison of Cardiac Output Measurement Techniques

Classification	Principle	Devices	Advantages	Limitations
Thermodilution-based monitors	Involves injecting a bolus of cold fluid into the venous circulation. The downstream temperature change is recorded, allowing cardiac output calculation	PAC, PiCCO	Direct measurement, high accuracy in unstable patients	Invasive Requires initial calibration Intermittent measurements Risk of infection and arrhythmias
Arterial waveform analysis	Analyzes the arterial pressure waveform to estimate stroke volume and cardiac output. The shape and area under the pressure curve are assessed, often calibrated by initial thermodilution or lithium dilution measurement	ProAQT Pulsioflex LiDCOrapid PRAM (Mostcare) (no external calibration) FloTrac/Vigileo	Continuous, minimally invasive	Requires dedicated transducer or initial calibration Affected by vascular tone and arrhythmias
Doppler ultrasound-based monitors	Measures blood flow velocity in major arteries, deriving stroke volume from velocity data combined with vessel diameter measurements	ED, TTE, TEE	Rapid ED can continue with arterial waveform analysis TTE non-invasive TEE, ED minimally invasive	Operator-dependent, intermittent measurements ED requires initial calibration
Bioimpedance and bioreactance-based monitors	Measures changes in thoracic electrical impedance or phase shifts (reactance) as blood flows through the aorta, calculating stroke volume from variations in impedance during the cardiac cycle	EC, Starling SV (bioreactance), NICaS (Bioimpedance)	Non-invasive, continuous	Requires external calibration sensitive to motion artifacts, electrocautery, and thoracic conditions, difficult use during intraoperative period

PAC, pulmonary artery catheter; ED, esophageal Doppler; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; EC, electrical cardiometry

diastole, especially correlates with cardiac preload and can assess whether preload has sufficiently increased during volume loading.[5] Furthermore, it can be used even with non-sinus rhythms and spontaneous ventilation. EVLW refers to fluid accumulated in the extravascular space of the lungs, such as in the interstitial and alveolar spaces. It increases with higher hydrostatic pressures (fluid loading) or increased pulmonary vascular permeability [as in acute respiratory distress syndrome (ARDS)]. EVLW can help in diagnosing and assessing the severity of pulmonary edema and ARDS. However, like the other static variables, GEDV and EVLW are less reliable indicators of fluid responsiveness compared to dynamic variables.[6]

Fluid Responsiveness

Fluid responsiveness is traditionally defined as a 10-15% increase in SV or CO following a fluid bolus.[7] In moderate- and high-risk patients or surgeries, inadequate intravenous fluid (IV) replacement may lead to insufficient tissue perfusion, cellular hypoxia, and subsequent organ dysfunction or failure.[8] Conversely, poor outcomes are also associated with excessive fluid loading.[9,10] Positive fluid balance can cause interstitial edema, impaired microvascular flow, and an increase in CVP (limiting venous return). Studies across various patient populations show that only about 50% of hemodynamically unstable patients are fluid responders.[11,12] As such, the primary reason for fluid loading in patients is to increase CO. Therefore, reliable determinants of fluid responsiveness should be selected based on individual hemodynamic responses and applied only when an increase in CO is anticipated (Figure 1).

Previously, static parameters such as filling pressures and volumetric changes were used to predict fluid responsiveness, but studies have shown that these static indicators do not reliably do so.[5] Instead, dynamic variables, such as SV variation (SVV), systolic pressure variation (SPV), and pulse pressure variation (PPV), which are measured using a less invasive method based on the interaction between the heart and lungs during mechanical ventilation, have

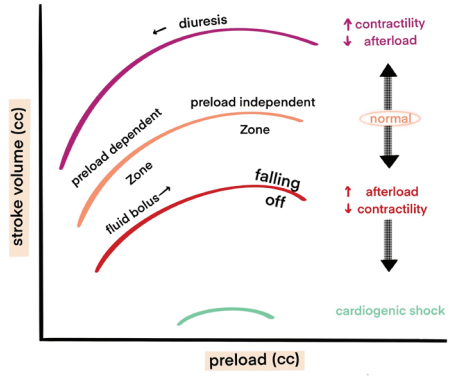

Figure 1. Frank-Starling curve.

been shown to predict fluid responsiveness more reliably.[13] Additionally, several clinical studies using SVV and PPV to guide individualized fluid therapy have demonstrated reduced postoperative complications and shorter hospital stays.[14] The pleth variability index (PVI), a non-invasive alternative to PPV, is also based on changes observed during the respiratory cycle. Other intermittent dynamic maneuvers, such as passive leg raising (PLR), fluid loading tests, and the end-expiratory occlusion test (EEOT), have proven useful in predicting which patients will benefit from volume expansion.[15] Dynamic parameters have also shown potential benefits in reducing the duration of mechanical ventilation in patients with fluid overload.[16] The use of these dynamic parameters in guiding fluid therapy has been widely accepted and recommended in guidelines.[17,18]

During "positive pressure" ventilation, an increase in intrathoracic pressure during inspiration leads to decreased venous return (right ventricular preload) and SV. At the same time, the afterload on the right ventricle increases due to the rise in transpulmonary pressure during inspiration. The decrease in right ventricular SV subsequently leads to a reduction in left ventricular filling. This change is minimal during expiration.

SVV and PPV are calculated as the ratio of the maximum difference in the values measured during a single ventilation cycle (Figure 2). SPV is the difference between the maximum and minimum systolic arterial pressures during a mechanical breath. Increased SV and PPV are more pronounced in fluid responder patients, as they lie on the steeper portion of the Starling curve (Figure 2).[19] In patients receiving controlled mechanical ventilation with tidal volumes ≥7-8 mL kg^{-1} of ideal body weight (IBW), a PPV greater than 13% strongly suggests existing fluid responsiveness, while a PPV of less than 9% is unlikely to be fluid-responsive. Values between 9% and 13% refer to inconclusive results (the "gray zone").[20-22] PPV is generally considered the most accurate dynamic variable under mechanical ventilation and is often regarded as the gold standard for evaluating new dynamic parameters.[23] Threshold values for SVV are also defined within the 9-13% range. Although SVV is slightly less accurate than PPV, this is likely due to the computational limitations of real-time pulse wave analysis (Figure 2).

Several limitations exist when interpreting PPV/SVV. Obtaining accurate results from these monitors requires good-quality arterial waveform data. On the other hand, PPV decreases at high respiratory rates (30-40 breaths per minute) regardless of fluid status.[24] Patients should be mechanically ventilated with adequate tidal volumes, and without any spontaneous respiratory efforts. The hemodynamic effects of spontaneous respiration are different from those during mechanical ventilation. During spontaneous inspiration, intrathoracic pressure decreases,

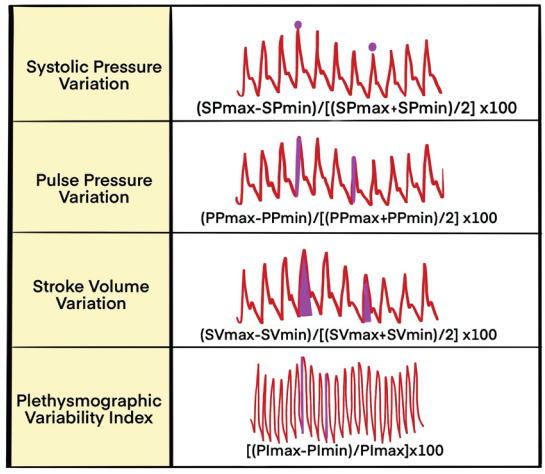

Figure 2. Illustration of dynamic hemodynamic parameters used for assessing fluid responsiveness in mechanically ventilated patients.

increasing venous return and SV. The effects of this pressure change can vary from breath to breath. Conversely, in a hypovolemic shock patient with spontaneous breathing, inspiration can cause vena caval collapse, leading to reduced venous return, and blood pressure (pulsus paradoxus). Thus, dynamic parameters represent limitations in patients with spontaneous breathing and may require additional maneuvers. For example, combining dynamic parameters with maneuvers that provoke cyclic changes of intrathoracic pressures (e.g., deep inspiration or forced inspiratory breathing) has been shown to improve the assessment of fluid responsiveness.[25] Recently, PPV has been reported to predict fluid responsiveness in patients who are spontaneously breathing with mechanical assistance and generate low inspiratory effort (airway occlusion pressure <1.5 cmH_2O).[26] Another factor that limits the use of dynamic variables in clinical practice is the necessity of very low tidal volumes (e.g., 6 mL kg^{-1} IBW or less) for lung-protective ventilation modality, which is preferred in such conditions as ARDS. During low-tidal ventilation, low PPV does not rule out fluid "responsiveness", yet high PPV still indicates the existence of such responsiveness.[27] Considering those limitations, alternative maneuvers have been proposed. For instance, an absolute increase of PPV/SVV via a tidal volume challenge (a temporary increase from 6 mL kg-1 IBW, to 8 mL kg^{-1}), or an absolute decrease via a mini-fluid challenge may help predict fluid responsiveness.[28,29] Contrary to what is normally expected, SVV is shown to be a stronger predictor of fluid responsiveness than PPV during lung-protective mechanical ventilation (<8 mL kg^{-1} tidal volume, no arrhythmias or spontaneous respiratory efforts), particularly in cardiac surgery or septic shock patients.[30]

Cardiac arrhythmias, severe aortic valve disease, and right and left ventricular failure are additional limitations of PPV

and SVV. Several mechanisms are valid for this proposition. For example, arrhythmias cause increased variability in SV. In patients with right heart failure, mechanical ventilation-induced preload may reduce right ventricular CO, which may be mistakenly attributed to hypovolemia or pneumoperitoneum. Increased intra-abdominal pressure reduce thoracic compliance and may lead to incorrect interpretation of PPV/SVV. Reduced venous return due to increased intra-abdominal pressure leads to preload dependence, which causes a false-positive misinterpretation. Similar issues can occur in different surgical positions (prone, lateral etc.), where intra-abdominal pressure and lung compliance are affected, and dynamic parameters must be interpreted with caution. Increased lung and chest wall compliance, air trapping, and high tidal volumes, inflation pressures, or positive end-expiratory pressure (PEEP) settings may also cause false positives, where dynamic indices rise without true fluid responsiveness. Lastly, these methods are also inefficient for predicting fluid responsiveness under open-chest conditions during cardiac and/or thoracic surgery.

In cases where dynamic parameters are questionable, alternative tests such as the PLR test, EEOT, lung recruitment maneuvers, or mini-fluid tests are recommended. In particular, both tidal volume challenge and EEOT have been shown to be good predictors in critically ill patients ventilated with lower tidal volumes (<8 mL kg^{-1}) without arrhythmias or respiratory effort.[30] EEOT involves pausing the ventilation at the end of expiration for 15 seconds, which causes the airway pressure to drop to the actual positive end-expiratory pressure (PEEP) level, thus reducing intrathoracic pressure and increasing cardiac preload. The diagnostic threshold for this test is a >5% increase in CO.[31] In a different clinical scenario, elevated PPV and SVV values accompanied by hypotension following anaesthesia induction may result from widespread vasodilation; in such situations, vasoactive treatment can be considered, and whether or not fluid bolus therapy is administered. Similarly, in sepsis or cardiac surgery patients, dynamic variables may be elevated with vasoplegia itself. While vasopressors may increase preload, inotropes shift the Starling curve upwards, potentially altering the clinical assessment of true volume deficit. Therefore, in situations with reduced CO, fluid responsiveness should be evaluated along with afterload and contractility parameters in a comprehensive manner.

Non-invasive methods for fluid responsiveness assessment include pulse oximeter plethysmographic waveform amplitude changes (ΔPOP) and the automatic PVI.[32] The perfusion index (PI) is the ratio of pulsatile to non-pulsatile blood flow in the capillary bed. The PVI is calculated as the ratio of the difference between the maximum and minimum PI values to the maximum PI, representing the ratio of pulsatile to non-pulsatile infrared light absorption. PVI, an indirect marker of PPV, predicts fluid responsiveness with a cut-off of 14% based on an algorithm that continuously evaluates ΔPOP using the PI, where mechanical ventilation is required.[33,34] While the limitations of invasive dynamic parameters also apply to PVI, its reliability is further reduced in cases of hypothermia, circulatory failure, vasoactive drug use, and vasoconstriction.

An alternative dynamic test for assessing fluid responsiveness is the fluid loading test. Since the ideal organ perfusion value for a patient is unknown, fluid titration using small incremental boluses (100 to 250 mL crystalloid infusion over 5 to 10 minutes limited to 4 mL kg^{-1}) guided by changes in SV, and PP is recommended.[35] More than 10-12% increase in SV, observed one minute after fluid infusion, indicates fluid-responsiveness, exhibiting blood flow and tissue perfusion recovery via the replacement. The absence of an increase following fluid bolus is the most reliable indicator of potential congestion and edema due to additional volume. The "mini-fluid" loading test involves the rapid infusion of 100 mL IV fluid, and is assumed to predict an increase in SV as though 500 mL had been infused. However, excessive or repeated volume boluses may lead to undesirable fluid overload and reduced oxygen delivery due to hemodilution in patients who are not fluid-responsive.[36]

Another method to assess fluid responsiveness is the PLR test. The patient is positioned with their legs raised at a 45-degree angle while the upper body remains flat, resulting in a semi-recumbent position. This maneuver helps return approximately 300 mL of venous blood from the abdomen and lower extremities to the heart. A more than 10% increase in CO after PLR has been shown to reliably predict fluid responsiveness in adults with acute circulatory failure.[37] PLR-induced changes in CO reliably predict fluid responsiveness; however, arterial blood pressure is often monitored instead of CO. In such cases, it is important to note that PLR-induced changes in PP or SAP can serve as a feasible alternative, albeit with lower predictive accuracy.[38] This finding highlights that relying solely on blood pressure changes during PLR can be misleading, and the use of CO monitoring is recommended. PLR is a reversible, repeatable, and easy-to-perform test. In situations such as spontaneous respiration, cardiac arrhythmias, low tidal volume ventilation, and low lung compliance, PLR may represent advantages over SVV-based indices.[31] Performing the test may be difficult or directly interfere with ongoing surgical procedures and requires special attention. On the other hand, clinical limitations of PLR may include amputated lower extremities, severe hypovolemia, and intra-abdominal hypertension. Other limitations include potential increases in intracranial pressure, reduced lung compliance, and increased aspiration risk. It is important to note that, unlike the mainstream dynamic parameters, those alternative dynamic tests (fluid loading, EEOT, and PLR) are measured "intermittently". Continuous dynamic variables can

detect hemodynamic changes much earlier than intermittent variables, offering significant clinical benefits.

Ventriculo-Arterial Coupling

Ventriculo-arterial coupling (VAC) is a macrohemodynamic parameter that reflects the mechanical interactions between the ventricle and the arterial system. Although the left ventricle and aorta have distinct volume dynamics, they converge at a single common point defined as end-systolic pressure (ESP). At this pressure, effective arterial elastance (Ea) is calculated based on the SV ejected into the arterial system, while ventricular elastance (Ees) is derived from the remaining volume within the ventricle. ESP should ideally be measured at the dicrotic notch pressure; however, when this is not feasible, it can be approximately calculated as 90% of the systolic blood pressure, since the aortic valve closes shortly after the systolic descent. The Ea/Ees ratio, a dimensionless parameter, defines VAC and quantifies the coupling between the arterial system and the ventricle. VAC serves as a critical determinant of myocardial oxygen demand and ventricular contraction efficiency. In the cardiovascular system, energy balance is optimal when VAC equals 1 (normal values: 1.0±0.36), while maximum cardiac efficiency is observed at a VAC ratio of approximately 0.5.[39] Deviations in this ratio are not only indicative of disease severity but also serve as an independent predictor of clinical outcome. VAC represents a measure of cardiac work efficiency. A thorough understanding of arterial elastance (a parameter of afterload) and Ees (a parameter of contractility) is essential for interpreting and utilizing VAC effectively.

Afterload, Arterial Impedance, and Arterial Elastance

Afterload is defined as the total load or resistance the ventricle encounters while pumping blood into the arterial system. Although this qualitative definition is partially accurate, a quantitative description is only possible through the concept of arterial impedance, which reflects the resistance blood faces while traversing the arterial system. This resistance depends on the physical properties of arteries (e.g., elasticity and diameter) and the characteristics of blood flow (e.g., viscosity). While vascular resistance applies to steady flows, pulsatile flows can only be described using impedance.[40] Arterial impedance is typically calculated via frequency analysis of blood pressure and flow. In this analysis, harmonics (repeating sinusoidal waves) at different frequencies are considered.[41] The ratio of a pressure harmonic to a flow harmonic at the same frequency is termed impedance at that frequency. The structural characteristics of arteries (e.g., size and elasticity) determine the characteristic impedance, which represents the pressure-to-flow ratio as a wave propagates along the artery.[41] However, the arterial system also includes reflected pressure and flow waves originating distally. "Input impedance" is the term for combined effects of all arterial components, including characteristic impedance and reflected waves, and is thus a more comprehensive measure of afterload.

PRAM is used for CO monitoring via pulse contour analysis, that incorporates arterial impedance (Ztot = mmHg·s mL) for SV measurement. While ztot shows a strong clinical correlation with Ea (mmHg mL^{-1}), the inclusion of time (s) as a factor distinguishes ztot from Ea, offering a more dynamic perspective by taking the temporal effects on pressure into account. Although normal ztot ranges have not been definitively established in the literature, the authors of this manuscript propose an ideal range of 0.35-0.8 mmHg·s mL based on their experience when accurate arterial waveforms and stable SVs are observed. Additionally, the correlation between ztot and Ea is crucial for accurate and reliable CO data. Though conditions like arterial vasospasm may lead to discordance between these parameters, highlighting a potential limitation of these methods.

Ea is a parameter encompassing peripheral resistance, vascular compliance, characteristic impedance, and systolic-diastolic time intervals. Ea can also be calculated as the ratio of ESP to SV (ESP/SV) derived from the pressure-volume loop. A more than 90% correlation between Ea and input impedance has been described.[42] Ea offers a simplified yet highly useful approach for assessing afterload in clinical practice.

Ventricular Elastance

Although myocardial contractility is a primary determinant of ventricular systolic function, ventricular performance is not solely limited to contractility. Structural properties of ventricular myocytes (e.g., elastance, compliance, fibrosis), synchronized involvement in contraction, and geometric remodeling of the cavity significantly influence performance as well.[43] In clinical practice, the most common method for assessing ventricular systolic function is the estimation of ejection fraction (EF) via echocardiography. EF is an important indicator in heart failure and acute myocardial infarction; it is accepted as a major factor in therapeutic decision-making. However, EF is a preload-dependent and afterload-sensitive parameter. On the other hand, Ees is a measure derived from the complex interplay between inotropic activity and the structural, geometric, and functional properties of the Ees is recognized as a true intrinsic indicator of ventricular inotropy.[44] It is calculated by dividing ESP by ventricular end-systolic volume (ESP/ESV).[45] The modified single-beat method, as described by Chen et al.,[46] is the only validated non-invasive approach for measuring Ees when compared to invasive gold-standard methods. This technique calculates Ees in a single cardiac cycle by integrating systolic and diastolic blood pressures with echocardiographic parameters, including ventricular end-systolic and end-diastolic areas, EF, SV, pre-ejection period, and systolic time interval.

Advanced hemodynamic monitoring allows easy interpretation of VAC through the relationship between Ea and Ees, offering insights into varying hemodynamic states. While Ees is preferred in VAC calculations due to its unique role as an intrinsic predictor of contractility, its subjective reliance on echocardiographic measurements remains a limitation. Alternative parameters for assessing contractility should also be considered.

dp/dt and dp/dt(max) as Measures of Barometry

The dp/dt, the first derivative of the rise in left ventricular pressure, and dp/dt(max), representing its maximum rate of increase, are parameters used to assess myocardial contractility. These values can also be calculated non-invasively using echocardiography by measuring the slope of the regurgitant jet velocity from the mitral valve to the left atrium over time. However, ventricular dp/dt(max) measurements are often invasive, technically demanding, and or dependent on the presence of mitral regurgitation, limiting their routine application.

In contrast, arterial dp/dt(max) can be evaluated through pulse contour analysis by measuring the slope of the upstroke in the arterial waveform's anacrotic limb over time. Normal values are between 0.9-1.3 mmHg msec; excessively high values (e.g., >1.7 mmHg msec) may indicate underdamping in arterial waveform analysis, as they may not correlate with physiology.[47,48]

Correlation among dp/dt(max) measurements obtained from various anatomical sites under differing hemodynamic conditions has been demonstrated.[47] However, arterial dp/dt(max) measurements can be inaccurately low in conditions such as insufficient preload, low afterload, or arrhythmias affecting ventricular filling time.[48] Additionally, in cases of aortic stenosis or dynamic left ventricular outflow tract obstruction, the correlation between left ventricular and arterial measurements may be disrupted.

Cardiac Function Index and Global Ejection Fraction

Cardiac function index (CFI) and global ejection fraction (GEF) are easily measured parameters with the PiCCO system. CFI equals the ratio of CO to GEDV (CO/GEDV), while GEF equals the ratio of SV to GEDV/4. Due to having a temporal component, CFI is considered a more dynamic parameter. In contrast, GEF, which lacks a time constant, is accepted as a static parameter and is recommended for trend monitoring to correlate with preoperative EF. In patients with right ventricular dysfunction, these measurements may be misleading, and echocardiographic evaluation of right ventricular involvement is advised. Despite being preload-dependent, both CFI and GEF are reliable indicators for assessing cardiac contractility.[49]

Cardiac Power Output

Cardiac power output (CPO) measures the heart's pumping capacity by evaluating the work performed through pressure and volume. It is calculated using the formula CPO=COxMAP/451 and is expressed in watts. This parameter reflects the myocardial contractility reserve required to maintain the current hemodynamic state, based on two key parameters targeted in hemodynamic management. In conditions with low cardiac performance, such as heart failure, a low CPO value is associated with poor prognosis. Additionally, CPO may be used for monitoring the response to treatment in cardiac diseases.[50]

Cardiac Cycle Efficiency

The evaluation of the cardiovascular system involves various hemodynamic parameters, each providing insights into different aspects of its function. While these parameters offer specific measurements, it is valuable to express the system's overall efficiency and individual patient conditions with a single variable. In this context, energy-based assessments have gained prominence. Cardiac cycle efficiency (CCE) emerges as a dimensionless parameter that evaluates the system's global performance based on energy utilization. CCE is calculated as the ratio of energy expended during systole to the total energy expended throughout the cardiac cycle. Theoretically, a perfectly efficient system would have a CCE value of 1. However, due to entropy and other energy losses inherent in biological systems, this level of efficiency is never achieved. Under normal circumstances, CCE values are expected to range between 0 and 1. Negative values, however, indicate that the cardiovascular system is undergoing a hemodynamic compensation process. The clinical significance of CCE, as a global indicator of cardiovascular performance, underscores its utility in both comprehensive system evaluation and the development of personalized assessment and treatment strategies.[51]

Dynamic Arterial Elastance (Eadyn)

Dynamic arterial elastance (Eadyn) is calculated as the ratio of PPV to SVV during the respiratory cycle. It is intended to reflect the responsiveness of the arterial system to pressure changes, thereby representing dynamic arterial tone characteristics. Unlike static indices of afterload, Eadyn offers real-time assessment and has been proposed as a tool for predicting MAP changes following fluid administration or the development of hypotension after the reduction of vasopressor support. Studies conducted under controlled mechanical ventilation have demonstrated that Eadyn can predict a MAP decrease greater than 10%, achieving a sensitivity of 71% and specificity of 89% at a cut-off value of 0.84 (area under the curve: 0.84).[52] These findings suggest that Eadyn may serve as a valuable guide not only for fluid responsiveness but also for vasopressor titration. The use of Eadyn as a dynamic indicator of VAC can be

better understood by considering the physiological relevance of its components. During the respiratory cycle, variations in PPV—under constant SV—are considered to reflect the elastic properties of the arterial system (Ea). Conversely, SVV represents the response of the left ventricle to fluctuations in preload and can be viewed as a dynamic surrogate of left ventricular contractility (end-systolic elastance, Ees). Accordingly, Eadyn may be interpreted as a continuously monitorable, non-invasive surrogate for the Ea/Ees ratio, reflecting VAC. Experimental studies have demonstrated a positive correlation between Eadyn and left ventricular mechanical efficiency, and a negative correlation between Eadyn and the Ea/Ees ratio.[53] These data indicate that Eadyn is not merely a measure of variation, but a functional parameter that evaluates the interaction between CO and arterial load. Moreover, it has been reported that invasively measured Eadyn values during deep inspiration may play a significant role in predicting post-induction hypotension.[54]

Role of Echocardiography in Hemodynamic Assessment

As a rapid diagnostic method, hemodynamic-focused echocardiography offers an excellent opportunity to examine signs of filling abnormalities, cardiac preload, myocardial contractility, and valve function (Figures 3-5). A summary of all echocardiographic findings, including clinical symptoms, provides a comprehensive evaluation of the patient's cardiovascular function, thereby helping guide pathophysiology-focused and individualized hemodynamic treatment to optimize/maintain CO. Proper patient selection, acquisition, interpretation, synthesis, and the subsequent application of evidence-based therapy will continue to be a critical goal for future research, aiming to enhance the use of echocardiography in critically ill patients.

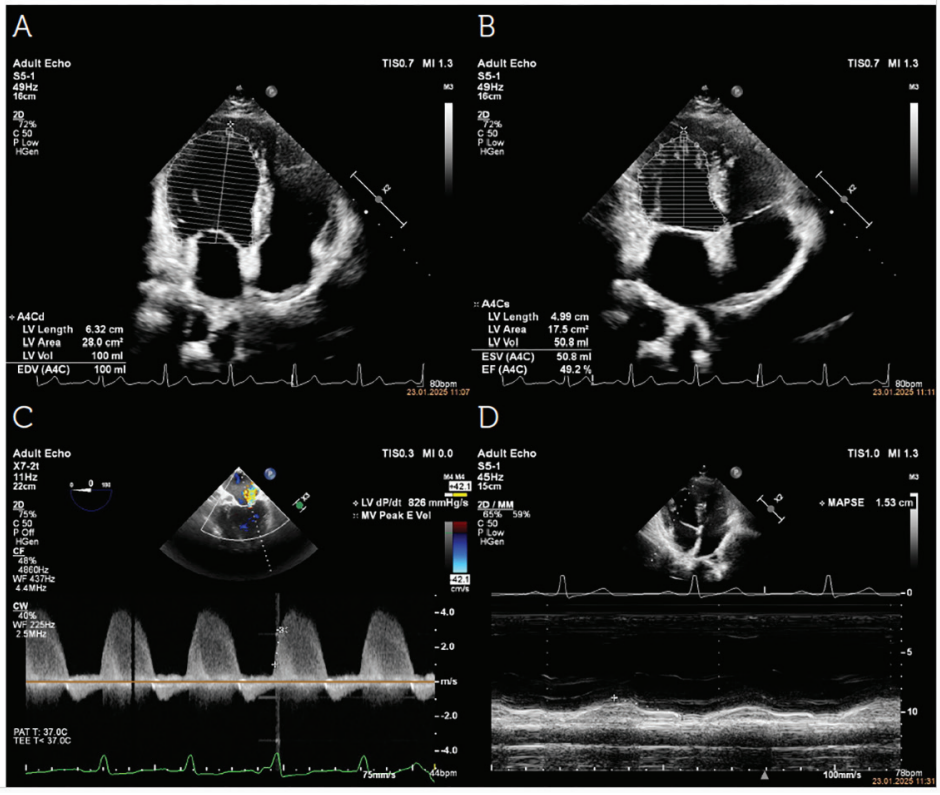

Figure 3. Echocardiographic assessment of left ventricular (LV) function. A) Apical four-chamber view demonstrating the LV end-diastolic volume (EDV), measured to assess LV filling and chamber dimensions. B) Apical four-chamber view illustrating the LV end-systolic volume (ESV), utilized for ejection fraction (EF) calculation. EF (%)=(LVEDV-LVESV)/(LVEDV)x100. C) Continuous-wave Doppler echocardiographic recording of mitral regurgitation (MR) jet, used to calculate dp/dt max, an index of LV contractility. The dp/dt max is determined by measuring the rate of pressure rise across the mitral valve during early systole. D) M-mode echocardiographic assessment of mitral annular plane systolic excursion (MAPSE), a parameter reflecting longitudinal LV function. MAPSE is obtained by tracking the systolic displacement of the mitral annulus, serving as a surrogate marker for global LV systolic performance.

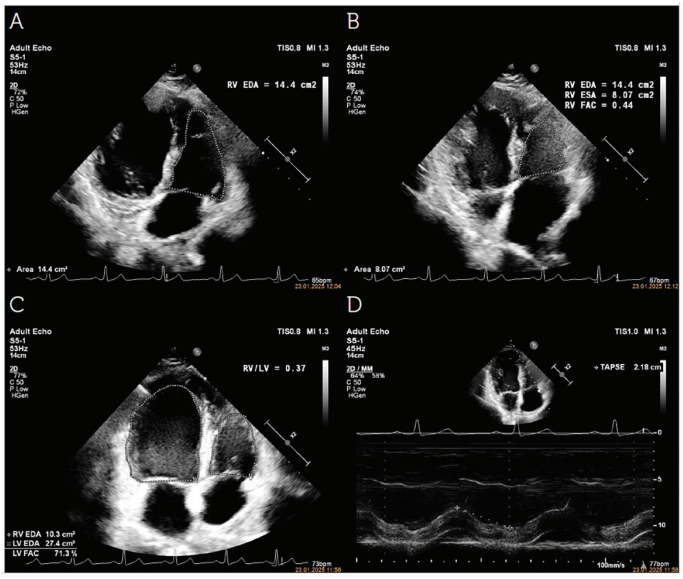

Figure 4. Echocardiographic assessment of left ventricular (LV) function. A) Apical four-chamber view demonstrating the LV end-diastolic volume (EDV), measured to assess LV filling and chamber dimensions. B) Apical four-chamber view illustrating the LV end-systolic volume (ESV), utilized for ejection fraction (EF) calculation. EF (%)=(LVEDV-LVESV)/(LVEDV)x100. C) Continuous-wave Doppler echocardiographic recording of mitral regurgitation (MR) jet, used to calculate dp/dt max, an index of LV contractility. The dp/dt max is determined by measuring the rate of pressure rise across the mitral valve during early systole. D) M-mode echocardiographic assessment of mitral annular plane systolic excursion (MAPSE), a parameter reflecting longitudinal LV function. MAPSE is obtained by tracking the systolic displacement of the mitral annulus, serving as a surrogate marker for global LV systolic performance.

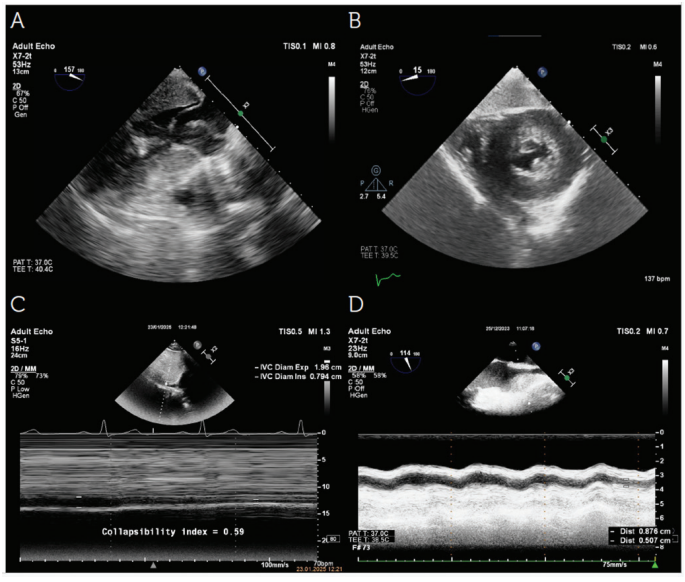

Figure 5. Echocardiographic assessment of volume status. A, B) Echocardiographic images demonstrating "kissing ventricles," a hallmark of hypovolemia. In severe hypovolemia, left ventricular walls nearly touch at end-systole due to reduced preload, with minimal residual cavity. Additionally, diastolic filling is significantly impaired, further supporting volume depletion. C) Inferior vena cava (IVC) collapsibility index (IVC-CI) measurement using M-mode echocardiography in a spontaneously breathing patient. IVC-CI=(IVCmax–IVCmin)/(IVCmax)x100. >50% suggests a low central venous pressure (< 5 mmHg), indicating hypovolemia. IVC distensibility index (IVC-DI) is applied in mechanically ventilated patients and is calculated as follows: IVC-DI=(IVCmax–IVCmin)/(IVCmin)x100. >18% suggests fluid responsiveness. D) Superior vena cava (SVC) collapsibility index (SVC-CI) measurement using transesophageal echocardiography, which is primarily applied in mechanically ventilated patients. SVC-CI=(SVCmax-SVCmin)/(SVCmax)x100. >36-40% suggests volume responsiveness.

Conclusion

In this review, we have examined advanced hemodynamic parameters and their integration into clinical practice, aiming to refine perioperative hemodynamic assessment with a more comprehensive and targeted approach. Accurate interpretation of key parameters such as CO, vascular resistance, fluid responsiveness, VAC, arterial elastance, and impedance is essential for maintaining hemodynamic stability in surgical patients. Furthermore, echocardiographic parameters provide valuable insights into myocardial function and volume status, contributing to a more nuanced understanding of perioperative cardiovascular dynamics. The transition from traditional static measurements to dynamic parameters enables more precise fluid and vasopressor management, ultimately optimizing perioperative patient care. The implementation of advanced hemodynamic assessment algorithms has the potential to reduce perioperative complications and enhance patient safety. Further integrating these parameters into clinical decision-making frameworks will further refine individualized patient management strategies, fostering advancements in perioperative hemodynamic optimization.

Footnotes

Author Contributions: Concept - M.E.A., E.S.B., Z.A.D., B.D.; Design - M.E.A., A.A., B.A.; Data Collection and/or/Processing - M.E.A., A.A., B.A., Analysis and/or/Interpretation - E.S.B., Z.A.D.; Literature Search - Ü.K., G.T., B.A.; Writing - M.E.A., A.A., Ü.K., E.S.B., Z.A.D., G.T., B.A., B.D.

Declaration of Interests: Three authors of this article, Zeliha Aslı Demir, Başak Akça and Burhan Dost, are a member of the Editorial Board of the Turkish Journal of Anaesthesiology and Reanimation. However, he did not involved in any stage of the editorial decision of the manuscript. The other authors declared no conflict of interest.

Declaration Regarding the Use of AI and AI-Assisted Technologies: During the preparation of this work, the author(s) utilized OpenAI's ChatGPT to assist in drafting sections of the manuscript. The outputs generated by the AI were cross-verified with primary literature sources and reviewed by subject matter experts to ensure accuracy and contextual appropriateness. After carefully reviewing and editing the content as necessary, the author(s) take full responsibility for the publication's content. This incorporation of AI tool usage primarily impacted the efficiency of manuscript drafting and the clarity of expression in the text.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Geerts BF, Aarts LP, Jansen JR. Methods in pharmacology: measurement of cardiac output. *Br J Clin Pharmacol*. 2011;71(3):316-330. [CrossRef]
2. Han JC, Pham T, Taberner AJ, Loiselle DS, Tran K. Solving a century-old conundrum underlying cardiac force-length relations. *Am J Physiol Heart Circ Physiol*. 2019;316(4):781-793. [CrossRef]
3. Delicce AV, Makaryus AN. Physiology, Frank Starling Law. *StatPearls, StatPearls Publishing*, 2023. [CrossRef]
4. Hamzaoui O, Teboul JL. Central venous pressure (CVP). *Intensive Care Med*. 2022;48(10):1498-1500. [CrossRef]
5. de Keijzer IN, Scheeren TWL. Perioperative hemodynamic monitoring: an overview of current methods. *Anesthesiol Clin*. 2021;39(3):441-456. [CrossRef]
6. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med*. 2009;37(9):2642-2647. [CrossRef]
7. Marik PE. Fluid responsiveness and the six guiding principles of fluid resuscitation. *Crit Care Med*. 2016;44(10):1920-1922. [CrossRef]
8. Shin CH, Long DR, McLean D, et al. Effects of intraoperative fluid management on postoperative outcomes: a hospital registry study. *Ann Surg* 2018; 267:1084-1092. [CrossRef]
9. Sakr Y, Rubatto Birri PN, Kotfis K, et al. Higher fluid balance increases the risk of death from sepsis: results from a large international audit. *Crit Care Med*. 2017;45:386-394. [CrossRef]
10. Oh TK, Song IA, Do SH, Jheon S, Lim C. Association of perioperative weight-based fluid balance with 30-day mortality and acute kidney injury among patients in the surgical intensive care unit. *J Anesth*. 2019;33:354-363. [CrossRef]
11. Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care*. 2011;1(1):1. [CrossRef]
12. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA*. 2016;316(12):1298-1309. [CrossRef]
13. Fellahi JL, Futier E, Vaisse C, et al. Perioperative hemodynamic optimization: from guidelines to implementation-an experts' opinion paper. *Ann Intensive Care*. 2021;11(1):58. [CrossRef]
14. Benes J, Giglio M, Brienza N, Michard F. The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. *Crit Care*. 2014;18(5):584. [CrossRef]
15. Chaves RCF, Barbas CSV, Queiroz VNF, et al. Assessment of fluid responsiveness using pulse pressure variation, stroke volume variation, plethysmographic variability index, central venous pressure, and inferior vena cava variation in patients undergoing mechanical ventilation: a systematic review and meta-analysis. *Crit Care*. 2024;28(1):289. [CrossRef]
16. Castro R, Born P, Roessler E, et al. Preload responsiveness-guided fluid removal in mechanically ventilated patients with fluid overload: a comprehensive clinical-physiological study. *J Crit Care*. 2024;84:154901. [CrossRef]
17. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(12):1795-1815. [CrossRef]
18. Rhodes A, Evans LE, Alhazzani W, et al. surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304-377. [CrossRef]
19. Perel A, Pizov R, Cotev S. Respiratory variations in the arterial pressure during mechanical ventilation reflect volume status and fluid responsiveness. *Intensive Care Med*. 2014;40(6):798-807. [CrossRef]
20. Cannesson M, Le Manach Y, Hofer CK, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a "gray zone" approach. *Anesthesiology*. 2011;115(2):231-241. [CrossRef]
21. Michard F, Chemla D, Teboul JL. Applicability of pulse pressure variation: how many shades of grey? *Crit Care*. 2015;19(1):144. [CrossRef]
22. Le Manach Y, Hofer CK, Lehot JJ, et al. Can changes in arterial pressure be used to detect changes in cardiac output during volume expansion in the perioperative period? *Anesthesiology*. 2012;117(6):1165-1174. [CrossRef]

23. Perel A. Using dynamic variables to guide perioperative fluid management. *Anesthesiology.* 2020;133(4):929-935. [CrossRef]
24. De Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology*. 2009;110(5):1092-1097. [CrossRef]
25. Chaves RCF, Corrêa TD, Neto AS, et al. Assessment of fluid responsiveness in spontaneously breathing patients: a systematic review of literature. *Ann Intensive Care*. 2018;8(1):21. [CrossRef]
26. Chen H, Liang M, He Y, et al. Inspiratory effort impacts the accuracy of pulse pressure variations for fluid responsiveness prediction in mechanically ventilated patients with spontaneous breathing activity: a prospective cohort study. *Ann Intensive Care.* 2023;13(1):72. [CrossRef]
27. Teboul JL, Monnet X, Chemla D, Michard F. Arterial pulse pressure variation with mechanical ventilation. *Am J Respir Crit Care Med.* 2019;199(1):22-31. [CrossRef]
28. Mallat J, Meddour M, Durville E, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth.* 2015;115(3):449-456. [CrossRef]
29. Nimje GR, Goyal VK, Singh P, Shekhrajka P, Mishra A, Mittal S. Assessment of fluid responsiveness after tidal volume challenge in renal transplant recipients: a nonrandomized prospective interventional study. *Clin Transplant Res*. 2024;38(3):188-196.
30. Alvarado Sánchez JI, Caicedo Ruiz JD, Diaztagle Fernández JJ, Amaya Zuñiga WF, Ospina-Tascón GA, Cruz Martínez LE. Predictors of fluid responsiveness in critically ill patients mechanically ventilated at low tidal volumes: systematic review and meta-analysis. *Ann Intensive Care*. 2021;11(1):28. [CrossRef]
31. Monnet X, De Backer D, Pinsky MR. Using the ventilator to predict fluid responsiveness. *Intensive Care Med*. 2025;51:150-153. [CrossRef]
32. Sandroni C, Cavallaro F, Marano C, Falcone C, De Santis P, Antonelli M. Accuracy of plethysmographic indices as predictors of fluid responsiveness in mechanically ventilated adults: a systematic review and meta-analysis. *Intensive Care Med.* 2012;38(9):1429-1437. [CrossRef]
33. Natalini G, Rosano A, Franceschetti ME, Facchetti P, Bernardini A. Variations in arterial blood pressure and photoplethysmography during mechanical ventilation. *Anesth Analg.* 2006;103(5):1182-1188. [CrossRef]
34. Cannesson M, Desebbe O, Rosamel P, et al. Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. *Br J Anaesth.* 2008;101(2):200-206. [CrossRef]
35. Alvarado Sánchez JI, Caicedo Ruiz JD, Diaztagle Fernández JJ, et al. Variables influencing the prediction of fluid responsiveness: a systematic review and meta-analysis. *Crit Care.* 2023;27(1):361. [CrossRef]
36. Bubenek-Turconi ŞI, Văleanu L, Popescu M, et al. Continuous noninvasive hemoglobin monitoring reflects the development of acute hemodilution after consecutive fluid challenges. *Anesth Analg* 2020;130(3):696-703. [CrossRef]
37. Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. *Intensive Care Med.* 2016;42(12):1935-1947. [CrossRef]
38. Cavallaro F, Sandroni C, Marano C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med.* 2010;36(9):1475-1483. [CrossRef]
39. Chirinos JA. Ventricular-arterial coupling: Invasive and non-invasive assessment. *Artery Res.* 2013;7(1):10.1016/j.artres.2012.12.002. [CrossRef]
40. Li W, Ahn AC. Pulsatile hemodynamics of hypertension: systematic review of aortic input impedance. *J Hypertens*. 2012;30(8):1493-1499. [CrossRef]
41. Qureshi MU, Colebank MJ, Schreier DA, et al. Characteristic impedance: frequency or time domain approach? *Physiol Meas*. 2018;39(1):014004. [CrossRef]
42. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. *Circulation*. 1992;86(2):513-521. [CrossRef]
43. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. *Heart Fail Clin.* 2008;4(1):23-36. [CrossRef]
44. Kass DA. Age-related changes in venticular-arterial coupling: pathophysiologic implications. *Heart Fail Rev*. 2002;7(1):51-62. [CrossRef]
45. Sagawa K, Suga H, Shoukas AA, Bakalar KM. End-systolic pressure/volume ratio: a new index of ventricular contractility. *Am J Cardiol*. 1977;40(5):748-53. [CrossRef]
46. Chen CH, Fetics B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *J Am Coll Cardiol*. 2001;38(7):2028-2034. [CrossRef]
47. Monge Garcia MI, Jian Z, Settels JJ, et al. Performance comparison of ventricular and arterial dP/dt_{max} for assessing left ventricular systolic function during different experimental loading and contractile conditions. *Crit Care*. 2018;22(1):325. [CrossRef]
48. Hamlin RL, del Rio C. dP/dt(max)--a measure of 'baroinometry'. *J Pharmacol Toxicol Methods.* 2012;66(2):63-65. [CrossRef]
49. Perny J, Kimmoun A, Perez P, Levy B. Evaluation of cardiac function index as measured by transpulmonary thermodilution as an indicator of left ventricular ejection fraction in cardiogenic shock. *Biomed Res Int.* 2014;2014:598029. [CrossRef]
50. Harada T, Yamaguchi M, Omote K, et al. Cardiac power output is independently and incrementally associated with adverse outcomes in heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging*. 2022;15(2):e013495. [CrossRef]
51. Romano SM. Cardiac cycle efficiency: a new parameter able to fully evaluate the dynamic interplay of the cardiovascular system. *Int J Cardiol.* 2012;155(2):326-327. [CrossRef]
52. Persona P, Tonetti T, Valeri I, et al. Dynamic arterial elastance to predict mean arterial pressure decrease after reduction of vasopressor in septic shock patients. *Life (Basel)*. 2022;13(1):28. [CrossRef]
53. Monge García MI, Jian Z, Hatib F, et al. Dynamic arterial elastance as a ventriculo-arterial coupling index: an experimental animal study. *Front Physiol*. 2020;6(11):284. [CrossRef]
54. Oh EJ, Min JJ, Kwon E, Choi EA, Lee JH. Evaluation of pre-induction dynamic arterial elastance as an adjustable predictor of post-induction hypotension: a prospective observational study. *J Clin Anesth*. 2023;87:111092. [CrossRef]

DOI: 10.4274/TJAR.2024.241646

Original Article
Paediatric Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):208-216

Underestimating Children's Self-reported Pain: Agree/Disagree?

Şefika Başoğlu, Özlem Selvi Can, Volkan Baytaş, Hakan Yılmaz, Fatma Nur Erkent

Ankara University Faculty of Medicine, Department of Anaesthesiology and Intensive Care, Ankara, Türkiye

Cite this article as: Başoğlu Ş, Can ÖS, Baytaş V, Yılmaz H, Erkent FN. Underestimating children's self-reported pain: agree/disagree? *Turk J Anaesthesiol Reanim.* 2025;53(5):208-216.

Abstract

Objective: To compare postoperative pain after different surgical types and grades using the visual analogue scale (VAS) and numeric rating scale (NRS) evaluated by the patient, parent, and nurse.

Methods: After approval from the local ethics committee and written informed consent from the patient and parent, a single-center, prospective, randomized study was designed. A total of 180 children with American Society of Anesthesiologists I-III physical status between the ages of 7-12 (n = 90) and 13-18 (n = 90) years were included in the study who underwent elective surgery at Ankara University Faculty of Medicine Hospitals between January and December 2022. Pain was assessed postoperatively at 2 hours using two pain scales. Patients who underwent mini-intermediate or major surgery were evaluated separately.

Results: Four children from each age group were excluded from the study due to insufficient data recording, and data from 172 children were analyzed. Including all age groups and surgical grades, all children had excellent agreement with the parent [VAS/NRS: intraclass correlation coefficient (ICC)= 0.903/ICC= 0.900] and good agreement was found between the child and nurse (VAS/NRS: ICC= 0.852/ ICC= 0.842). For the VAS and NRS, when parent and nurse compliance scores were compared, no significant difference was observed between the two scores. For VAS and NRS, fathers were found to be better at predicting pain for children than mothers.

Conclusion: Self-reported pain is the gold standard for pain evaluation. The parents assessed pain scores that were similar to those of their children using NRS and VAS. Nurses underestimated a child's pain with both scores.

Keywords: Child, pain measurement, paediatric anaesthesia, postoperative pain, proxy

Main Points

- Pain is a subjective experience, and self-reporting is the gold standard for assessment and treatment.
- Furthermore, a child's self-report on pain must be used whenever possible to guide pain management. Sometimes, it is not possible (due to developmental, linguistic, and cognitive limitations) for parents' or nurses' evaluations to be vital to managing pain therapy.
- Children's self-pain reports are similar to those of their parents and are more reliable than nurses' evaluations.
- In this study, the parents evaluated the children's postoperative pain similarly using the visual analogue scale and numeric rating scale. Nurses underestimated children's pain with both pain scores.

Introduction

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or threat".[1] It is every patient's right to receive relief from their suffering and pain. The manner in which children express pain varies depending on their age and developmental stage. Because children sometimes have limited experience reporting pain, their inability to verbally

Corresponding author: Şefika Başoğlu, MD, e-mail: sefikabasoglu@gmail.com

Received: July 16, 2024 Accepted: September 18, 2024
Epub: January 10, 2025 Published date: October 14, 2025

express pain or feelings sometimes makes pain assessment difficult in children.[2]

Historically, assessing and reporting pain has been the gold standard for effective pain assessment.[3] Paediatric patients comprise a broad population ranging from newborns to 18 years of age. Different pain assessment tools are available to evaluate pain types according to age in this large population.[2-4]

There are only a limited number of studies with different results regarding parents' and nurses' evaluations of children's pain. Different results emerged from studies in which parents or medical professionals assessed pain in children. In some of these studies, it has been found that parents and doctors/nurses sometimes evaluate pain similarly to children but often give lower or higher scores than it is.[5-13] Given the limited number of studies on this topic within our country, we undertook this research to address this gap. Due to the different ages of paediatric patients and difficulties they experience in expressing themselves, pain treatment in children should be evaluated and managed by an observer. In practice, a nurse in the hospital, as well as parents and other caregivers at home, perform this evaluation after discharge.[2] It has been found that parents and nurses often underrate or overestimate pain.[8,14] There are risks in overestimating pain and unnecessary treatment, as well as in underestimating pain and inadequate treatment. Parents' false beliefs that medications should only be given if their child has unbearable pain, their fear that their child may become addicted, or their belief that their child expresses pain to attract attention may lead to inadequate pain treatment.[15]

In postoperative pain management guidelines, some pain assessment tools have been validated for their precision in detecting the presence of pain and determining its severity. The visual analogue scale (VAS) and numeric rating scale (NRS) are commonly used one-dimensional pain scales and are widely used in children older than 4 years for self-reporting or assessment of their proxies in pain.[2,4,16]

Our study was planned to evaluate pain at the 2nd postoperative hour first using the VAS and then using the NRS 11 by the child, parent, and nurse separately. Our primary aim was to determine which parents or nurses would perform the closest pain assessment for the child. This study also aimed to reveal whether the parent and nurse had differences in VAS or NRS pain scores when estimating the child's pain most closely. Our secondary aims are to identify factors that may cause differences in pain assessment between the child, parent, and nurse, as well as differences or compatibility between the parent and nurse. The children included in our study were at the appropriate age and mental and health status to express their pain appropriately using both scores. Based on the results obtained from these children who can express themselves, we will have an idea about the effectiveness of treatment given by a proxy (parent and nurse) in children who cannot express themselves and which pain score can be used to determine the pain intensity most compatible with the child in terms of proxies. Although the validity of this methodology has not been definitively established, parent and nurse assessments using the VAS and NRS are frequently used as proxy measures for pain assessment in children who are unable to self-report.[12]

Methods

This study is a prospective randomized study conducted in the Pediatric Surgery, Orthopedics and Traumatology, Ear Nose and Throat, and Ophthalmology Operating Rooms at Ankara University Faculty of Medicine Hospitals between January and December 2022 after the approval of Ankara University Faculty of Medicine, Human Research Ethics Committee (approval no.: İ9-576-21, dated: October 14, 2024).

Children scheduled for elective minor-intermediate or major surgery between the ages of 7-12 and 12-18 years old, with the American Society of Anesthesiologists (ASA) health status level I-III and their parents were included in the study after giving written informed consent. The patient and/or parents who did not agree to participate in the study, the patient and/or the parent who has cognitive dysfunction, the child who has an ASA health status of level IV-V, liver or kidney dysfunction, receiving daily analgesic treatment due to chronic pain, and has a history of allergy to any of the medications used were excluded.

Patients, their parents, and nurses were informed before enrollment about the visual pain scale and NRS, which will be used in pain assessment. It was explained that on the visual pain scale, one end of a 100-mm line represents no pain, while the other end represents the most severe pain experienced. Measurement was performed after the assessor marked the pain on the chart. Additionally, it was explained that "0" on the NRS indicates no pain, while "10" indicates the most severe pain experienced. On the NRS, the evaluator was asked to express pain using a number between "0 and 10". Although the nurses participating in the study were assigned to different wards, they possessed substantial knowledge and experience with both pain scales commonly utilized in surgical clinics. However, they were informed about the pain scales to be used in the study, and their consent was obtained.

All assessments were performed at the 2nd postoperative hour. All three participants (child, parent, nurse) were unaware of each other, and the procedure was performed separately via VAS and NRS at the clinical ward and recorded by the same anaesthesiologist. Upon entering the child's room to assess pain levels, the parent was respectfully requested to step outside, ensuring that pain assessments from both the

child and parent could be obtained independently. Pain scores from the child and parent were recorded separately to prevent mutual influence. Additionally, the nurse conducting the assessment remained blinded to both the child's and parent's scores to avoid any potential bias. Pain was then systematically evaluated using standardized assessment scales, with all findings documented.

Patients were randomized according to the age of the children and the extent of surgery to be performed and were divided into four groups:

• Group 1A: children aged 7-12 years old who will undergo minor or intermediate surgery;

• Group 1B: children aged 7-12 years old who will undergo major surgery;

• Group 2A: children aged 13-18 years old who will undergo minor or intermediate surgery;

• Group 2B: children aged 13-18 who would undergo major surgery.

Factors such as the child's gender, age, weight, height, comorbidities, use of medication, previous surgeries that could affect pain assessment, and type of planned surgical procedure were recorded preoperatively. Furthermore, the gender (mother or father), age, marital status (currently married or divorced), number of children, and education level of the parents participating in the study were questioned and recorded.

In all patients, anaesthesia and pain management were routine departmental practices and were not interfered with by the researchers. The same investigator provided all preoperative briefings, discharged the patients from the recovery unit, and visited the child, his or her parents, and the nurse for pain assessment at the 2nd postoperative hour (ŞB).

Since children may perceive disturbing factors, such as intravenous lines and blood pressure cuffs, etc., as pain, it was confirmed that the body region they complained about was compatible with the surgery site before the children were asked to evaluate for pain.

Statistical Analysis

The number of children was 172 in total, including 86 major and 86 minor-intermediate surgeries to detect an effect of 0.25 (Cohen-f) between family, nurse, and patient in terms of VAS scores after minor-intermediate or major surgical procedures in paediatric patients of different ages with a power of 0.80 at a significance level of 0.05. The sample size calculation was performed using G*Power software (version 3.1.9.2).

The SPSS 11.5 program was used to analyze the data. Mean ± standard deviation and median (minimum-maximum) were used as descriptive variables for quantitative variables, and the number of patients (percentage) was used for qualitative variables. The intraclass correlation coefficient (ICC) was used to examine parent, nurse, and child agreement on VAS and NRS. Univariate and multivariate linear regression analyses were performed to investigate factors affecting the child-parent VAS and NRS differences. $P < 0.05$ was considered as the statistical significance level.

Results

A total of 180 children, 90 patients in each age group (7-12 years and 13-18 years), and their parents were included in the study, taking into account data loss. Four children from each age group were excluded from the study due to insufficient data recording, and data from 172 children were analyzed (Figure 1). 27.9% of the children included in the study had minor/intermediate surgery between the ages of 7-12 years (Group 1A), 22.1% had major surgery between the ages of 7-12 (Group 1B), 25.6% had minor/intermediate surgery and surgery between the ages of 13-18 (Group 2A), and 24.4% were in the major surgery group between the ages of 13-18 years (Group 2B) (Table 1).

Values for VAS and NRS, which were reported separately by the child, parent, and nurse, are shown for all children in Table 2, regardless of the surgery grade.

The results of the ICC method were used to examine the compliance scores of the VAS scores for each study group (child-parent and child-nurse), as presented in Table 3.

When the child-parent and child-nurse harmony scores were compared, it was concluded that the parent's VAS reporting was better than the nurse's in Group 1A, 2A, and 2B. In Group 1B; it was concluded that the VAS reporting of the parent and nurse were similar (Table 3).

When all children were evaluated using the VAS, excellent (ICC=0.903) agreement was found between the child and parent, and good agreement (ICC=0.852) was found between the child and nurse. When the child-parent and child-nurse harmony scores were compared, it was concluded that the parent's VAS reporting was better than the nurse's (Table 3).

The results of the ICC method were used to examine the compliance scores of the NRS values for each study group (child-parent and child-nurse), as shown in Table 4. When the child-parent and child-nurse harmony scores were compared, it was concluded that the parent's NRS reporting was better than the nurse's in all groups.

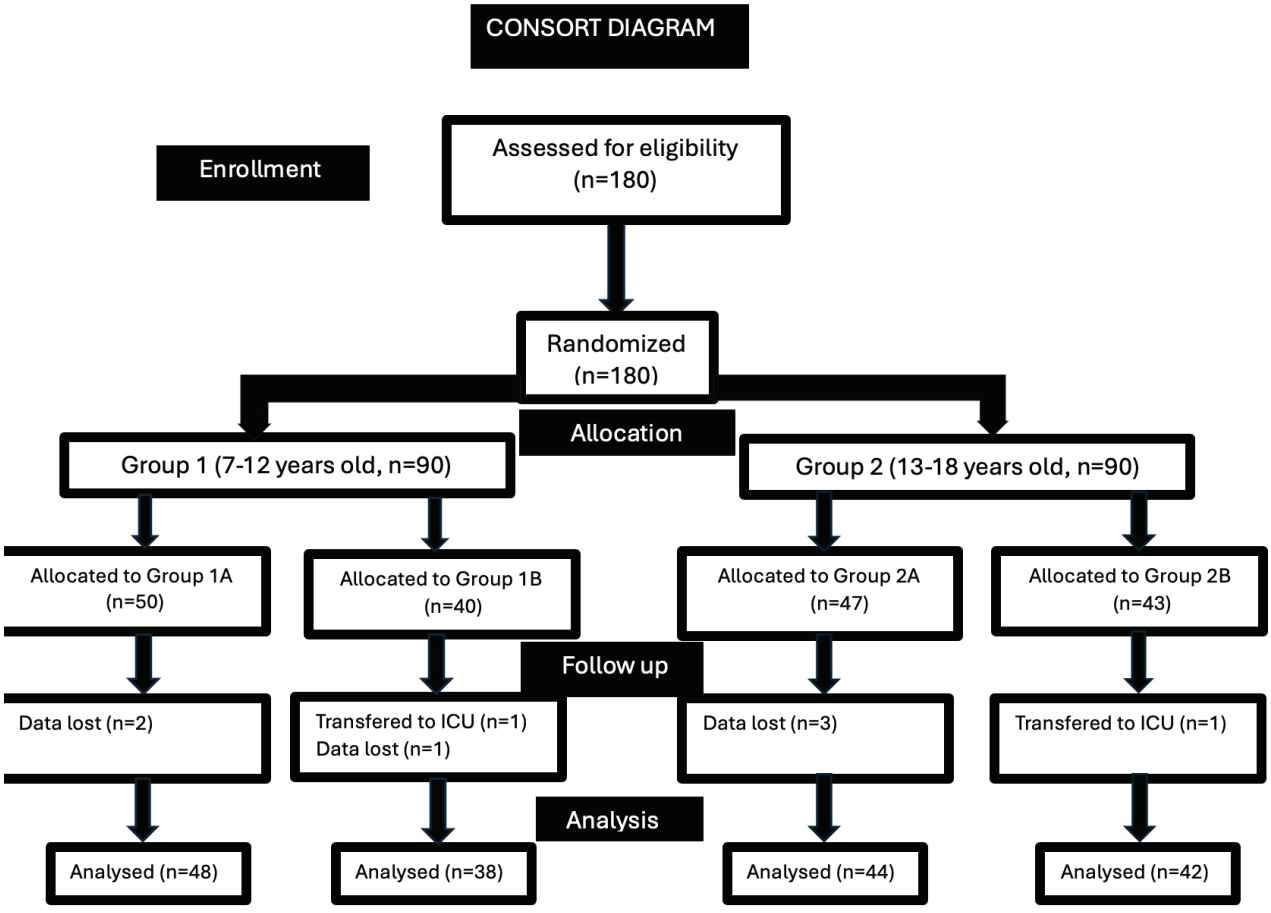

Figure 1. CONSORT flow diagram for the study.

ICU, intensive care unit.

When all children were evaluated using the NRS, excellent (ICC =0.900) agreement was found between the child and parent, and good agreement (ICC =0.842) was found between the child and nurse. When the child-parent and child-nurse harmony scores were compared, it was concluded that the parent's NRS reporting was better than that of the nurse (Table 4). When the general ICC scores for VAS and NRS scores were compared for both parents and nurses, it was seen that the VAS and NRS scores gave very similar results.

When the child-parent harmony scores for the mother and father were compared, it was concluded that the father's VAS reporting was better than the mother's. When the child-parent adjustment scores for the mother and father were compared, it was concluded that the father's NRS score was slightly better than the mother's (Table 5). The literature review revealed a notable gap, as no studies specifically examined whether mothers or fathers are more accurate in predicting a child's pain. This finding is a significant and noteworthy aspect of our study and has the potential to make a valuable contribution to the existing literature.

There were no significant differences between the groups in terms of the gender of the patient, previous surgery, parents' education level, marital status, or number of children they had.

In Table 6, the effect of previous surgery on pain scores was examined, and only the effect on the VAS child pain score was found to be significant (P=0.038). The VAS child score in patients who had previously undergone surgery was 0.961 units lower than that in patients who had not undergone surgery. Previous surgery alone explained 2.5% of the variation in the VAS score of children. For the other pain scores, patients who had undergone previous surgery had lower pain scores than those who had not previously undergone surgery; however, this difference was not significant.

Table 1. Basic Patient and Parent Characteristics		
Variables		
Group, n (%)	1A	48 (27.9%)
	1B	38 (22.1%)
	2A	44 (25.6%)
	2B	42 (24.4%)
Age (years)	Mean ± SD	11.8±3.5
	Median (Min.-Max.)	12.0 (7.0-18.0)
Sex, n (%)	Girl	53 (30.8%)
	Boy	119 (69.2%)
Operation Grade, n (%)	Minor/intermediate surgery	92 (53.5%)
	Major surgery	80 (46.5%)
Operation history, n (%)	No	95 (55.2%)
	Yes	77 (44.8%)
Parents, n (%)	Mother	139 (80.8%)
	Father	33 (19.2%)
Parental educational status, n (%)	Primary	65 (37.7%)
	High school	51 (29.7%)
	University	56 (32.6%)

Mean, average; SD, standard deviation; Min., minimum; Max., maximum.

Table 2. VAS and NRS Scores		
	95% CI (Lower-Upper limit)	**Median (Min.-Max.)**
Children VAS	3.94-4.85 ($P < 0.001$)	4.5 (0.0-10.0)
Parent VAS	3.77-4.64 ($P < 0.001$)	4.0 (0.0-10.0)
Nurse VAS	2.58-3.29 ($P < 0.001$)	3.0 (0.0-8.0)
Children NRS	4.46-5.41 ($P < 0.001$)	5.0 (0.0-10.0)
Parent NRS	3.88-4.57 ($P < 0.001$)	4.0 (0.0-10.0)
Nurse NRS	2.58-3.29 ($P < 0.001$)	3.0 (0.0-8.0)

CI, confidence interval; Min., minimum; Max., maximum; VAS, visual analogue scale; NRS, numerical rating scale.

Table 3. ICC Values for the VAS Study Groups						
Groups	**Child-Parent**			**Child-Nurse**		
	ICC	**95% CI (Lower-Upper limit)**	***P* value**	**ICC**	**95% CI (Lower-Upper limit)**	***P* value**
1A	0.903	0.833-0.944	<0.001	0.804	0.676-0.885	<0.001
1B	0.802	0.651-0.892	<0.001	0.804	0.654-0.893	<0.001
2A	0.860	0.758-0.921	<0.001	0.766	0.609-0.865	<0.001
2B	0.885	0.797-0.937	<0.001	0.807	0.668-0.891	<0.001
All patients	0.903	0.871-0.927	<0.001	0.852	0.805-0.888	<0.001

CI, confidence interval; ICC, intraclass correlation coefficient; VAS, visual analogue scale.

Table 4. ICC Values of the Study Groups for NRS

Groups	Child-Parent			Child-Nurse		
	ICC	95% CI (Lower-Upper Limit)	*P* value	ICC	95% CI (Lower-Upper Limit)	*P* value
1A	0.895	0.820-0.940	<0.001	0.808	0.682-0.888	<0.001
1B	0.813	0.669-0.898	<0.001	0.744	0.559-0.858	<0.001
2A	0.883	0.795-0.934	<0.001	0.768	0.612-0.866	<0.001
2B	0.838	0.718-0.909	<0.001	0.784	0.633-0.878	<0.001
All patients	0.900	0.867-0.925	<0.001	0.842	0.792-0.880	<0.001

CI, confidence interval; ICC, intraclass correlation coefficient; NRS, numerical rating scale.

Table 5. Parental ICC Values for VAS and NRS Scores

Measurement	Parent	Child-Parent		
		ICC	95% CI (Lower-Upper limit)	*P* value
VAS	**Mother**	0.898	0.860-0.926	<0.001
	Father	0.935	0.872-0.967	<0.001
NRS	**Mother**	0.899	0.861-0.927	<0.001
	Father	0.905	0.816-0.952	<0.001

CI, confidence interval; ICC, intraclass correlation coefficient; NRS, numerical rating scale; VAS: visual analogue scale.

Table 6. Effect of Previous Surgery on Pain Score

Variables	β	SE	*P* value	R^2	95% CI
VAS Child	-0.961	0.460	0.038	0.025	-1,869-0.054
VAS Parent	-0.755	0.445	0.092	0.017	-1,634-0.123
VAS Nurse	-0.445	0.366	0.225	0.009	-1,167-0.277
NRS Child	-0.765	0.482	0.115	0.015	-1,716-0.187
NRS Parent	-0.750	0.451	0.098	0.016	-1,641-0.140
NRS Nurse	-0.389	0.365	0.289	0.007	-1,110-0.333

CI, confidence interval; VAS, visual analogue scale; NRS, numerical rating scale; SE, standard error.

Discussion

Acute pain is a stimulating, complex, dynamic, and subjective experience. The subjective nature of pain has led to self-reporting of pain as the most effective way to measure pain. The most important step in postoperative pain management is pain assessment during follow-up. In paediatric patients, caregivers must evaluate the severity of pain and contribute to and monitor pain treatment in terms of managing pain in children, especially in children who cannot express their pain for various reasons. However, it is important to accurately measure pain, which is a subjective but important complaint, both at the beginning and during treatment, to avoid adverse effects caused by less or more treatment than needed.

The results of this study show that when children between the ages of 7-18 years old underwent minor-intermediate or major surgery, their parents could perform a closer pain assessment with their children using VAS and NRS pain scales. Nurses were able to perform less similar assessments of children's pain than parents with both pain scores.

Similar to the results of this study, Rajasagaram et al.[8] examined 86 children between the ages of 3 and 15 years who underwent a painful procedure and found that nurses' scores were significantly lower than the children's scores for each age group and parents' scores were equal to or lower than the children's scores. Khin Hla et al.[12] showed that healthcare professionals tend to underestimate postoperative pain in children who undergo outpatient surgery. Our findings showed that nurses rated children's pain lower (in

other words, they underestimated it) in all groups, regardless of the children's age, surgical grade and gender. Nurses are a vital part of patient care and treatment, especially in inpatient settings. Nurses actively participate in patient treatment, monitoring, and follow-up. Moreover, nurses usually interact more frequently with patients during hospitalization than physicians. One explanation for this may be that the parent takes his/her own child's usual behavior as his/her frame of reference, while the nurse has extensive experience with other children who have undergone surgery. Another reason may be that nurse with different degrees of expertise performed the evaluation, as in our study. Lack of knowledge or workload among nurses may have affected the evaluations. Our study was conducted with nurses working in the surgical department of a university hospital, mostly in paediatric departments. Furthermore, despite the fact that all nurses were informed about the pain scales that were planned to be used before starting the study, they underestimated the children's pain with both pain scores. Insufficient knowledge about pain assessment despite pre-study information may also be a reason, but children and parents gave similar scores with similar information. A more likely cause may be the difference in experience levels and workload of nurses because they were randomly selected because they were working in shift patterns. In fact, nurses can take into account parameters that can be affected by pain, such as concurrent heart rate, oxygen saturation, blood pressure, body posture, and facial expressions, albeit unintentionally (which is necessary for patient follow-up and treatment). Increasing the level of knowledge and awareness of nurses and healthcare workers about pain, pain measurement, and treatment will make a very important contribution to pain management in all patient groups, especially those who cannot report their pain levels, such as paediatric patients. Furthermore, if healthcare providers keep themselves up-to-date on pain, they will be able to provide information to patients and their families on this matter.

The VAS and NRS pain scores used together in this study showed that children rated their pain at a similar intensity. Additionally, when the general compliance scores of the parents and nurses who assessed the child's pain were compared, very similar results were obtained with the two scores. For this reason, we believe that VAS or NRS can be used to evaluate pain in children between the ages of 7-18 years effectively and reliably.

In our study, it was observed that as the age of children increased in minor-intermediate surgeries, the compatibility between the child and parent decreased in both the VAS and NRS scores. Knutsson et al.[14] also reached a conclusion similar to our study. When they questioned the pain of children aged between 3 and 10 years who underwent adenoidectomy, a surgery that can be considered minor intermediate, using the VAS score, they concluded that harmony with the parents decreased as the age of the children increased.[14]

In children who underwent major surgery, we found that as the age of the child increased, the compatibility between the child and parent increased in terms of both the VAS and NRS scores. The reason for the increase in compliance with major surgeries with age may be that families made a closer prediction of their children by scoring them higher than normal due to their perception that major surgeries would be more painful. In our literature review, we did not find any data showing the compatibility between age and the age of the child and parent during major surgeries. For this reason, it is possible to consider it an important result of our study.

In a study by Kaminsky et al.[17] which included children between the ages of 2 and 15 years who underwent adenoidectomy and/or tonsillectomy, parents estimated their children's postoperative pain to be higher than their children. However, the amount of analgesic administered did not exceed the safe limits and was not considered unnecessary. The fact that Kaminsky et al.'s[17] study was conducted in different hospitals, used pain scores that were different from our study, and evaluated a 3-day pain score and analgesic treatment may have caused differences in our results.

When we evaluated the effect of whether the parent was a mother or father on the ICC values of the child's pain using VAS and NRS, we found that fathers were better at estimating their children's pain than mothers. Although the mothers were compliant, they scored lower. The lower number of fathers participating in our study (19.2% vs. 80.8%) may be due to the differences in mother-child and father-child relationships in society. No study has been found in the literature on which mother and father predict the child's pain more closely. This result is also one of the most remarkable and important points of our study.

In a study of 102 patients conducted by Logan and Rose[18] adolescent girls reported higher rates of "lowest daily pain" and "average daily pain" than adolescent boys after an overnight hospital stay after surgery. In this study, no significant difference was found in terms of sex.

Another significant finding of our study was that 44.8% of the children had previously undergone surgery. The elevated scores on the VAS and NRS for pain observed in these children, regardless of age group or type of surgery, could be attributed to heightened anxiety and apprehension about the potential adverse outcomes associated with earlier surgical interventions. This suggests that prior surgical experiences may significantly influence pain perception and anxiety in children, highlighting the importance of

comprehensive preoperative psychological assessment and tailored postoperative care strategies to mitigate these concerns.

It is expected that our study will inform more accurate assessments of postoperative pain and serve as a foundation for future research, particularly in paediatric patients undergoing the same type of surgery. Additionally, providing education to both children and their parents about the use of pain scales before surgery could improve the validity of pain evaluations and enhance the overall understanding of pain management in paediatric surgical populations.

Study Limitations

As with the limitations of postoperative pain assessments, our study has several limitations. First, we performed the evaluation only once postoperatively. The results of evaluations performed at different postoperative periods may differ. Another limitation is that not knowing the baseline psychological state of the parent conducting the pain assessment, how much time they spend with their children in their normal social life, and their relationship characteristics may have affected their evaluation. Finally, nurses with different levels of experience in various surgical clinics evaluated the patients.

Conclusion

The results of this study showed that two hours after surgery, parents were better at approximating their child's pain level than nurses in children aged 7-18 years old who could easily express themselves based on the VAS and NRS. When a child cannot express their pain, parents can use both pain scales to measure pain effectively and reliably. These results also show that parents' assessments can be used during post-discharge follow-up and the regulation of children's pain management at home. In our study, nurses underestimated the child's pain for both pain scores. Clearly, there is a need for continuing education and awareness among nurses and other healthcare professionals regarding pain, pain measurement, and treatment. There is a need for studies to determine the appropriate pain scale in order to make an accurate assessment for children and as a proxy to be used in the initiation and follow-up of pain treatment in different age and patient groups.

Ethics

Ethics Committee Approval: Ethics committee approval was received from the Ankara University Faculty of Medicine, Human Research Ethics Committee (approval no.: İ9-576-21, dated: October 14, 2024) before the study execution.

Informed Consent: Written informed consent was obtained from all participants.

Acknowledgments

All authors express their sincere appreciation for the patients who participated in this study.

Footnotes

Author Contributions: Surgical and Medical Practies - Ş.B., Ö.S.C., H.Y.; Concept - Ş.B., Ö.S.C., F.N.E.; Design - Ş.B., Ö.S.C., H.Y., F.N.E.; Data Collection and/or/Processing - Ş.B., V.B.; Analysis and/or/Interpretation - Ş.B., Ö.S.C.; Literature Search - Ş.B., V.B., H.Y.; Writing - Ş.B., Ö.S.C., F.N.E.

Declaration of Interests: One author of this article, Özlem Selvi Can, is a member of the Editorial Board of the Turkish Journal of Anaesthesiology and Reanimation. However, he did not involved in any stage of the editorial decision of the manuscript. The other authors declared no conflict of interest.

Funding: No funding was received for this study.

References

1. Raja SN, Carr DB, Cohen M, et al. The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. *Pain.* 2020;161(9):1976-1982. [CrossRef]
2. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the american pain society, the american society of regional anesthesia, and pain medicine, and the american society of anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. *J Pain.* 2016;17(2):131-157. [CrossRef]
3. Makhlouf MM, Garibay ER, Jenkins BN, Kain ZN, Fortier MA. Postoperative pain: factors and tools for improving pain management in children. *Pain Manag.* 2019;9(4):389-397. [CrossRef]
4. Vittinghoff M, Lonnqvist PA, Mossetti V, et al. Postoperative pain management in children: guidance from the pain committee of the European Society for Pediatric Anesthesiology (ESPA pain management ladder initiative). *Paediatr Anaesth.* 2018;28(6):493-506. [CrossRef]
5. Pope N, Tallon M, McConigley R, Leslie G, Wilson S. Experiences of acute pain in children who present to a healthcare facility for treatment: a systematic review of qualitative evidence. *JBI Database System Rev Implement Rep.* 2017;15(6):1612-1644. [CrossRef]
6. Duignan M, Dunn V. Congruence of pain assessment between nurses and emergency department patients: a replication. *Int Emerg Nurs.* 2008;16(1):23-28. [CrossRef]
7. Puntillo K, Neighbor M, O'Neil N, Nixon R. Accuracy of emergency nurses' assessment of patients' pain. *Pain Manag Nurs.* 2003;4(4):171-175. [CrossRef]
8. Rajasagaram U, Taylor DM, Braitberg G, Pearsell JP, Capp BA. Pediatric pain assessment: differences between the triage nurse, child and parent. *J Paediatr Child Health.* 2009;45(4):199-203. [CrossRef]
9. Singer AJ, Gulla J, Thode HC, Jr. Parents and practitioners are poor judges of young children's pain severity. *Acad Emerg Med.* 2002;9(6):609-612. [CrossRef]
10. Zhou H, Roberts P, Horgan L. Association between self-reported pain ratings of children and parents, child and nurse, and parent and nurse dyads: meta-analysis. *J Adv Nurs.* 2008;63(4):334-342. [CrossRef]
11. Sng QW, He HG, Wang W, Taylor B, Chow A, Klainin-Yobas P et al. A meta-synthesis of children's experiences of postoperative pain management. *Worldviews Evid Based Nurs.* 2017;14(1):46-54. [CrossRef]

12. Khin Hla T, Hegarty M, Russell P, Drake-Brockman TF, Ramgolam A, von Ungern-Sternberg BS. Perception of pediatric pain: Comparison of postoperative pain assessments between children, parents, nurses, and independent observer. *Paediatr Anaesth.* 2014;24(11):1127-1131. [CrossRef]
13. Ofosu Dwamena SO, Druye AA, Asamoah Ampofo, E. Experience of registered nurses in postoperative pain assessment using objective measures among children at Effia Nkwanta Regional Hospital in Ghana. *J Caring Sci.* 2020;9(3):125-132. [CrossRef]
14. Knutsson J, Tibbelin A, Von Unge M. Postoperative pain after pediatric adenoidectomy and differences between the pain scores of the recovery room staff, the parent and the child. *Acta Otolaryngol.* 2006;126(10):1079-83. [CrossRef]
15. Zisk RY, Gray M, MacLaren JE, Kain ZN. Exploring sociodemographic and personality characteristic predictors of parental pain perceptions. *Anesth Analg* 2007;104(4):790-798. [CrossRef]
16. Zielinski J, Morawska-Kochman M, Zatonski T. Pain assessment and management in children during the postoperative period: A review of the most commonly used postoperative pain assessment tools, new diagnostic methods, and the latest guidelines for postoperative pain therapy in children. *Adv Clin Exp Med.* 2020;29(3):365-374. [CrossRef]
17. Kaminsky O, Fortier MA, Jenkins BN, et al. Children and their parents' assessment of postoperative surgical pain: Do you agree or disagree? *Int J Pediatr Otorhinolaryngol.* 2019;123:84-92. [CrossRef]
18. Logan DE, Rose JB. Gender differences in postoperative pain and patient-controlled analgesia use among adolescent surgical patients. *Pain.* 2004;109(3):481-487. [CrossRef]

DOI: 10.4274/TJAR.2025.251900

Original Article
Regional Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):217-225

The Application of Regional Anaesthesia in Türkiye: National Survey Study

Elvin Kanat, Zeynep Çağıran, Nezih Sertöz

Ege University Faculty of Medicine, Department of Anaesthesiology and Reanimation, İzmir, Türkiye

Cite this article as: Kanat E, Çağıran Z, Sertöz N. The application of regional anaesthesia in Türkiye: national survey study. *Turk J Anaesthesiol Reanim.* 2025;53(5):217-225.

Abstract

Objective: This study was designed to determine why anaesthesiologists working in various institutions in our country prefer current regional anaesthesia methods and to evaluate the use and prevalence of ultrasonography in these methods.

Methods: A questionnaire created on SurveyMonkey.com was sent electronically or face-to-face to anaesthesiology and reanimation physicians working in different provinces of our country, and they were asked to fill it out. The survey was intended to be administered to at least 200 volunteer anaesthesiologists. The questionnaire consisted of 34 questions, including demographic characteristics, neuraxial block and peripheral nerve block (PNB) applications, drug choices, preferences in paediatric cases, training, and safety measures.

Results: A total of 215 anaesthesiologists participated in our questionnaire. 39.2% were working in a university hospital, and 38.2% were working in a training and research hospital. PNB training was received by 89.2% of the participants during specialty training. For analgesic purposes, the interscalene block was preferred for shoulder surgery (57.4%), the axillary block for elbow, forearm, and hand surgery (49.8%), the erector spinae plane block for thoracic surgery (33.8%), and the transverse abdominis and rectus block for open abdominal surgery (51.5%).

Conclusion: Regional anaesthesia is an essential part of multimodal analgesia and is used both as an anaesthetic and analgesic in routine practice. In recent years, many new techniques have been utilized as a result of advancements. However, for these to be implemented in practice, up-to-date information should be closely followed, and anaesthetists should be supported in terms of training and equipment.

Keywords: Adjuvant drugs, local anaesthetics, multimodal analgesia, regional anaesthesia

Main Points

- Regional anaesthesia (RA), particularly peripheral nerve blocks, is increasingly used and becoming more popular among young physicians. Its importance in reducing opioid consumption, enhancing multimodal analgesia, and shortening hospital stays has been recognized.
- Despite its benefits, RA is sometimes limited by equipment shortages and insufficient training. These barriers have been partly overcome, but hospitals providing training still need additional resources, particularly ultrasound equipment, to better support RA education and practice.
- RA plays a significant role in postoperative pain management, especially in reducing opioid consumption, which can lead to fewer side effects and complications. Additionally, RA contributes to reduced healthcare costs through its efficiency in pain management and shorter recovery times.
- The safety of RA procedures is paramount. One of the recommended safety measures is having intralipid solutions available in clinics performing these procedures to mitigate the risks associated with local anaesthetic toxicity.
- This study aims to provide a reference for future research, offering insights into the use of RA applications. This can help further develop protocols, improve training, and ensure patient safety.

Corresponding author: Assoc. Prof. Nezih Sertöz, e-mail: nezihsertoz@gmail.com

Received: February 05, 2025 Accepted: March 10, 2025
Epub: May 21, 2025 Published date: October 14, 2025

Introduction

Regional anaesthesia (RA) techniques are commonly used both for anaesthesia during surgical interventions and for postoperative pain management. The advancements in needles and catheters used in RA, as well as the introduction of new and safer local anaesthetics into clinical practice, have increased interest in RA.[1] Additionally, in recent applications of ultrasound-(USG) guided RA, target structures, anatomical relationships, and drug distribution can be visualized.[2] Therefore, it has significantly expanded the scope of anaesthetists' practices, leading to the introduction of new blocks in clinical settings and changes in preferences between existing blocks.[3] In our country, basic and advanced clinical USG courses for anaesthesiologists are organized by anaesthesia associations to support USG and RA education. However, there is no comprehensive recent study in our country investigating RA applications, USG usage, or the changes caused by USG in clinical practice.

This study aims to explore the preferences of anaesthesiologists regarding RA techniques and the extent to which USG is utilized in these practices. Specifically, it seeks to identify factors influencing these preferences and assess how widespread the use of USG is in the administration of RA across different institutions.

Methods

The survey study titled "Regional Anaesthesia Applications in Türkiye: A National Survey Study" was conducted between September 2023 and March 2024, after obtaining approval from the Ege University Medical Research Ethics Committee (approval no.: 2023-0291, dated: 11.05.2023). The survey, created on SurveyMonkey.com, was distributed electronically or in-person to anaesthesiology and reanimation specialists working in various provinces of Türkiye. The survey was designed to be filled out by a minimum of 200 anaesthesiologists. The purpose and objectives of the study were explained to the participating anaesthesiologists. Participation in the study was entirely voluntary. The survey consists of 34 questions, addressing topics such as demographic characteristics, neuraxial block and peripheral nerve block (PNB) applications, drug selection, education, and safety measures (Appendix 1: Survey form).

The first six questions were aimed at identifying the demographic characteristics of the participants, (age, gender, institution where specialist training was received, current institution, job title, and education related to peripheral block application). Questions 7-14 asked about RA preferences: in upper extremities, lower extremities, abdominal surgery, and day-case surgeries. Questions 15-24 addressed the choice of needles, application methods, and safety precautions taken in neuraxial anaesthesia. Questions 25-29 inquired about the drugs used for peripheral blocks, methods, precautions taken to avoid nerve damage, and RA complications. Questions 30-31 asked about sedation preferences during RA. Finally, questions 33 and 34 evaluated anaesthesiologists' RA preferences for paediatric patients.

Statistical Analysis

Our analyses were performed using SPSS 26.0 software, with a 95% confidence level. In the analyses, frequency and percentage values were calculated for categorical variables, while the mean and standard deviations were computed for age. The relationship between job title, current institution, and categorical variables was analyzed using the chi-square test.

Results

A total of 215 anaesthesiologists started the survey, with 204 completing all questions. 32.4% of participants were 30 years old or younger, 37.3% were between 31 and 40 years old, and 30.4% were 41 years old or older. The average age was 35.98, with a standard deviation of 7.85 (Table 1).

The most common reason for not choosing RA is the patient's refusal, which was cited by 85.8% of respondents, followed by insufficient time (37.7%) and concerns about complications (22.1%).

Among the most common positions for performing routine neuraxial techniques, sitting (53.9%) and condition-dependent positions (36.8%) are prominent. For spinal anaesthesia, sharp-tipped needles (73.0%) and 25G needles (68.1%) are generally preferred. The most commonly used local anaesthetic for spinal anaesthesia is bupivacaine, which accounts for 99.0% of cases.

The most frequently used method for defining the epidural space is the loss of resistance to fluid (89.2%), while the most commonly used drugs for epidural test doses are 3 mL of 2% lidocaine (52.0%) and 3 mL of 1.5% lidocaine with 15 µg of adrenaline (41.2%). The most commonly used drugs for postoperative epidural analgesia are opioids and local anaesthetics, used together (73.5%) (Table 2).

The percentage of people using epidural catheters for postoperative analgesia is 88.7%, while 39.2% use adjunct medications for spinal block. Among the adjunct medications used, fentanyl (70.5%) and morphine (29.5%) are the most common (Table 3).

There is a request to rank the frequency of complications after RA. The most common complication is postspinal headache, at 67.2%. The second most frequent is Horner's syndrome, at 32% (Table 4).

When examining the postoperative RA method preferences in paediatric patients, peripheral block (40.7%) and caudal

block (39.7%) are the most commonly preferred methods. These are followed by the epidural catheter procedure (3.4%) and spinal anaesthesia (2.5%), demonstrating their respective proportions. Additionally, the proportion of those who do not prefer regional techniques in children is also noteworthy, with 33.3% (Table 4).

When examining the age limits for applying regional analgesia in paediatric patients, it is observed that a significant portion of participants (45.6%) do not apply it to very young children. Some participants (22.1%) stated that they applied regional analgesia to all children without specifying age limits, while others (32.4%) mentioned that they did not apply regional analgesia to paediatric patients (Table 4).

There is a significant relationship between the institution where the participant works and the percentage of surgeries performed under RA ($P < 0.05$). According to this, 43.8% of those working in university hospitals perform surgeries under RA in 40-60% of cases; 59.0% of those working in teaching and research hospitals perform them in more than 60% of cases; 44.7% of those working in state hospitals perform them in 40-60% of cases; and 62.5% of those working in private hospitals perform them in 40-60% of cases.

There is a significant relationship between the institution where the participant works and the preference for PNB or catheter infusion for postoperative analgesia ($P < 0.05$). According to this, 53.8% of those working in university hospitals, 76.9% of those in teaching and research hospitals, 60.5% of those in state hospitals, and 87.5% of those in private hospitals prefer PNBs or catheter infusions for postoperative analgesia (Table 5).

There is a significant relationship between the institution where the participant works and the first choice of analgesia in open abdominal surgery ($P < 0.05$). According to this, 63.8% of university hospital workers and 55.3% of state hospital workers prefer transversus abdominis and rectus blocks, while 55.1% of teaching and research hospital workers and 62.5% of private hospital workers prefer epidural analgesia.

There is a significant relationship between the institution where the participant works and the most commonly used technique in PNB ($P < 0.05$). According to this, 78.8% of those working in university hospitals use USG plus nerve stimulator (USG+NS), 60.3% of those in teaching and research hospitals use USG, 42.1% of those in state hospitals use either USG+NS or USG, and 50.0% of those in private hospitals use USG.

Discussion

RA has become a widely used technique in recent years, both worldwide and in Türkiye. The growing popularity of RA can be attributed to its advantages, including the reduction in opioid consumption, decreased stress response during surgery, reduced intraoperative and postoperative blood loss, provision of high-quality analgesia specific to the region, enhanced early mobilization and rehabilitation, and the ability to communicate with the patient and better guide

Table 1. Demographic Characteristics of Participants

Category	n (%)	Category	n (%)
Age		**Institution**	
30 years or younger	66 (33)	University hospital	80 (39)
31-40 years	76 (37)	Training and research hospital	78 (38)
41 years or older	62 (30)	State hospital	38 (19)
		Private hospital	8 (4)
Gender		**Years of professional experience**	
Male	85 (42)	Less than 5 years	75 (37)
Female	119 (58)	5-10 years	54 (26)
Position		10-15 years	24 (12)
Resident	85 (42)	More than 15 years	51 (25)
Specialist	**92 (45)**	**Peripheral block training (multiple choices allowed)**	
Doctor of medical sciences	8 (4)	Specialization training	182 (90)
Associate professor	11 (5)	Association courses	75 (37)
Professor	8 (4)	Fellowship programs	32 (16)
		Internet	80 (39)
		Other (e.g., textbooks, current literature)	4 (2)

Table 2. Preferences in Neuraxial Block Technique and Postoperative Analgesia	
	n (%)
Reason for not choosing RA (multiple choices allowed)	
Insufficient time	77 (37)
Patient refusal	175 (86)
Low success rate	9 (4)
Concerns about complications	45 (22)
Most commonly used position for routine neuraxial technique	
Sitting	110 (54)
Lateral decubitus	19 (9)
Prone	0 (0)
Dependent on the patient's condition	75 (37)
Preferred needle type for spinal anaesthesia	
Pencil point (side-hole) needle	55 (27)
Sharp-pointed (Quincke) needle	149 (73)
Preferred needle size for spinal anaesthesia (multiple choices allowed)	
22G	55 (27)
25G	139 (68)
26G	133 (65)
27G	33 (16)
Most frequently used local anaesthetic for spinal anaesthesia (multiple choices allowed)	
Bupivacaine	202 (98)
Ropivacaine	2 (1)
Lidocaine	2 (1)
Method used for identifying the epidural space (Multiple choices allowed)	
Loss of resistance to fluid	182 (89)
Loss of resistance to air	35 (17)
Hanging drop method	31 (15)
Ultrasound	3 (2)
Medications used for epidural test dose	
3 mL lidocaine 1.5% + 15 mcg adrenaline	84 (41)
3 mL lidocaine 2%	106 (52)
No test dose used	14 (7)
Most frequently used medication for postoperative epidural analgesia	
Opioids	35 (17)
Local anaesthetics	17 (8)
Both opioids and local anaesthetics	150 (74)
Tramadol	2 (1)
Do you use an epidural catheter for postoperative analgesia?	
Yes	181 (89)
	n (%)
No	23 (11)
Do you use adjuvant medications for spinal block for postoperative analgesia?	
Yes	80 (40)
No	124 (60)
Medications used	
Fentanyl	57 (70)
Morphine	23 (30)

RA, regional anaesthesia; G, gauge

treatment due to the patient being conscious. Developments in RA techniques, such as advancements in needles, catheters, and imaging methods, have further contributed to its increased popularity.

The younger population has followed the developments in RA more closely. It is believed that the higher percentage of residents who are still in ongoing training contributed to this trend. A similar age, professional experience, and role distribution was found in a thesis study conducted in Türkiye.[4] When the distribution of participants by institution was compared, it was found to be similar to that in the study by Gürkan et al.[3] and the distribution of aneasthesiologists in the country. The basis of RA education was based on specialist training. RA education is of a certain standard in all hospitals providing training and is supported by practical training by the Regional Anesthesia Association. The facilities of hospitals, patient profiles, and the knowledge, skills, interests, and experience of the educators may vary, which could make standardization more challenging.

In postoperative pain management guidelines, the importance of multimodal analgesia is emphasized and its use is recommended. The widespread and successful application of RA and analgesia methods has shown positive outcomes in reducing opioid use. Regarding the participants' preferences for postoperative analgesia, the most common choice was acetaminophen and non-steroidal anti-inflammatory drugs, followed by PNBs or catheter infusion (Table 6).

The widespread use of PNB is thought to be due to its anaesthetic properties and effectiveness in pain management.

Postoperative pain management following shoulder surgery can be challenging. A systematic review of 2,391 articles on postoperative pain following shoulder surgery suggested that interscalene blocks were ideal for early postoperative analgesia.[5] In a study by Lin et al.[6], the interscalene block was identified as the most beneficial PNB for shoulder

Table 3. Ranking of RA Complications from Most to Least Common

Complication	1st rank n (%)	2nd rank n (%)	3rd rank n (%)	4th rank n (%)	5th rank n (%)	6th rank n (%)
Local anaesthetic systemic toxicity	0 (0.0%)	0 (0.0%)	2 (1%)	15 (13%)	23 (48%)	15 (50%)
Postspinal headache	137 (66%)	49 (23%)	16 (9%)	3 (2%)	0 (0.0%)	0 (0.0%)
Hematoma (subcutaneous)	36 (18%)	63 (31%)	49 (27%)	20 (17%)	0 (0.0%)	0 (0.0%)
Hemopneumothorax	0 (0.0%)	0 (0.0%)	3 (2%)	1 (1%)	18 (38%)	13 (44%)
Nerve damage	2 (1%)	26 (13%)	56 (31%)	47 (40%)	2 (4%)	1 (3%)
Horner's syndrome	29 (14%)	65 (32%)	56 (31%)	33 (28%)	5 (10%)	1 (3%)

RA, regional anaesthesia

Table 4. Postoperative Regional Anaesthesia Methods and Age Limits for Regional Analgesia in Paediatric Patients

	n (%)
Postoperative RA method in paediatric patients (multiple choices allowed)	
Spinal	5 (2)
Epidural catheter	7 (3)
Caudal	81 (40)
Peripheral block	83 (41)
I do not prefer regional techniques in children	68 (33)
Age limit for applying regional analgesia in paediatric patients	
I do not apply it to very young children	93 (46)
I have no age limit, I apply it to all children	45 (22)
I do not apply regional analgesia to paediatric patients	66 (32)

RA, regional anaesthesia

surgery, while the supraclavicular block was suggested as an alternative. In our study, more than half of the participants preferred the interscalene block as their first choice. The axillary block, which is simple, easy to apply, and safe, is the most commonly used PNB, especially for elbow, forearm, and hand surgeries.[3,7]

A meta-analysis published in 2024 highlighted the importance of the Enhanced Recovery After Surgery protocol, in improving recovery after hip and knee surgeries, with nerve blocks and infiltration analgesia, which are key components of this protocol.[8] A significant portion of participants in our study preferred spinal and epidural anaesthesia for postoperative analgesia in both surgeries. In recent years, there has been a trend towards peripheral blocks due to undesirable complications of neuraxial anaesthesia.

Thoracic epidural analgesia has long been the gold standard for multimodal analgesia in thoracotomy.[9] With the widespread use of USG, ESP block applications are used more frequently than the more invasive thoracic epidural and paravertebral applications. The ESP block has also been shown to improve chronic post-thoracotomy pain syndrome in patients, weeks after surgery.[10] Regional blocks play a significant role in abdominal surgery, improving postoperative recovery.[11] Recently, the interest in transversus abdominis plane blocks has increased substantially, and they have been shown to provide sufficient analgesia for abdominal surgery.[12]

In our study, the most common reason for not choosing RA was found to be the patient's refusal. This result is consistent with studies conducted in Türkiye.[3,4] However, a study in China found that the most common reason for not using RA was concern about complications.[13] In our study, concern about complications was found to be the third most common reason, at a rate of 22.1%. We think that real-time block application with USG in RA reduces the concern for complications.

The most common position for performing routine neuraxial techniques was found to be the sitting position. A study by Aksu et al.[14] showed that the interspinous distance was wider in the sitting position than in the lateral decubitus position. This suggests that the sitting position may enhance the success of neuraxial blocks. It was observed that spinal anaesthesia was typically performed using sharp-tipped 25G needles, with bupivacaine being the most commonly preferred local anaesthetic due to its long duration of action and availability. A study conducted in India in 2021 yielded results similar to those in our country.[15] In defining the epidural space, the loss of resistance using fluid, was the most common method, although this technique requires experience and is subjective. In inexperienced hands, the failure rate can be as high as 15%. Using air, on the other hand, is associated with adverse effects such as headache, nerve injury, and insufficient spread of the medication, which are not observed with fluid. To increase success rates, new techniques with high sensitivity and specificity should be preferred.[16] Many participants indicated that they use a test dose, with 3 mL of 2% lidocaine being the most commonly used.

The use of epidural catheters for postoperative analgesia was found to be very common. Their widespread use is

likely due to their ability to provide both anaesthesia and analgesia. The combination of opioids and local anaesthetics was the most common choice for this purpose. The use of adjuvants can enhance the effect of local anaesthetics and prolong intraoperative and postoperative analgesia. Studies have shown that a smaller dose of bupivacaine is associated with less hypotension and faster recovery.[17] Fentanyl was the most commonly used adjuvant. However, prolonged opioid use can lead to adverse effects like respiratory depression, nausea, and vomiting.

In PNB, the use of blind techniques has largely been abandoned due to the serious complications they can cause and the widespread use of USG. In comparison with other countries, blind techniques were still used in China, NS was common in Greece, and USG was the preferred method in India.[1,13,18] It was observed that the choice of local anaesthetic in PNB was bupivacaine-prilocaine or bupivacaine and lidocaine combination, which provides a rapid onset of action and long duration of effect. It is advisable that lidocaine should be preferred because of the methemoglobinemia-inducing effect of prilocaine. Fentanyl and dexamethasone were commonly used as adjuvants in PNBs, helping to reduce the required dose of local anaesthetics while maintaining effective anaesthesia without enhancing motor blockade. Despite the benefits of these drugs, many are not approved by the Food and Drug Administration, and caution should be exercised in their use.[19]

The incidence of local anaesthetic systemic toxicity (LAST) in PNBs was found to be 20/10,000, while in epidural blocks, it was 4/10,000.[20] LAST is a serious and life-threatening complication that requires immediate intervention. The standard treatment for LAST is the administration of Intralipid solution, which should be readily available in

Table 5. Examination of the Relationship Between the Institution and Variables

		The institution you work for				*P* value
		University hospitals	Teaching and research hospitals	State hospitals	Private hospitals	
		n (%)	n (%)	n (%)	n (%)	
Percentage of surgeries performed under regional anaesthesia	20% or less	4 (5.0)	3 (3.8)	3 (7.9)	0 (0.0)	0.026*
	20-40%	8 (10.0)	6 (7.7)	4 (10.5)	3 (37.5	
	40-60%	35 (43.8)	23 (29.5)	17 (44.7)	5 62.5	
	More than 60%	33 (41.3)	46 (59.0)	14 (36.8)	0 0.0	
Postoperative analgesia preference (multiple choices)	Parasetamol and NSAIDs	77 (96.3)	73 (93.6)	35 (92.1)	8 (100.0)	0.681
	IM or IV opioids	36 (45.0)	38 (48.7)	18 (47.4)	6 (75.0)	0.449
	PCA	21 (26.3)	32 (41.0)	13 (34.2)	2 (25.0)	0.246
	Peripheral nerve block or catheter infusion	43 (53.8)	60 (76.9)	23 (60.5)	7 (87.5)	0.009*
	Infiltration analgesia	12 (15.0)	10 (12.8)	1 (2.6)	0 (0.0)	0.161
First choice of analgesia in open abdominal surgery	Epidural	21 (26.3)	43 (55.1)	10 (26.3)	5 (62.5)	0.004*
	TAP + RSB	51 (63.8)	30 (38.5)	21 (55.3)	3 (37.5)	
	QLB	1 (1.3)	0 (0.0)	3 (7.9)	0 (0.0)	
	ESP	1 (1.3)	2 (2.6)	0 (0.0)	0 (0.0)	
	Other	6 (7.5)	3 (3.8)	4 10.5	0 (0.0)	
Most commonly used technique in peripheral nerve block (PNB)	Blind technique	1 (1.3)	0 (0.0)	1 (2.6)	0 (0.0)	0.000*
	NS	4 (5.0)	7 (9.0)	4 (10.5)	1 (12.5)	
	USG	10 (12.5)	47 (60.3)	16 (42.1)	4 (50.0)	
	USG + NS	63 (78.8)	24 (30.8)	16 (42.1)	3 (375)	
	USG + NS + PM	2 (2.5)	0 (0.0)	1 (2.6)	0 (0.0)	

PNB, peripheral nerve block; NSAIDs, non-steroidal anti-inflammatory drugs; IM, intramuscular; IV, intravenous; PCA, patient-controlled IV or epidural analgesia; TAP, transversus abdominis plane; RSB, rectus sheath block; QLB, quadratus lumborum block; ESP, erector spinae plane; NS, nerve stimulator; USG, ultrasonography; PM, pectoralis major

Table 6. Regional Anaesthesia Preferences for Upper Extremity, Lower Extremity, Thoracic, and Abdominal Surgery

Category	n (%)
Percentage of surgeries performed under regional anaesthesia	
Less than 20%	10 (5)
20-40%	21 (10)
40-60%	80 (39)
More than 60%	93 (46)
Postoperative analgesia preferences (multiple choices allowed)	
Paracetamol and NSAIDs	193 (95)
IM or IV opioids	98 (48)
PCA	68 (33)
Peripheral nerve block or catheter infusion	133 (65)
Infiltration analgesia	23 (11)
Shoulder surgery analgesic first preference	
Interscalene block	117 (57)
Supraclavicular + suprascapular block	33 (16)
Interscalene + cervical block	31 (15)
Shoulder infiltration analgesia	3 (2)
Other (paracetamol, tramadol, morphine, and NSAIDs)	20 (10)
Elbow, forearm, and hand surgery analgesic first preference	
Interscalene block	6 (3)
Supraclavicular block	26 (13)
Infraclavicular block	69 (34)
Axillary block	100 (50)
Hip surgery analgesic first preference	
Spinal, epidural	157 (77)
Lumbar plexus block	4 (2)
Fascia iliaca block	14 (7)
PENG block	28 (14)
Knee surgery analgesic first preference	
Spinal, epidural	142 (70)
Fascia iliaca block	2 (1)
Femoral block + IPACK	33 (16)
Adductor canal block + IPACK	25 (12)
LIA	1 (1)
Thoracic surgery analgesic first preference	
Thoracic epidural	66 (32)
Thoracic paravertebral	23 (11)
Erector spinae block	69 (34)
PECS and serratus block	20 (10)
Other (paracetamol, tramadol, morphine, and NSAIDs)	26 (13)
Open abdominal surgery analgesic first preference	
Epidural	79 (39)
Transversus abdominis and rectus block	105 (52)
Quadratus lumborum block	4 (2)
Erector spinae block	3 (1)
Other (paracetamol, tramadol, morphine, and NSAIDs)	13 (6)

NSAIDs, non-steroidal anti-inflammatory drugs; IM, intramuscular; IV, intravenous; PCA, principal component analysis; IPACK, infiltration between the popliteal artery and capsule of the knee LIA, local infiltration analgesia

clinics performing RA procedures, with expiration dates regularly monitored. Our study found that most clinics had intralipid solutions available.

It was noted that sedation was frequently used both before and after RA procedures. Sedation helps ensure patient cooperation, prevent sudden movements, and enhance procedural safety. However, some participants avoided sedation, arguing that it might mask the early warning signs of LAST.[21]

In our study, the use of peripheral block catheters for postoperative analgesia was found to be rare, and in most clinics, they were not used. (Table 7). We believe that the low usage could be attributed to a lack of materials and insufficient knowledge and training about their safety. Similar findings have been reported in other national studies.[1,13]

In our study, caudal blocks were the most commonly used peripheral blocks in children, but a significant proportion of participants also reported not preferring RA in paediatric cases. Most participants indicated that age limits were crucial in paediatric RA applications, with many avoiding the use of paediatric RA applications in very young children. The difficulty in recognizing surface landmarks, as well as the variability in the depth and location of nerves in growing children, makes RA more challenging. However, these difficulties have been overcome with the use of USG.[22]

RA application rates were higher in educational and research hospitals and university hospitals, likely due to the training provided to residents and the diversity of cases encountered. In contrast, PNB and catheter infusions were more common in private hospitals, likely due to better availability of equipment. However, the small number of participants from private hospitals in this study may not fully reflect the actual distribution.

Study Limitations

There are several limitations to our study. We created a heterogeneous group of experts in RA, experienced

physicians outside of RA, and resident physicians in training. The survey was administered both online and face-to-face and using a single method, particularly face-to-face administration, could have reduced measurement errors. Due to the low number of participants, we believe the results may not fully reflect national preferences, and larger studies with more participants are needed.

Table 7. Medications and Methods Used for Peripheral Block, Sedation Preferences Before and Intraoperative Period

	n (%)
Which technique(s) do you most frequently use for PNB (multiple choices allowed)?	
Blind technique	2 (1)
Neurostimulator	16 (8)
USG	77 (38)
Ultrasound + Neurostimulator	106 (52)
Ultrasound + Neurostimulator + Pressure monitor	3 (1)
Most frequently used LA agents in PNB?	
Bupivacaine	5 (3)
Bupivacaine + Lidocaine	92 (45)
Bupivacaine + Prilocaine	103 (50)
Lidocaine	4 (2)
Most frequently used adjuvants in PNB for extremity surgery?	
Dexamethasone	56 (37)
Dexmedetomidine	18 (12)
Clonidine	1 (1)
Opioids	62 (41)
Other	14 (9)
Is intralipid solution available in the operating room?	
Yes	187 (92)
No	17 (8)
Do you apply sedation before performing RA?	
I always apply sedation	151(74)
No, I do not apply sedation	15 (7)
I apply it to selected patients	38 (19)
Do you apply intraoperative sedation to patients undergoing RA?	
Yes	153 (75)
No	5 (2)
I apply it to selected patients	46 (23)
Do you use a peripheral block catheter for postoperative analgesia?	
Yes, frequently	2 (1)
Yes, occasionally	26 (13)
Yes, rarely	62 (30)
No	114 (56)

PNB, peripheral nerve block; USG, ultrasound; LA, local anaesthetic; RA, regional anaesthesia

Conclusion

RA is a widely used and developing field in our country frequently preferred by young physicians. The importance of supporting RA education during residency training has become more prominent. It was observed that the limited use of PNBs due to equipment shortages and insufficient training, has been partially overcome, and their application has become more widespread. Hospitals providing training should be supported with the necessary equipment and USG resources.

RA plays a crucial role in postoperative multimodal analgesia. By reducing opioid consumption and providing long-lasting analgesia, RA contributes to shorter hospital stays and reduced healthcare costs. The most common contraindication for RA was found to be the patient's refusal. The application rate can be increased by adequately explaining the procedure to the patient and discussing its advantages. It is essential to implement the recommended safety measures for RA, and clinics where these procedures are performed must have intralipid solutions available. This would likely reduce morbidity and mortality associated with local anaesthetic toxicity.

Our study can serve as a reference for future research, providing valuable insights into the detailed use of RA applications.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ege University Medical Research Ethics Committee (approval no.: 2023-0291, dated: 11.05.2023).

Informed Consent: Survey study.

Footnotes

Author Contributions: Concept - N.S.; Design - N.S.; Data Collection and/or/Processing - E.K., Z.Ç.; Analysis and/or/Interpretation - N.S.; Literature Review - E.K., Z.Ç.; Writing - E.K., N.S.

Declaration of Interests: One author of this article, Nezih Sertöz, is a member of the Editorial Board of the Turkish Journal of Anaesthesiology and Reanimation. However, he did not involved in any stage of the editorial decision of the manuscript. The other authors declared no conflict of interest.

Funding: No funding was received for conducting this study.

References

1. Ramachandran S, Malhotra N, Velayudhan S, et al. Regional anaesthesia practices in India: A nationwide survey. *Indian J Anaesth*. 2021;65(12):853-861. [CrossRef]

2. Sargın M, Kara İ. The criteria that anesthesiologists consider in the decision of regional anesthesia: A national survey study. *J Cukurova Anesth Surg.* 2019;2(2):61-69. [CrossRef]
3. Gürkan Y, Kuş A, Aksu C, Ohtaroğlu C, Solak M, Toker K. [Changing trends and regional anesthesia practices in Turkey]. *Agri.* 2014;26(3):131-137. [CrossRef]
4. Zincirci M. Türkiye'de rejyonal anestezi uygulamalarının kullanımı ve yaygınlığı ile deneyimlerin ve eğitim koşullarının değerlendirilmesi. Dissertation. İstanbul University; 2020. [CrossRef]
5. Xiao M, Cohen SA, Cheung EV, Freehill MT, Abrams GD. Pain management in shoulder arthroplasty: a systematic review and network meta-analysis of randomized controlled trials. *J Shoulder Elbow Surg.* 2021;30(11):2638-2647. [CrossRef]
6. Lin E, Choi J, Hadzic A. Peripheral nerve blocks for outpatient surgery: evidence-based indications. *Curr Opin Anaesthesiol.* 2013;26(4):467-474. [CrossRef]
7. Hadzić A, Vloka JD, Kuroda MM, Koorn R, Birnbach DJ. The practice of peripheral nerve blocks in the United States: a national survey [p2e comments]. *Reg Anesth Pain Med.* 1998;23(3):241-246. [CrossRef]
8. Zhang Q, Chen Y, Li Y, et al. Enhanced recovery after surgery in patients after hip and knee arthroplasty: a systematic review and meta-analysis. *Postgrad Med J.* 2024;100(1181):159-173. [CrossRef]
9. Marshall K, McLaughlin K. Pain management in thoracic surgery. *Thorac Surg Clin.* 2020;30(3):339-346. [CrossRef]
10. Forero M, Rajarathinam M, Adhikary S, Chin KJ. Erector spinae plane (ESP) block in the management of post thoracotomy pain syndrome: A case series. *Scand J Pain.* 2017;17:325-329. [CrossRef]
11. Peršec J, Šerić M. Regional analgesia modalities in abdominal and lower limb surgery - comparison of efficacy. *Acta Clin Croat.* 2019;58(Suppl 1):101-107. [CrossRef]
12. Finnerty O, Sharkey A, Mc Donnell JG. Transversus abdominis plane block for abdominal surgery. *Minerva Anestesiol.* 2013;79(12):1415-1422. [CrossRef]
13. Huang J, Gao H. Regional anesthesia practice in China: A survey. *J Clin Anesth.* 2016;34:115-123. [CrossRef]
14. Aksu F, Kartufan F, Köner Ö, Görmez A, Keleş EÇ. Comparison of two different positions for ultrasound-guided ıntervertebral distance evaluation. *Turk J Anaesthesiol Reanim.* 2023;51(6):470-476. [CrossRef]
15. Ramachandran S, Malhotra N, Velayudhan S, et al. Regional anaesthesia practices in India: A nationwide survey. *Indian J Anaesth.* 2021;65(12):853-861. [CrossRef]
16. Teng WN, Tsou MY, Chang WK, Ting CK. Eyes on the needle: Identification and confirmation of the epidural space. *Asian J Anesthesiol.* 2017;55(2):30-34. [CrossRef]
17. Ebrie AM, Woldeyohanis M, Abafita BJ, et al. Hemodynamic and analgesic effect of intrathecal fentanyl with bupivacaine in patients undergoing elective cesarean section; a prospective cohort study. *PLoS One.* 2022;17(7):e0268318. [CrossRef]
18. Argyra E, Moka E, Staikou C, et al. Regional anesthesia practice in Greece: A census report. *J Anaesthesiol Clin Pharmacol.* 2015;31(1):59-66. [CrossRef]
19. Kalagac Fabris L. Pro and contra on adjuvants to neuroaxial anesthesia and peripheral nerve blocks. *Acta Clin Croat.* 2022;61(Suppl 2):57-66. [CrossRef]
20. Ruppen W, Derry S, McQuay H, Moore RA. Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. *Anesthesiology.* 2006;105(2):394-399. [CrossRef]
21. Bernards CM, Hadzic A, Suresh S, Neal JM. Regional anesthesia in anesthetized or heavily sedated patients. *Reg Anesth Pain Med.* 2008;33(5):449-460. [CrossRef]
22. Monfaredi R, Cleary K, Sharma K. MRI robots for needle-based interventions: Systems and technology. *Ann Biomed Eng.* 2018;46(10):1479-1497. [CrossRef]

Click for Appendix File 1 access link:

https://d2v96fxpocvxx.cloudfront.net/a2440bda-5c5c-4e7b-8a75-abf1691c9260/content-images/2bea5f97-bf7e-4c08-afd2-2afa316f7d7b.pdf

DOI: 10.4274/TJAR.2025.251934

Original Article
Paediatric Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):226-232

The Impact of Preoperative Duration of Fasting on the Intravascular Volume Status of Children Older than 5 Years of Age: A Prospective, Observational Study

Beliz Bilgili, Tümay Umuroğlu

Marmara University Faculty of Medicine, Department of Anaesthesiology and Intensive Care, İstanbul, Türkiye

Cite this article as: Bilgili B, Umuroğlu T. The impact of preoperative duration of fasting on the intravascular volume status of children older than 5 years of age: a prospective, observational study. *Turk J Anaesthesiol Reanim.* 2025;53(5):226-232.

Abstract

Objective: Preoperative fasting is a common practice aiming to reduce the risk of pulmonary aspiration during anaesthesia. It is advised to avoid fasting times longer than 6 hours in all children, whenever possible. Prolonged fasting can be uncomfortable for children and may lead to dehydration and other negative outcomes. The primary outcome of the study was the relationship between preoperative duration of fasting and cardiac index (CI) variability, used as a surrogate for intravascular volume status after the induction of anaesthesia, in paediatric patients undergoing surgery.

Methods: Prospective, observational study that included patients over 5 years of age, scheduled for surgery. Passive leg-raising-induced CI variability was evaluated for fluid responsiveness and intravascular volume after anaesthesia induction. Patients were termed fluid responders (Rs) if an increase in CI of >10% was obtained after passive leg raising, and non-responders (NRs) if the CI variability was <10%. CI and aortic peak velocity (V_{peak}) were measured through the suprasternal notch via an ultrasonic cardiac output monitor.

Results: There were 32 Rs and 53 (NRs). The mean duration of fasting for Rs was 11.53±2.61, while NR had a mean duration of fasting of 10.6±2.93 hours, showing an insignificant difference. Aortic V_{peak} change was significantly higher in Rs (0.24±0.17) compared to NRs (0.03±0.13) ($P < 0.001$). Duration of fasting showed no significant correlation with CI variability and peak aortic velocity.

Conclusion: With this study method, it was observed that preoperative fasting time had no effect on intraoperative intravascular volume.

Keywords: Cardiac index, fasting time, fluid responsiveness, intravascular volume, paediatric anaesthesia, passive leg raising

Main Points

- Paediatric patients have higher insensible losses due to relatively increased surface area, increased respiratory rate, and greater metabolic rate, and are therefore more prone to become hypovolemic in the perioperative period.
- Prolonged fasting can be uncomfortable for children and may lead to dehydration and other negative outcomes.
- Even extensively prolonged preoperative fasting times had no significant impact on intravascular volume status in children over 5 years of age under anaesthesia.

Introduction

Preoperative fasting is a common practice aiming to reduce the risk of pulmonary aspiration during anaesthesia. Guidelines typically recommend specific fasting times including clear fluids up to 2 hours, breast milk up to 4 hours, and a light meal up to 6 hours before elective procedures.[1] It is advised to avoid prolonged fasting times longer than 6 hours in all children, whenever possible.[2] Nevertheless, the actual duration of fasting is frequently much longer than advised, including clear fluids abstinence.[3,4] This undesirable situation is mostly inevitable and unpredictable, occurring because of delays in scheduling or overly cautious practices. Paediatric patients have higher insensible

Corresponding author: Assoc. Prof. Beliz Bilgili, e-mail: belizbilgili@gmail.com

Received: February 11, 2025 Accepted: March 19, 2025
Epub: May 16, 2025 Published date: October 14, 2025

losses due to increased surface area, increased respiratory rate, and greater metabolic rate, and are therefore more prone to become hypovolemic during the perioperative setting.[5] Prolonged fasting can be uncomfortable for children and may lead to dehydration and other negative outcomes.[6] Adequate hydration can prevent dehydration-related complications and delayed recovery.[7]

As prolonged fasting may lead to dehydration that may predispose paediatric patients to hemodynamic instability during anaesthesia it must be carefully managed. There may be a relationship between the duration of preoperative fasting and the occurrence of hypotension, which is a potential indicator of intravascular volume depletion. Fluid fasting times longer than 6 hours were associated with an increased risk of postinduction hypotension, during surgical preparation, although this association seemed to be non-linear.[8] However, another study found no association between fasting duration and hypotension.[9] The literature presents conflicting findings on this subject. Additionally, it should be noted that blood pressure is generally maintained in children with hypovolemia, and the lack of age-specific definitions for hypotension limits the ability of blood pressure to accurately reflect intravascular volume status.

The impact of preoperative fasting time on intravascular volume in paediatric patients remains a subject of debate and investigation. Understanding the impact of fasting time on intravascular volume status is crucial for optimizing perioperative care in paediatric patients. Recent research has focused on dynamic parameters and functional hemodynamic monitoring techniques to assess intravascular volume and fluid responsiveness. Since conventional static measures (e.g., blood pressure, urine output) may not accurately reflect real-time intravascular volume shifts, dynamic parameters such as cardiac index (CI) variability and aortic peak velocity (V_{peak}) serve as primary indicators of volume status. CI represents cardiac output (CO) normalized to body surface area, providing a better assessment of circulatory adequacy in paediatric patients than CO alone. Dynamic changes in CI following a preload challenge [such as passive leg raising (PLR)] offer insight into fluid responsiveness, which reflects intravascular volume status. Aortic V_{peak} serves as a non-invasive indicator of stroke volume variability.[10,11] PLR-induced >10% CI variability reflects fluid responsiveness and intravascular volume deficit.[11] Changes in V_{peak} following PLR correlate with fluid responsiveness and preload dependency, making it an important parameter for assessing circulatory volume status.[12] PLR avoids unnecessary fluid administration by identifying true volume-responsive patients. It is particularly useful in paediatric patients, where baseline hemodynamic values may fluctuate, and traditional static markers are less predictive.[13]

This study tested the hypothesis that preoperative fasting time has an impact on intravascular volume. The primary outcome was the relation between preoperative fasting time and CI variability after anaesthesia, induction in paediatric patients.

Methods

Study Design

This prospective, observational, single-center trial was conducted after receiving approval from the Institutional Ethics Committee of Marmara University Faculty of Medicine Clinical Research (approval no.: 09.2017.669, date: 08.12.2017) in accordance with the principles outlined in the Declaration of Helsinki.

The trial was registered prior to patient enrollment at clinicaltrials.gov (https://clinicaltrials.gov/). Written informed consent was obtained from all patients' legal representatives included in the study. The flow chart of the study is shown in Figure 1.

Patients over 5 years of age and with American Society of Anesthesiologists (ASA) physical status I, scheduled as outpatients for surgery, were asked to enroll in the study. Paediatric patients, who were otherwise healthy except for the need for surgery and who did not receive intravenous (IV) fluid prior to anaesthesia induction, were included. Patients who failed to meet inclusion criteria and refused to give informed consent were excluded.

Anaesthesia Management

In the operating room, patients were monitored with an electrocardiogram, non-invasive blood pressure monitoring a pulse oximeter, monitors for anaesthetic gases, and a carbon dioxide (CO_2) analyzer. Anaesthesia, was initiated through an IV route, with 1 μg kg^{-1} of remifentanil hydrochloride, 5 mg kg^{-1} of sodium thiopental, and 0.6 mg kg^{-1} of rocuronium bromide. Following induction, the patient's airway was secured via tracheal intubation, and a maintenance dose of 2% sevoflurane in a mixture of 50% nitrous oxide and 50% oxygen was administered. Mechanical ventilation was controlled by the auto-flow mode of the Draeger Primus ventilator, with tidal volumes set at 8 mL per kg^{-1} of body weight. The respiratory rate was adjusted to maintain end-tidal CO_2 between 35 and 45 mmHg, and a PEEP of 4 cm H_2O was used for respiratory support. To keep the patient warm throughout the surgery, the active air warming system was employed.

Protocol

After tracheal intubation, hemodynamic stability had been maintained with the aim of keeping a heart rate (HR) change of less than 10% for three minutes. Then, measurements were performed. The baseline measurements (T1) were recorded

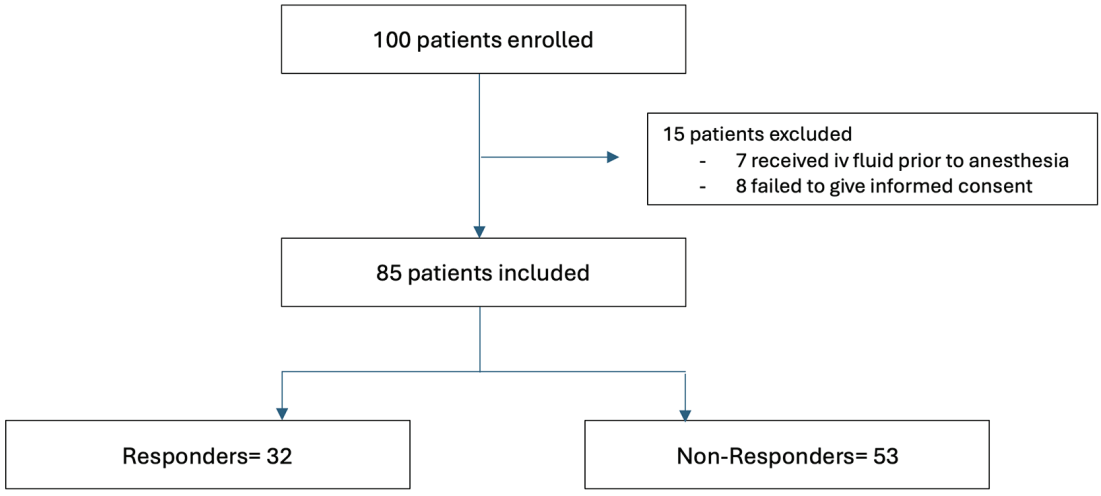

Figure 1. Flow chart

with the patient in the semi-recumbent position. Next, the PLR maneuver was carried out by placing the patient in the supine position and simultaneously raising the patient's leg to 45°; after 1 minute (T2), a second set of measurements was recorded. In every stage, CI, CO, and aortic V_{peak} were measured; HR, CI, and mean arterial pressure were recorded. Cardiac measurement was performed through the suprasternal notch, via the Ultrasonic CO Monitor (USCOM) system by the same operator. Each parameter was measured consecutively three times, and the mean value of these three measurements was recorded.

An increase in CI (ΔCI) >10% following PLR is considered indicative of fluid responsiveness and suggests a functional intravascular volume deficit. Patients were termed fluid responders (Rs) if ΔCI of >10% was obtained after PLR, or non-responders (NRs) if ΔCI was <10%.

Statistical Analysis

Data were evaluated for normality of distribution and reported as mean, standard deviation (SD), median, 25th and 75th interquartile, frequency, percentage, and minimum and maximum range. The independent t-test was employed to compare the means between two unrelated groups, and paired samples t-test was used to compare the means of two related groups. Qualitative data was compared using the Pearson chi-square test. Receiver operating characteristic (ROC) curves were built, sensitivity and specificity of variables were calculated for various values, and the value with the highest Youden index was taken as a cut-off point. Spearman correlation coefficient was used to test the association between variables. Statistical significance was defined as $P < 0.05$.

Sample size was calculated based on a previous adult study investigating the functional intravascular volume deficit in patients before surgery.[14] Flow time corrected (FTc) data of this study were taken into consideration. The FTc rise from 288 (±45) ms to 316 (±39) ms (before and after stroke volume maximization) was suspected to be significant. Accordingly, the minimum sample size required was 82 at an alpha level, and a beta level of 0.05 and 0.20, respectively. Based on possible dropouts, a total of 100 patients were planned for inclusion.

Results

As shown in Figure 1, a total of 100 paediatric patients with ASA I, scheduled for outpatient surgery, were initially assessed for eligibility. Fifteen patients were subsequently excluded due to either the preoperative administration of IV fluids or their declining participation. A total of 85 patients were included. There were 32 R and 53 NR. The patient characteristics of two groups were comparable in terms of age, gender, height, and body weight. The mean age of the participants was 7.82±2.43 years. The mean fasting time was 10.95±2.84 hours. The mean fasting time for Rs was 11.53 hours, with a SD of 2.61, while NR had a mean fasting time of 10.6 hours, with a SD of 2.93. This difference was not statistically significant, with a *P* value of 0.145 (Table 1).

The hemodynamic parameters before (T1) and after (T2) PLR are shown in Table 2. HR significantly decreased after PLR in both R and NR ($P < 0.001$, $P < 0.001$, respectively), but showed an insignificant difference between the study groups. Mean arterial pressure values were comparable among the groups at all study time points. CO was significantly lower in R than in NR in T1 (P=0.043). CO significantly increased after PLR in R ($P < 0.001$) but remained similar in NR. ΔCO was significantly higher in R (0.89±0.56) than in NR (-0.12±0.49) ($P < 0.001$). V_{peak} was comparable among the groups in T1. Rs had a significantly increased V_{peak} in T2 ($P < 0.001$), and ΔV_{peak} was significantly

Table 1. Patient Characteristics

	Total (n = 85)	Responders (n = 32)	Non-responders (n = 53)	*P* value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	7.82±2.43	7.69±2.61	7.91±2.33	[a]**0.690**
Gender n (%)				[b]**0.637**
Female	27 (100)	9 (33.3)	18 (66.7)	
Male	58 (100)	23 (39.7)	35 (60.3)	
Height	124.36±18.11	124.59±20.54	124.23±16.68	[a]**0.928**
Weight	27.33±9.72	29.59±11.84	25.96±7.99	[a]**0.131**
Fasting time	10.95±2.84	11.53±2.61	10.6±2.93	[a]**0.145**

a, Independent t-test; b, pearson chi-square test. SD, standard deviation

Table 2. Hemodynamic Parameters Recorded Before (T1) and After (T2) PLR

Mean ± SD		Responders (n = 32)	Non-responders (n = 53)	[a]*P* (inter group)
		Mean ± SD		
HR	T1	110.63±20.05	110.04±14.66	**0.877**
	T2	98.38±17.03	96.15±14.27	**0.519**
	Δ	-12.25±8.93	-13.89±7.83	**0.378**
	[c]***P* (intra group)**	**< 0.001****	**< 0.001****	
MAP	T1	71.38±12.6	69.26±8.27	**0.403**
	T2	69.16±13.21	68.98±7.18	**0.945**
	Δ	-2.22±9.48	-0.28±6.63	**0.272**
	[c]***P***	0.195	0.757	
CI	T1	2.91±0.81	3.58±0.94	**0.001****
	T2	3.8±1.08	3.44±0.82	**0.092**
	Δ	0.89±0.53	-0.13±0.44	**< 0.001****
	[c]***P***	**< 0.001****	**0.032***	
CO	T1	2.93±0.81	3.39±1.12	**0.043***
	T2	3.81±1.16	3.27±0.97	**0.023***
	Δ	0.89±0.56	-0.12±0.49	**< 0.001****
	[c]***P***	**< 0.001****	**0.076**	
V_{peak}	T1	0.93±0.25	1.02±0.24	**0.101**
	T2	1.17±0.27	1.05±0.21	**0.029***
	Δ	0.24±0.17	0.03±0.13	**< 0.001****
	[c]***P***	**< 0.001****	**0.055**	

a, Independent t-test; c, Paired Samples t-test, **P* < 0.05, ***P* < 0.01

PLR, passive leg raising; HR, heart rate; MAP, mean arterial pressure; CI, cardiac index; CO, cardiac output; V_{peak}, aortic peak velocity Δ: change; SD, standard deviation

higher in Rs (0.24±0.17) compared to NRs (0.03±0.13) (*P* < 0.001). The optimal cut-off value for ΔV_{peak} is >0.17, which corresponds to the highest Youden index of 0.63. It has a sensitivity of 84.9% and specificity of 78.1%. The area under ROC (AuROC) curve is 0.872 [95% CI (0.784, 0.961), *P* < 0.001]. Upon evaluating the relationships between fasting time and various cardiac measurements, including CI, CO, and V_{peak}, fasting time showed no significant correlation with parameters (Table 3).

Table 3. Correlation Between Fasting Time and Cardiac Measurements

	ΔCI	ΔCO	ΔV_{peak}
Fasting time			
r	0.117	0.126	0.199
[a]*P*	**0.285**	**0.249**	**0.067**

a, Independent t-test; r, pearson correlation coefficient; ΔCI, change in cardiac index; ΔCO, change in cardiac output; ΔV_{peak}, change in aortic peak velocity

Discussion

The objective of this study was to evaluate the impact of preoperative fasting duration on intravascular volume status in paediatric patients undergoing elective surgery. Using dynamic hemodynamic assessment via PLR, we found that prolonged fasting had no significant effect on intravascular volume status, as determined by CI variability (ΔCI), CO, and aortic V_{peak}.

The actual duration of preoperative fasting in paediatric patients is often longer than current recommendations, varying between 11-13 hours.[15-17] Guidelines suggest reducing the clear fluid fasting period to approximately 2 hours before surgery to minimize discomfort and lower the incidence of hypotension in the perioperative period. However in clinical practices, paediatric fasting guidelines are often not applicable, resulting in longer fasting periods than recommended, with a high incidence of discomfort due to hunger and thirst.[16] The present study, which found an average fasting time of 11 hours fasting time revealed similar prolonged fluid abstinence times in children scheduled for outpatient surgery.

In this study, the patients having more than 10% increase in CI following PLR had comparable fasting times with NRs. There was no correlation between the duration of fasting and CO and V_{peak}. A study has suggested that prolonged fasting (more than 6 hours for liquid and 12 hours for solid) may increase the risk of hypotension during anaesthesia induction, particularly in paediatric patients.[9] A retrospective analysis was conducted focusing on clear fluids fasting times in children after implementing a 1 hour clear fasting rule. This study noted that longer fasting times, particularly those significantly exceeding the recommendations of guidelines, were associated with adverse events related to hypovolemia dehydration, such as difficulty in vein cannulations, electrocardiogram alterations, and episodes of hypotension.[16] Our findings contrast with prior studies that have reported associations between fasting duration and intraoperative hypotension. However, these studies primarily evaluated blood pressure changes as a surrogate for intravascular volume depletion, without incorporating dynamic assessments of fluid responsiveness.

Dynamic parameters, rather than static ones, have proven to be more reliable for predicting volume responsiveness in mechanically ventilated children.[10] In contrast to static indicators of preload, dynamic tests analyze the effect of a defined change in preload on stroke volume or CO, thus giving an indication of the patient's position on the Frank-Starling curve. Dynamic indices, therefore, are better predictors of changes in preload on the steep portion of the Frank-Starling curve and have been validated in predicting the response to volume expansion in both adults and children.[18,19] CI changes following PLR can identify patients who will benefit from fluid administration.[20] The effectiveness of the PLR test partly depends on the ability to significantly alter venous return by elevating the legs. In smaller children, particularly in infants and toddlers, the relative volume shift achieved by lifting the legs may not significantly change the preload due to their smaller blood volume and different body proportions. PLR induced CI changes reliably reflects fluid responsiveness in children older than 5 years of age,[20] but under this group of age it cannot identify all Rs with certainty.[13] This is the reason why study included children older than 5 years of age. Also, aortic ΔV_{peak} predicted fluid responsiveness with an AuROC of 0.872 in the present study, supporting the evidence that aortic blood flow velocity is a reliable index to predict fluid responsiveness in children.[11] USCOM measuring CO via a probe applied to the suprasternal notch revealed stroke volume variation as a reliable index in the prediction of fluid responsiveness.[21] The change in V_{peak} measured by USCOM showed a significant correlation with the measurements obtained through the apical 5-chamber view.[22] In light of these findings, we measured dynamic indices using USCOM.

Given the similar fasting times of Rs and NRs, it was suggested that fluid responsiveness cannot be directly related to the abstinence of oral intake. One-third of the children in our study were resistant; the reason for this could be attributed to the vasodilatory effects of the anaesthetic agents during the induction period. CO is directly related to the so-called stressed volume of the circulation.[23] For optimal cardiac preload, it's essential to have an adequate portion of the blood volume under stress, which depends on the state of the intravascular volume (normovolemia) and the tension within the blood vessels (vasotension).[24] One potential explanation for the lack of correlation between fasting duration and hemodynamic changes is anaesthesia -induced vasodilation, which significantly alters intravascular dynamics independent of fasting status. General anaesthesia induction and neuraxial anaesthesia lead to vasodilation, reducing the stressed volume and causing a functional intravascular deficit.[14,25] The presence of a functional intravascular deficit could lead to changes in the CI when a PLR test is performed. Muller et al.[27] showed that blood volume assessed by a dynamic test did not decrease after

preoperative fasting. As measurements were performed before anaesthesia, hemodynamics were not affected by anaesthesia induction. At this point, our study assesses the impacts on both the duration of fasting and anaesthesia by evaluating dynamic parameters following anaesthesia induction. Thus, in our study population, any fasting-related reduction in circulating volume may have been overshadowed by the hemodynamic effects of anaesthesia, explaining the absence of a significant correlation between fasting time and fluid responsiveness.

Children exhibit unique physiological adaptations that allow them to maintain hemodynamic stability despite fasting-related changes in intravascular volume. Unlike adults, where stroke volume plays a dominant role in CO regulation, young children primarily rely on HR adjustments to preserve CO. In paediatric patients, stroke volume is relatively fixed due to less compliant ventricles, meaning HR plays the primary role in adjusting CO[23]. Even if fasting led to mild intravascular depletion, children may compensate by increasing HR, thereby preserving CO and preventing a detectable change in CI or CO.[19]

Study Limitations

While our study provides important insights into fasting and hemodynamics in paediatric patients, certain limitations should be acknowledged. Primarily, it was conducted in a single institution, which may affect the generalizability of the findings. Additionally, the study included only children who were older than 5 years and were otherwise healthy apart from their surgical requirements. This selection criterion may restrict the applicability of our results to younger children, such as infants and toddlers, as well as to children with other comorbidities. Our study assessed volume status after anaesthesia induction, which means we could not evaluate fasting-induced changes before anaesthesia. While we assessed intravascular volume status, we did not measure interstitial fluid shifts, which could also play a role in perioperative hemodynamics.

Future studies may focus on a wider age range of children and those with cardiac, renal, and pulmonary comorbidities to assess the impact of fasting time on intravascular volume status more comprehensively and monitor longitudinal hemodynamic parameters before and after anaesthesia induction.

Conclusion

In conclusion, preoperative fasting time had no effect on intraoperative intravascular volume. Anaesthesia-induced vasodilation and paediatric compensatory mechanisms (HR-driven CO maintenance, sympathetic activation) likely mitigate any fasting-related hemodynamic effects, explaining the lack of correlation between fasting time and fluid responsiveness. These findings emphasize the importance of using dynamic assessments over static indicators when evaluating perioperative fluid status and highlight the need for further research on fasting and hemodynamic adaptations in paediatric patients.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the Institutional Ethics Committee of Marmara University Faculty of Medicine Clinical Research (approval no.: 09.2017.669, date: 08.12.2017).

Informed Consent: Written informed consent was obtained from all patients' legal representatives included in the study.

Footnotes

Author Contributions: Surgical and Medical Practices - B.B., T.U.; Concept - B.B., T.U.; Design - B.B., T.U.; Data Collection and/or/Processing - B.B., T.U.; Analysis and/or/Interpretation - B.B., T.U.; Literature Review - B.B., T.U.; Writing - B.B., T.U.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: No funding was received for conducting this study.

References

1. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: Application to healthy patients undergoing elective procedures: An updated report by the American Society of Anesthesiologists Task Force on preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration. *Anesthesiology.* 2017;126(3):376-393. [CrossRef]
2. Frykholm P, Disma N, Andersson H, et al. Pre-operative fasting in children: a guideline from the European Society of Anaesthesiology and Intensive Care. *Eur J Anaesthesiol.* 2022;39(1):4-25. [CrossRef]
3. Joshi GP, Abdelmalak BB, Weigel WA, et al. 2023 American Society of Anesthesiologists Practice Guidelines for preoperative fasting: carbohydrate-containing clear liquids with or without protein, chewing gum, and pediatric fasting duration-a modular update of the 2017 American Society of Anesthesiologists Practice Guidelines for preoperative fasting. *Anesthesiology.* 2023;138(2):132-151. [CrossRef]
4. Dolgun E, Yavuz M, Eroğlu B, Islamoğlu A. Investigation of preoperative fasting times in children. *J Perianesth Nurs.* 2017;32(2):121-124. [CrossRef]
5. Kight BP, Waseem M. Pediatric fluid management. *StatPearls.* Treasure Island (FL): *StatPearls Publishing*
6. Copyright© 2024, StatPearls Publishing LLC; 2024. [CrossRef]
7. Buller Y, Sims C. Prolonged fasting of children before anaesthesia is common in private practice. *Anaesth Intensive Care.* 2016;44(1):107-110. [CrossRef]
8. Derieg S. An overview of perioperative care for pediatric patients. *Aorn j.* 2016;104(1):4-10. [CrossRef]
9. Simpao AF, Wu L, Nelson O, et al. Preoperative fluid fasting times and postinduction low blood pressure in children: a retrospective analysis. *Anesthesiology.* 2020;133(3):523-533. [CrossRef]
10. Hajian P, Shabani M, Khanlarzadeh E, Nikooseresht M. The impact of preoperative fasting duration on blood glucose and hemodynamics in children. *J Diabetes Res.* 2020;2020:6725152. [CrossRef]

11. Yenjabog P, Kanchongkittiphon W, Chutipongtanate S, Lertbunrian R, Ungprasert P. Dynamic parameters for fluid responsiveness in mechanically ventilated children: a systematic review. *Front Pediatr.* 2022;10:1010600. [CrossRef]
12. Gan H, Cannesson M, Chandler JR, Ansermino JM. Predicting fluid responsiveness in children: a systematic review. *Anesth Analg.* 2013;117(6):1380-1392. [CrossRef]
13. Sethasathien S, Jariyasakoolroj T, Silvilairat S, Srisurapanont M. Aortic peak flow velocity as a predictor of fluid responsiveness in mechanically ventilated children: a systematic review and meta-analysis. *Pediatr Crit Care Med.* 2023;24(7):e352-e361. [CrossRef]
14. El-Nawawy AA, Farghaly PM, Hassouna HM. Accuracy of passive leg raising test in prediction of fluid responsiveness in children. *Indian J Crit Care Med.* 2020;24(5):344-349. [CrossRef]
15. Bundgaard-Nielsen M, Jørgensen CC, Secher NH, Kehlet H. Functional intravascular volume deficit in patients before surgery. *Acta Anaesthesiol Scand.* 2010;54(4):464-469. [CrossRef]
16. Tsukamoto M, Hitosugi T, Yokoyama T. Influence of fasting duration on body fluid and hemodynamics. *Anesth Prog.* 2017;64(4):226-229. [CrossRef]
17. Aroonpruksakul N, Punchuklang W, Kasikan K, et al. The actual duration of preoperative fasting in pediatric patients, and its effects on hunger and thirst: a prospective observational study. *Transl Pediatr.* 2023;12(2):146-154. [CrossRef]
18. Li Y, Lu Q, Wang B, Tang W, Fan L, Li D. Preoperative fasting times for patients undergoing elective surgery at a pediatric hospital in Shanghai: the big evidence-practice gap. *J Perianesth Nurs.* 2021;36(5):559-563. [CrossRef]
19. Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. *Ann Intensive Care.* 2016;6(1):111. [CrossRef]
20. Lee JH, Kim EH, Jang YE, Kim HS, Kim JT. Fluid responsiveness in the pediatric population. *Korean J Anesthesiol.* 2019;72(5):429-440. [CrossRef]
21. Lukito V, Djer MM, Pudjiadi AH, Munasir Z. The role of passive leg raising to predict fluid responsiveness in pediatric intensive care unit patients. *Pediatr Crit Care Med.* 2012;13(3):e155-160. [CrossRef]
22. Cheng YW, Xu F, Li J. Identification of volume parameters monitored with a noninvasive ultrasonic cardiac output monitor for predicting fluid responsiveness in children after congenital heart disease surgery. *Medicine (Baltimore).* 2018;97(39):e12289. [CrossRef]
23. Devauchelle P, de Queiroz Siqueira M, Lilot M, Chassard D, Desgranges FP. Suprasternal notch echocardiography: a potential alternative for the measurement of respiratory variation in aortic blood flow peak velocity in mechanically ventilated children. *J Clin Monit Comput.* 2018;32(3):589-591. [CrossRef]
24. Jacob M, Chappell D. Effects of perioperative fasting on haemodynamics and intravascular volumes. *Best Pract Res Clin Anaesthesiol.* 2012;26(4):421-430. [CrossRef]
25. Maas JJ, Pinsky MR, Aarts LP, Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesth Analg.* 2012;115(4):880-887. [CrossRef]
26. Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol Scand.* 2007;51(3):331-340. [CrossRef]
27. Muller L, Brière M, Bastide S, et al. Preoperative fasting does not affect haemodynamic status: a prospective, non-inferiority, echocardiography study. *Br J Anaesth.* 2014;112(5):835-841. [CrossRef]

DOI: 10.4274/TJAR.2025.241831

Original Article

Pain

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):233-241

Retrospective Clinical and Radiological Comparison of Intradiscal Ozone and Ozone + PRP Therapy Results in Patients with Intervertebral Disc Degeneration

Gülseli Berivan Sezen[1], Osman Boyalı[2], Burak Karip[3], Selman Aktaş[4], Eyüp Can Savrunlu[2], Mourat Chasan[2], Necati Kaplan[5], Erdinç Civelek[2], Serdar Kabataş[2]

[1]Giresun Training and Research Hospital, Clinic of Neurosurgery, Giresun, Türkiye

[2]University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital, Clinic of Neurosurgery, İstanbul, Türkiye

[3]University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Department of Anatomy, İstanbul, Türkiye

[4]University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Department of Biostatistics, İstanbul, Türkiye

[5]Optimed International Çorlu Hospital, Clinic of Neurosurgery, Tekirdağ, Türkiye

Cite this article as: Sezen GB, Boyalı O, Karip B, et al. Retrospective clinical and radiological comparison of intradiscal ozone and ozone + PRP therapy results in patients with intervertebral disc degeneration. *Turk J Anaesthesiol Reanim*. 2025;53(5):233-241.

Abstract

Objective: This retrospective study aimed to evaluate and compare the clinical efficacy of intradiscal ozone therapy (OT) against a combination therapy of ozone and platelet-rich plasma (PRP) in patients diagnosed with intervertebral disc degeneration (IVDD).

Methods: The study included a cohort of 50 patients, divided equally into two groups of 25, who received either intradiscal OT or ozone + PRP combination therapy between February 2022 and February 2023. The sample comprised 20 females and 30 males, with ages ranging from 19 to 76 years (mean age 48.8). Pain intensity was measured using the visual analog scale (VAS), while disability levels were assessed using the oswestry disability index (ODI) prior to treatment and at 1, 3, and 6 months post-treatment. Additionally, lumbar magnetic resonance imaging was conducted at the 3-month mark post-treatment, with evaluations based on the Pfirrmann disc degeneration classification.

Results: Significant improvement in both VAS and ODI scores was observed in both treatment groups ($P < 0.001$). The ozone + PRP combination therapy group exhibited no statistically significant difference in VAS and ODI scores compared to the ozone-only group ($P > 0.05$).

Conclusion: Intradiscal OT and the ozone + PRP combination therapy represent effective minimally invasive treatment options for patients suffering from IVDD, yielding substantial clinical benefits with minimal side effects. That is why it is suggested as a potential preferred therapeutic approach prior to the consideration of surgical interventions.

Keywords: Intervertebral disc degeneration, intradiscal, low back pain, ozone, platelet-rich plasma

Main Points

- The study compared the effectiveness of intradiscal ozone and ozone + platelet-rich plasma (PRP) combination treatments for intervertebral disc degeneration (IVDD).
- Ozone therapy (OT) and ozone + PRP treatments both significantly improved pain and disability stages in patients with IVDD.
- There is no statistically significant difference between OT and ozone + PRP therapies in pain and disability reduction, indicating that both are equally effective.

Corresponding author: Gülseli Berivan Sezen, MD, e-mail: berivansezen@gmail.com

Received: December 04, 2024 Accepted: March 24, 2025
Epub: May 14, 2025 Published date: October 14, 2025

Introduction

Low back pain (LBP) is a widespread condition, impacting up to 85% of individuals at some stage in their lives.[1] While the majority of cases resolve spontaneously within a few weeks, a notable percentage of patients progress to develop chronic symptoms that can significantly diminish their quality of life.[2] Intervertebral disc degeneration (IVDD) is a prevalent etiology of chronic LBP, characterized by morphological and biochemical alterations in the disc tissue, leading to impaired mechanical function and pain. The management of IVDD presents considerable challenges due to the limited self-healing capacity of the disc, primarily attributed to its inadequate vascularization and the hypoxic microenvironment present within the disc.[3] As insights into the pathophysiology of IVDD continue to evolve, minimally invasive interventions such as intradiscal ozone therapy (OT) and platelet-rich plasma (PRP) therapy have garnered interest for their potential to alleviate pain and restore functionality.[4,5] It has been reported that PRP induces the release of bioactive proteins that influence macrophages, mesenchymal stem cells, osteoblasts and/or annulus fibrosus cells, as well as nucleus pulposus cells accelerating the absorption of necrotic tissues and promoting regeneration.[6] OT, which entails the injection of a gas mixture of oxygen and ozone into the affected disc, is thought to exert its therapeutic effects through the induction of oxidative stress, resulting in a reduction of disc volume and alleviation of nerve compression.[7,8] Conversely, PRP therapy employs autologous growth factors to facilitate tissue repair and mitigate inflammation.[9,10] Recent investigations indicate that the synergistic application of these therapies may enhance their individual therapeutic effects, thereby providing a more effective treatment alternative for patients suffering from IVDD.[11] This study aims to retrospectively compare the clinical and radiological outcomes of intradiscal OT with those of the ozone and PRP combination therapy in patients diagnosed with IVDD.

Methods

Ethical approval was received from the University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital, GETAT Clinical Research Ethics Committee (approval no.: SBllSAH-GETAT 2023-048, date: 13.12.2023). This retrospective analysis encompassed 50 patients (20 females and 30 males) aged between 19 and 76 years (mean age 48.8), who received either intradiscal OT or ozone + PRP combination therapy from February 2022 to February 2023. Patient selection was based on the presence of LBP that was unresponsive to conservative management, magnetic resonance imaging (MRI) findings indicative of disc protrusion or bulging, Pfirmann grade 3-6 and a visual analog scale (VAS) score of 5 or higher. Exclusion criteria included pregnancy, motor deficits, bleeding diathesis, glucose-6-phosphate dehydrogenase deficiency, active infection, and previous lumbar surgery. Pain intensity was quantified using the VAS, while disability levels were evaluated using the oswestry disability index (ODI) prior to treatment and at 1, 3, and 6 months post-treatment. VAS is a subjective pain assessment method in which patients rate their pain level on a scale from 0 (no pain) to 10 (unbearable pain).[12] ODI is a standardized 10-item questionnaire used to evaluate lower-back pain and functional disability. Patients subjectively score their daily living activities and the limitations they experience in these activities.[13] Additionally, lumbar MRI assessments conducted at 3 months post-treatment were analyzed according to the Pfirmann disc degeneration classification.

Procedure

In the study involving patients undergoing ozone + PRP therapy, a total of 20 cc of blood was collected and mixed with 1 cc of citrate per 9 cc of blood. This mixture was subsequently transferred into two 10 cc yellow tubes (sterile and preservative-free tubes) and centrifuged at 3000 rpm for 5 minutes to prepare the PRP. After centrifugation, 2 mL of PRP was obtained.

The patient was then positioned prone on the operating table, with a bilateral pillow placed under the abdomen for support. The procedures were performed under local anaesthesia. Fluoroscopy equipment was prepared for imaging purposes. The puncture site was sterilized (with povidone iodine), and sterile drapes were applied. The target intervertebral disc level was identified using fluoroscopic imaging, and the entry point was marked accordingly. A local anaesthesia solution containing 0.5% lidocaine was administered at the injection site. Under fluoroscopic guidance, utilizing anteroposterior and lateral and oblique views, a 22-gauge, 20 cm spinal needle was inserted posterolaterally into the nucleus pulposus of the disc suspected of causing pain, approximately 10-12 cm lateral to the midline at an angle of 30-45 degrees. For the OT component, 10 mL of an O_2-O_3 mixture (20 µg mL^{-1} O_3) was injected at each disc level. Procedures were performed only with intradiscal injections at a single level for each patient, while transforaminal injections were omitted. In patients receiving the combined ozone and PRP therapy, 2 mL of PRP, was administered first, followed by the 10 mL O_2-O_3 mixture.

Following the procedure, the patient was monitored for approximately 2 hours, before being mobilized and discharged after a 5-day rest period, with no complications reported during mobilization.

Statistical Analysis

Data were analyzed using two-way analysis of variance (ANOVA) for repeated measures to evaluate pre- and post-treatment scores both within and between groups.

Chi-square tests were employed to assess demographic characteristics. All statistical analyses were conducted using SPSS software (version 22; SPSS Inc., Chicago, IL, USA), with a significance threshold set at $P < 0.05$.

Results

Patient Demographics and Baseline Characteristics

The study sample consisted of 50 patients, including 20 females (40%) and 30 males (60%). The mean age of participants was 48.8 years, with an age range spanning from 19 to 76 years.

No statistically significant differences were observed between the two treatment groups concerning age, gender distribution, or baseline VAS and ODI scores, thereby ensuring comparability ($P > 0.05$) (Table 1).

Of the patients receiving OT, 7 were female (28%) and 18 were male (72%). The analysis revealed a statistically significant difference in VAS and ODI scores for patients undergoing isolated OT ($P < 0.05$). Specifically, VAS scores indicated that pre-procedure values were significantly higher than those recorded at the 1st, 3rd, and 6th months post-procedure ($P < 0.05$) (Table 2). Notably, the lowest VAS score was observed at the 3rd month post-procedure ($P < 0.05$) (Figure 1). ODI scores demonstrated that pre-procedure values were significantly higher than those at the 1st, 3rd, and 6th months post-procedure ($P < 0.05$), with the lowest ODI score recorded at the 6th month post-procedure ($P < 0.05$) (Figure 1).

Of the patients receiving ozone + PRP treatment, 15 were female (60%) and 10 were male (40%). In patients receiving ozone + PRP treatment, the analysis revealed a statistically significant difference in VAS and ODI scores ($P < 0.05$) (Table 3). The pre-procedure VAS scores were found to be higher than the scores recorded at the 1st, 3rd, and 6th months post-the procedure ($P < 0.05$). When the post-procedure VAS scores were examined, it was observed that the 6th-month VAS score was the lowest ($P < 0.05$) (Figure 2). In ODI scores, it was observed that the pre-procedure scores were higher than the 1st, 3rd and 6th month scores after the procedure ($P < 0.05$). The examinations conducted in the 1st, 3rd, and 6th months post-procedure revealed that the 6th month ODI score was the lowest ($P < 0.05$) (Figure 2).

The VAS and ODI scores at the 1st, 3rd, and 6th months post-procedure for both treatment groups were statistically significantly lower ($P < 0.05$) compared to the pre-operative scores (Figures 1, 2). However, no statistically significant differences were observed in VAS and ODI scores when comparing the 1st, 3rd, and 6th months scores within both groups ($P > 0.05$).

Table 1. Distributions of Variables

Group	Normality Tests	Kolmogorov-Smirnov		Shapiro-Wilk	
		Statistic	Sig.	Statistic	Sig.
Ozone	Pre-Procedure VAS	0.408	**0.000**	0.378	**0.000**
	Pre-Procedure ODI	0.112	0.200*	0.956	0.343
	After 1st month VAS	0.209	**0.006**	0.924	0.063
	After 1st month ODI	0.208	**0.007**	0.870	**0.004**
	After 3rd month VAS	0.223	**0.002**	0.893	**0.013**
	After 3rd month ODI	0.190	**0.021**	0.838	**0.001**
	After 6th month VAS	0.309	**0.000**	0.440	**0.000**
	After 6th month ODI	0.184	**0.028**	0.840	**0.001**
Ozone + PRP	Pre-Procedure VAS	0.234	**0.001**	0.919	**0.043**
	Pre-Procedure ODI	0.111	0.200*	0.932	0.086
	After 1st month VAS	0.241	**0.000**	0.926	0.063
	After 1st month ODI	0.179	**0.032**	0.879	**0.005**
	After 3rd month VAS	0.325	**0.000**	0.790	**0.000**
	After 3rd month ODI	0.290	**0.000**	0.728	**0.000**
	After 6th month VAS	0.338	**0.000**	0.720	**0.000**
	After 6th month ODI	0.243	**0.000**	0.734	**0.000**

*SPSS Kolmogorov-Smirnov test *P* normality
Bold values: $P < 0.200$
VAS, visual analog scale; ODI, oswestry disability index; Sig., significant; PRP, platelet-rich plasma

Radiological Outcomes

Disc Size and Morphology

Lumbar MRI examinations conducted at the 3rd month follow-up of the patients were compared to pre-treatment MRI assessments in patients who underwent OT. A decrease in disc size was observed in 9 patients, while no significant change in disc size was noted in 14 patients, and an increase in disc size was determined in 2 patients (Figures 3, 4, and Table 4).

Table 2. Comparison of Patients Receiving Ozone Therapy in Terms of Periods

Ozone	Median (Min.-Max.)	*P* value	Difference
Pre-Procedure VAS	8 (5-38)	<0.001	**1>4 1>3 1>2**
After 1st month VAS	4 (1-8)		
After 3rd month VAS	3 (1-8)		
After 6th month VAS	3 (1-33)		
Pre-Procedure ODI	31 (11-46)	<0.001	
After 1st month ODI	10 (2-35)		
After 3rd month ODI	8 (1-35)		
After 6th month ODI	7 (1-35)		

1, pre-procedure; 2, after 1st month; 3, after 3rd month; 4, after 6th month.
VAS, visual analog scale; ODI, oswestry disability index; Min.-Max., minimum-maximum

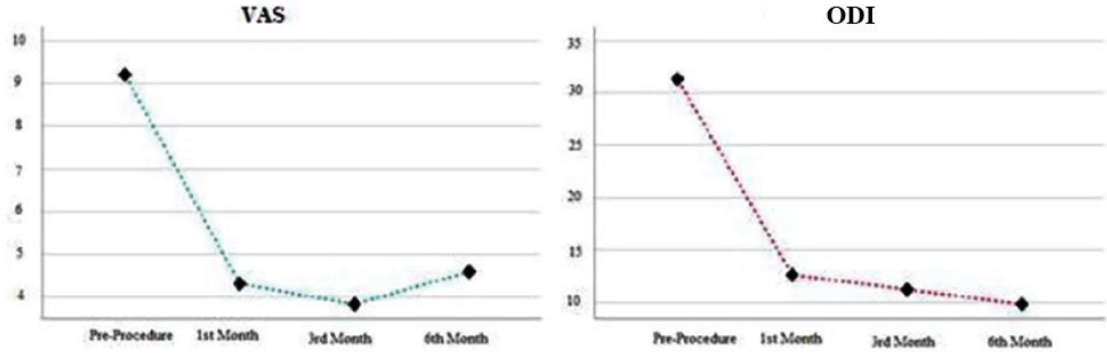

Figure 1. Comparison of VAS and ODI scores in patients receiving ozone therapy.

VAS, visual analog scale; ODI, oswestry disability index.

Table 3. Comparison of Patients Receiving Ozone + PRP Combine Therapy in Terms of Periods

Ozone + PRP	Median (Min.-Max.)	*P* value	Difference
Pre-Procedure VAS	8 (5-10)	<0.001	**1>4 1>3 1>2**
After 1st month VAS	4 (1-9)		
After 3rd month VAS	3 (1-9)		
After 6th month VAS	3 (1-9)		
Pre-Procedure ODI	25.5 (17-33)	<0.001	**2>4 1>4 1>3 1>2**
After 1st month ODI	10.5 (1-36)		
After 3rd month ODI	5.5 (2-36)		
After 6th month ODI	3.5 (1-36)		

1, pre-procedure; 2, after 1st month; 3, after 3rd month; 4, after 6th month.
VAS, visual analog scale; ODI, oswestry disability index; Min.-Max., minimum-maximum; PRP, platelet-rich plasma

Lumbar MRI examinations conducted at the 3rd month follow-up of the patients were compared to pre-treatment MRI assessments in patients receiving ozone + PRP combined therapy. A decrease in disc size was noted in 5 of the patients who received OT, while no significant change in disc size was noted in 18 patients, and an increase in disc size was noted in 2 patients (Figures 5, 6 and Table 4).

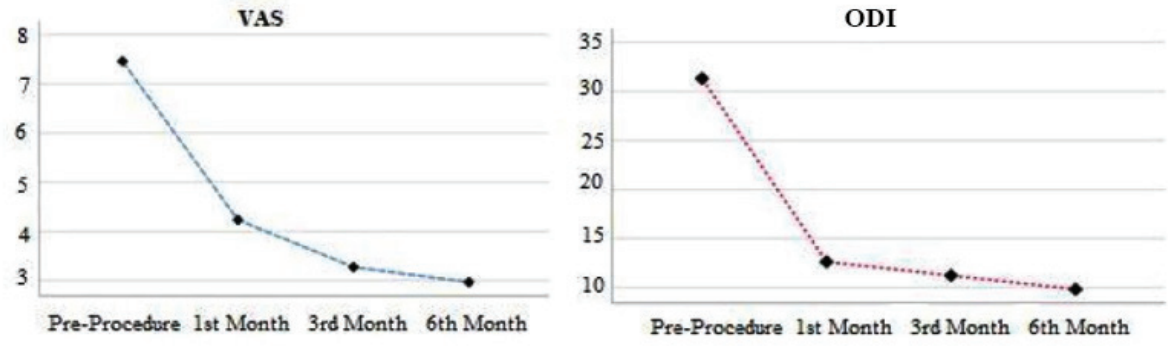

Figure 2. Comparison of VAS and ODI scores in patients receiving ozone + PRP combine therapy.

VAS, visual analog scale; ODI, oswestry disability index; PRP, platelet-rich plasma.

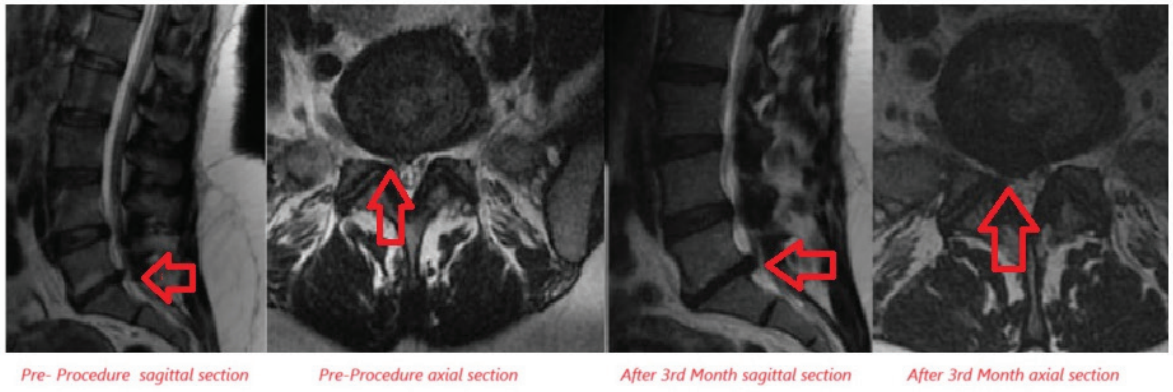

Figure 3. Examination of disc size increase after ozone therapy in lumbar MRI sagittal and axial sections.

MRI, magnetic resonance imaging.

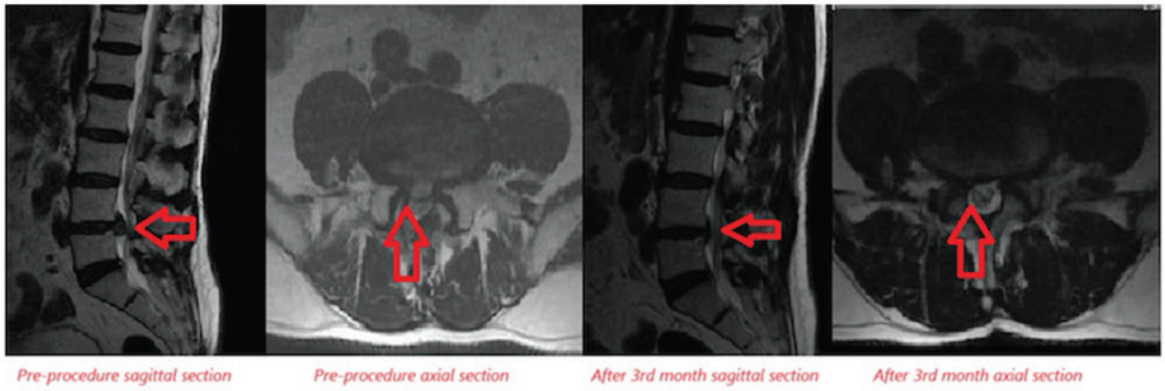

Figure 4. Examination of disc size reduction after ozone therapy in lumbar MRI sagittal and axial sections.

MRI, magnetic resonance imaging.

Although the group receiving ozone combined with PRP exhibited a lower percentage of patients with reduced disc size compared to the ozone-only group, the more pronounced clinical improvements (VAS and ODI scores) indicate that disc size reduction alone may not fully account for the therapeutic benefits of the combination therapy.

Outcome Assessment

In the repeated measures ANOVA test, comparing OT and ozone + PRP therapy results in terms of VAS scores, F (1.49)=2.549, P=0.117 was obtained. As a result of comparing the results of OT and ozone + PRP in terms of ODI scores, it was found that F (1.49)=1.190, P=0.281. These results indicate no statistically significant difference in VAS and ODI values between the two treatment methods (P > 0.05), suggesting no superiority of one treatment method over the other (Figure 7).

Table 4. Post-Treatment Evaluation of Disc Dimensions in Control Lumbar MRI

Lumbar MRI Disc Dimensions	Ozone Therapy (Number of patients)	Ozone + PRP Combine Therapy (Number of patients)
Increase in disk size	2	2
No change in disk size	14	18
Reduction/decrease in disk size	9	5

MRI, magnetic resonance imaging; PRP, platelet-rich plasma

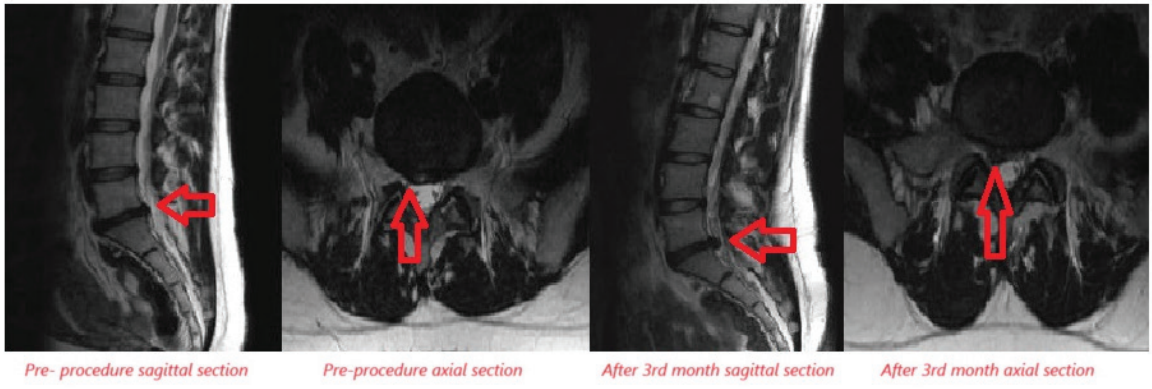

Figure 5. Examination of disc size increase after ozone + PRP combine therapy in lumbar MRI sagittal and axial sections.

MRI, magnetic resonance imaging; PRP, platelet-rich plasma.

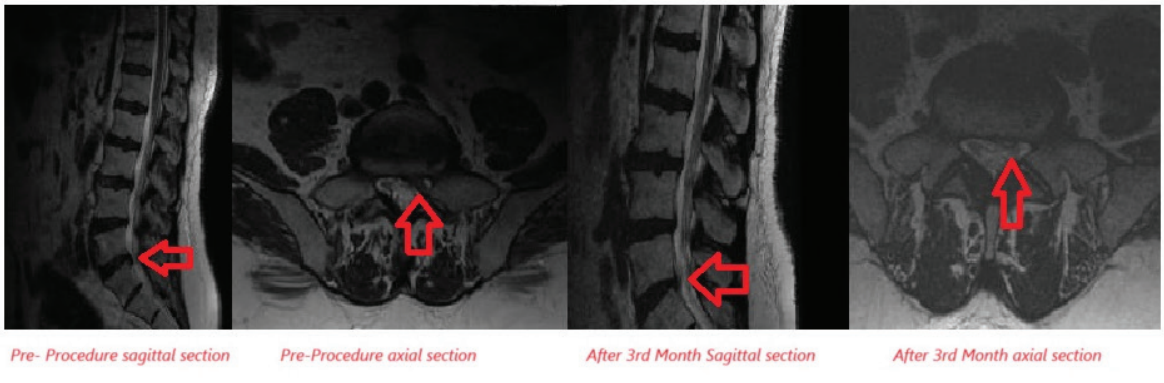

Figure 6. Examination of disc size reduction after ozone + PRP combine therapy in lumbar MRI sagittal and axial sections.

MRI, magnetic resonance imaging; PRP, platelet-rich plasma.

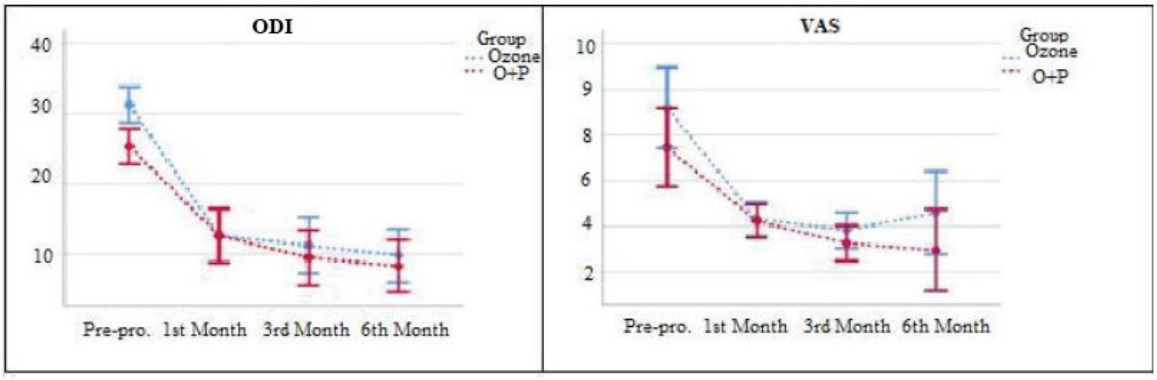

Figure 7. Comparison of ozone and ozone + PRP combine therapies.

ODI, oswestry disability index; VAS, visual analog scale; PRP, platelet-rich plasma.

Safety and Adverse Events

Both treatment groups were well-tolerated, with no major adverse events reported. No cases of infection, nerve damage, or allergic reactions were observed. High doses of ozone can result in adverse effects such as disc tissue toxicity and systemic complications.[11,14] In our study, no cases of spondylodiscitis or other infections were observed; such complications have been documented in the literature.[15,16] Ensuring precise dosing and adherence to safety protocols is essential for mitigating these risks and enhancing the overall safety profile of OT. Additionally, 4 patients (2 from each group) experienced worsening of symptoms due to increased disc size and were referred for surgical intervention (Table 4).

Discussion

The primary objective of this study was to evaluate and compare the clinical and radiological outcomes of intradiscal OT versus a combination of intradiscal ozone and PRP therapy in patients with IVDD. Our results indicated that both treatment methods resulted in significant improvements in pain and disability scores, and there is no difference in clinical benefit between ozone and the combination therapy.

Clinical Outcomes

Our study revealed significant reductions in VAS and ODI scores for both the OT and ozone + PRP combined therapy groups at 1, 3, and 6 months post-treatment. Specifically, the VAS scores in the ozone group showed a gradual decrease, with the lowest scores recorded at the 3-month follow-up (Table 2). This aligns with the results of Muto et al.,[11] who reported significant pain relief following intradiscal OT for lumbar disc herniation.[17] Histopathological examination of intervertebral disc spaces in animal studies has shown increased regeneration in the group treated with OT compared to the degenerated control group.[18]

Numerous studies have revealed long-term improvements in patient-reported pain and movement function following intradiscal PRP injections.[19-21] This suggests that the addition of PRP may enhance the overall efficacy of OT. This result is supported by recent studies, indicating that PRP has the potential to augment the effects of other treatments by enhancing tissue repair and mitigating inflammation.[22] Notably, PRP is recognized for its ability to deliver growth factors and cytokines that can facilitate tissue regeneration and reduce inflammation, potentially contributing to its synergistic effects when combined with OT.

Radiological Outcomes

Radiological evaluations conducted at the three-month follow-up indicated a reduction in disc size among 9 patients (36%) in the ozone treatment group and 5 patients (20%) in the ozone + PRP group (Table 4). These results align with the findings of Muto et al.,[11] who documented a decrease in disc volume following OT. The observation that a higher proportion of patients in the ozone-only group experienced disc shrinkage, may reflect variability in individual treatment responses influenced by factors such as the severity of disc degeneration and the specific injection techniques employed.[23] Notably, while both treatment modalities resulted in significant clinical improvements, the radiological changes did not consistently predict pain relief. This inconsistency mirrors the findings of Lehnert et al.,[24] who reported no direct correlation between reductions in disc size and pain alleviation following OT. In contrast, Negro et al.[25] found a significant association between disc shrinkage and reduced pain levels, suggesting that while disc volume reduction may contribute to pain relief, it is not the sole factor involved.

Synergistic Effects of Ozone + PRP

Although our study did not reveal a statistically significant difference between the ozone and ozone + PRP groups,

we posit that PRP exerts a synergistic effect, particularly within the combined treatment group. An experimental animal study demonstrated that intradiscal PRP treatment, administered following IVDD, resulted in the preservation of disc morphological characteristics and delayed degeneration, accompanied by reduction in the migration of inflammatory cytokines.[26-28]

Limitations and Future Directions

The need for fluoroscopy and/or tomography guidance could limit the feasibility of this treatment in the common rehabilitation setting due to radiation risk.[29] A limitation of our study is the relatively short follow-up duration, which restricts our ability to fully assess long-term outcomes and the sustainability of treatment effects. Future studies with extended follow-up periods and larger sample sizes are essential to validate these findings and to evaluate the long-term efficacy and safety of combined ozone and PRP therapy.

Conclusion

In this study, we observed a significant reduction in pain scores following treatment in both the ozone and ozone + PRP groups, attributable to IVDD. This suggests that these treatment modalities may serve as viable alternatives to surgical intervention, particularly for patients without neurological deficits. The integration of diverse treatment approaches aims to facilitate the regeneration of disc tissue, alleviate associated pain, and enhance patients' overall quality of life. There is a need to develop and experimentally evaluate new treatment modalities.

Ethics

Ethics Committee Approval: Ethical approval was received from the University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital, GETAT Clinical Research Ethics Committee (approval no.: SBllSAH-GETAT 2023-048, date: 13.12.2023).

Informed Consent: Written informed consent was obtained from all patients' legal representatives included in the study.

Footnotes

Author Contributions: Surgical and Medical Practices - G.B.S., O.B, M.C., S.K.; Concept - G.B.S., O.B, B.K., E.C.S., M.C., E.C., S.K.; Design - G.B.S., S.A., B.K., E.C.S., M.C., N.K.; Data Collection and/or/Processing - G.B.S., S.A., E.C.S.; Analysis and/or/Interpretation - G.B.S., O.B., S.A., B.K., N.K., S.K.; Literature Review - G.B.S., O.B., E.C., S.K.; Writing - G.B.S.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: No funding was received for conducting this study.

References

1. van Tulder M. Treatment of low back pain: myths and facts. *Schmertz*. 2001;15(6):499-503. [CrossRef]
2. Dönmez GM, Bel ağrısı sorunlarında lomber bölge egzersizlerinin eklem hareket açıklığı ve ağrı durumuna etkisi, Bilimsel Tez, 2011 Ulusal Tez Merkezi Tez No: 282361
3. Peng BG. Pathophysiology, diagnosis, and treatment of discogenic low back pain. *World J Orthop.* 2013;4(2):42-52. [CrossRef]
4. Andreula C. Percutaneous disc treatments. *Neuroradiol J.* 2009;22(1):141-143. [CrossRef]
5. Guarnieri G, Vassallo P, Pezzullo MG, et al. A comparison of minimally invasive techniques in percutaneous treatment of lumbar herniated discs. A review. *Neuroradiol J.* 2009;22(1):108-121. [CrossRef]
6. Everts PA, van Erp A, DeSimone A, Cohen DS, Gardner RD. Platelet rich plasma in orthopedic surgical medicine. *Platelets.* 2021;32(2):163-174. [CrossRef]
7. Bocci VA. Scientific and medical aspects of ozone therapy. State of the art. *Arch Med Res.* 2006;37(4):425-435. [CrossRef]
8. Aytaçoğlu S. Ozon treatment. *Ankara Acupuncture and Complementary Medicine Journal*. 2014;2(1):31-36. [CrossRef]
9. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med.* 2009;37(11):2259-2272. [CrossRef]
10. Belebecha V, Casagrande R, Urbano MR, et al. Effect of the platelet-rich plasma covering of polypropylene mesh on oxidative stress, inflammation, and adhesions. *Int Urogynecol J.* 2020;31(1):139-147. [CrossRef]
11. Muto M, Andreula C, Leonardi M. Treatment of herniated lumbar disc by intradiscal and intraforaminal oxygen-ozone (O2-O3) injection. *J Neuroradiol.* 2004;31(3):183-189. [CrossRef]
12. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health.* 1990;13(4):227-236. [CrossRef]
13. Fairbank JC, Pynsent PB. The oswestry disability index. *Spine (Phila Pa 1976).* 2000;25(22):2940-2952; discussion 2952. [CrossRef]
14. Bocci V, Borrelli E, Travagli V, Zanardi I. The ozone paradox: ozone is a strong oxidant as well as a medical drug. *Med Res Rev.* 2009;29(4):646-682. [CrossRef]
15. Fort NM, Aichmair A, Miller AO, Girardi FP. L5-S1 achromobacter xylosoxidans infection secondary to oxygen-ozone therapy for the treatment of lumbosacral disc herniation: a case report and review of the literature. *Spine (Phila Pa 1976).* 2014;39(6):E413-416. [CrossRef]
16. Erroi F, Rotondo C, Sciacca S, Trotta A, Cantatore FP, Corrado A. Serious spondylodiscitis, septic sacroiliitis and multiple abscesses after ozone therapy for low back pain: a case report on good response to combined treatment with empiric antibiotic and neridronate. *Int J Rheum Dis.* 2023;26(8):1590-1593. [CrossRef]
17. Andreula CF, Simonetti L, De Santis F, Agati R, Ricci R, Leonardi M. Minimally invasive oxygen-ozone therapy for lumbar disk herniation. *AJNR Am J Neuroradiol.* 2003;24(5):996-1000. [CrossRef]
18. Baysoy Avınçsal B., Deneysel intervertebral disk dejenerasyonu modelinde intradiskal ozon uygulanması ile intervertebral disk rejenerasyonunun histopatolojik değerlendirilmesi, Bilimsel Tez, 2023 Ulusal Tez Merkezi Tez No:797873
19. Jain D, Goyal T, Verma N, Paswan AK, Dubey RK. Intradiscal platelet-rich plasma injection for discogenic low back pain and correlation with platelet concentration: a prospective clinical trial. *Pain Med.* 2020;21(11):2719-2725. [CrossRef]
20. Akeda K, Ohishi K, Masuda K, et al. Intradiscal injection of autologous platelet-rich plasma releasate to treat discogenic low back pain: a preliminary clinical trial. *Asian Spine J.* 2017;11(3):380-389 [CrossRef]
21. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, Lumbar intradiskal platelet-rich plasma (PRP) injections: a prospective, double-blind, randomized controlled study. *PM R.* 2016;8(1):1-10;quiz 10. [CrossRef]

22. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med.* 2011;39(10):2135-2240. [CrossRef]

23. Levi D, Horn S, Tyszko S, Levin J, Hecht-Leavitt C, Walko E. Intradiscal platelet-rich plasma injection for chronic discogenic low back pain: preliminary results from a prospective trial. *Pain Medicine*. 2016;17(6): 1010-1022. [CrossRef]

24. Lehnert T, Naguib NN, Wutzler S, et al. Analysis of disk volume before and after CT-guided intradiscal and periganglionic ozone-oxygen injection for the treatment of lumbar disk herniation, *J Vasc Interv Radiol Nov*. 2012;23(11):1430-1436. [CrossRef]

25. Negro A, Paolucci A, Russo C, et al. Predictive factors of volumetric reduction in lumbar disc herniation treated by O2-O3 chemiodiscolysis. *Acta Biomed.* 2020;91(8-S):89-97. [CrossRef]

26. Gullung GB, Woodall WB, Tucci MA, James J, Black DA, McGuire RA. Platelet-rich plasma effects on degenerative disc disease: analysis of histology and imaging in an animal model. *Evid Based Spine Care J*. 2011;2(4):13-18. [CrossRef]

27. Li P, Zhang R, Zhou Q. Efficacy of platelet-rich plasma in retarding intervertebral disc degeneration: a meta-analysis of animal studies. *Biomed Res Int.* 2017;2017:7919201. [CrossRef]

28. Gelalis ID, Christoforou G, Charchanti A, et al. Autologous platelet-rich plasma (PRP) effect on intervertebral disc restoration: an experimental rabbit model. *EJOST*. 2019;29(3):545-551. [CrossRef]

29. de Sire A, Agostini F, Lippi L, et al. Oxygen-ozone therapy in the rehabilitation field: state of the art on mechanisms of action, safety and effectiveness in patients with musculoskeletal disorders. *Biomolecules.* 2021;11(3):356. [CrossRef]

DOI: 10.4274/TJAR.2025.251895

Original Article
Perioperative Care

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):242-248

A Randomized Controlled Study to Compare the Efficacy of High Frequency Nasal Oxygenation with Conventional Oxygen Therapy for Postoperative Oxygenation in Patients Undergoing Exploratory Laparotomies

Geetanjali T. Chilkoti, Poonam Sehrawat, Medha Mohta, Michell Gulabani

University College of Medical Sciences & Guru Teg Bahadur Hospital, Hospital, Clinic of Anaesthesiology, Delhi, India

Cite this article as: Chilkoti GT, Sehrawat P, Mohta M, Gulabani M. A randomized controlled study to compare the efficacy of high frequency nasal oxygenation with conventional oxygen therapy for postoperative oxygenation in patients undergoing exploratory laparotomies. *Turk J Anaesthesiol Reanim.* 2025;53(5):242-248.

Abstract

Objective: Postoperative pulmonary complication (PPC) is one of the leading causes of poor surgical outcome leading to longer hospital or intensive care unit stay and mortality especially with upper abdominal surgeries having long duration. High-frequency nasal oxygenation (HFNO) has recently been employed for postoperative oxygenation following extubation in surgical patients.

Methods: Fifty consenting adult patients aged 18-65 years of either sex scheduled for exploratory abdominal surgeries under general anaesthesia (GA) with Assess Respiratory Risk in Surgical Patients in Catalonia score ≥26 i.e., moderate to high risk were enrolled. After instituting all routine the American Society of Anesthesiologists recommended monitoring, baseline haemodynamic parameters were recorded. Patients were preoxygenated with 100% oxygen and GA was administered as per standard institutional protocol. Following extubation, patients were randomly allocated into one of the groups comprising 25 patients each where Group C and Group H received conventional oxygen therapy via simple face mask and HFNO respectively. The FiO_2 was titrated (from 45% to 100%) by the anaesthesiologist to maintain a SpO_2 of 95% or more. Arterial blood samples were collected after extubation at various designated time points i.e. 2nd, 6th,12th and 24th hr, The P/F ratio, PaO_2, $PaCO_2$, SaO_2/FiO_2 ratio along with haemodynamic parameters, incidence of PPCs/acute hypoxemic respiratory failure (AHRF), atelectasis and comfort score were also recorded.

Results: Significant improvement in all oxygenation parameters following the use of HFNO for postoperative oxygenation; however, $PaCO_2$, haemodynamic variables, complications, incidence of PPCs/AHRF and atelectasis remained comparable between the two groups.

Conclusion: Preventive use of HFNO for post operative oxygenation amongst moderate to high-risk patients scheduled for exploratory abdominal surgery improves oxygenation.

Keywords: Hypoxemia, laparotomies, oxygen, postoperative period, patient comfort

Main Points

- Reported incidence of postoperative pulmonary complications (PPCs) is as high as 40% following abdominal surgeries.
- Recently, high frequency nasal cannula (HFNC) has been increasingly used for providing postoperative oxygenation.
- Its definite role following major abdominal surgeries needs further exploration.
- We observed that the preventive use of HFNC for postoperative oxygenation amongst patients scheduled for exploratory abdominal surgery improves oxygenation; however, no difference in acute hypoxemic respiratory failure/PPCs, reintubation rate, Chest X-ray proven atelectasis and complications.

Corresponding author: Geetanjali T. Chilkoti, MD, e-mail: geetanjalidr@yahoo.co.in

Received: February 05, 2025 Accepted: April 16, 2025
Epub: July 16, 2025 Published date: October 14, 2025

Introduction

Postoperative pulmonary complications (PPCs) are known to be the second most common complication after surgery, with an incidence ranging from 2% to 19% in non-cardiac procedures and as high as 40% following abdominal surgeries.[1] Hypoxemia is one of the most frequent PPCs, making postoperative oxygen administration essential.[2]

Low-flow conventional oxygen therapy (COT) continues to be the primary method for oxygen delivery in the postoperative period. However, high-frequency nasal oxygenation (HFNO) has recently been introduced due to its benefits, such as delivering a more predictable FiO_2, improved humidification, reduced anatomical dead space, and greater patient comfort.[3] Despite these advantages, HFNO failure in patients with pulmonary complications can result in delayed intubation, leading to increased morbidity and mortality.[4] As a result, its safety and effectiveness are being more frequently studied in the literature, although the findings have been inconsistent.[5,6]

Most of the studies evaluating the efficacy of HFNO for postoperative oxygenation have been conducted in obese patients and following cardio-thoracic surgeries.[7-9] It's role in routine surgical procedures like laparotomies with long surgical duration has not yet been extensively studied except a single large multicentric trial that evaluated the efficacy of HFNO along with lung-protective ventilation strategy for postoperative oxygenation following major abdominal surgeries but lacked the measurement of all blood oxygenation parameters.[2] Additionally, it also did not incorporate any radiological method to rule out PPCs and quality of recovery (QoR).

Therefore, the present study was undertaken to evaluate the efficacy of HFNO compared with COT for prevention of PPCs in patients undergoing exploratory abdominal laparotomies during the immediate post-operative period. The primary outcome was arterial oxygen tension to inspiratory oxygen fraction partial pressure of oxygen (PaO_2)/FiO_2 (P/F) ratio at the end of day one between the two groups. Various secondary outcomes included the PaO_2, arterial oxygen saturation (SaO_2) SaO_2/FiO_2 (S/F) ratio, partial pressure of carbon dioxide ($PaCO_2$), incidence of PPCs and complications at various time points in the first 24 hours postoperatively.

Methods

This prospective randomised controlled study was conducted in a tertiary care centre following approval from the Institutional Ethics Committee of Human Research (IEC-HR) University College of Medical Sciences, University of Delhi (approval no.: IECHR-2022-55-71, date: 30.08.2022) and subsequently registered under the Clinical Trials Registry-India (CTRI) with number (CTRI/2023/01/049207).

A written informed consent from each participant was taken prior to their recruitment. The study was carried out in accordance with the principles of the Declaration of Helsinki 2013 and confirmed the use of patient data for research and educational purposes. Fifty consenting adult patients aged 18-65 years of either sex scheduled for exploratory abdominal surgeries under general anaesthesia (GA) with Assess Respiratory Risk in Surgical Patients in Catalonia score ≥26 i.e., moderate to high risk[10] were enrolled. Patients with a history of cardiac disease, restrictive or obstructive pulmonary disease or asthma causing functional limitations, body mass index >40 kg m^{2-1}, inability to comprehend oral or written information were excluded from the study.

In the operating room, all routine the American Society of Anesthesiologists (ASA) recommended mandatory monitoring were instituted and baseline haemodynamic parameters i.e. heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure were recorded. Patients received normal tidal volume preoxygenation with 100% oxygen for three minutes. GA was administered as per standard institutional protocol and trachea was intubated using an endotracheal tube (ETT). At the end of surgery, patients were randomised into one of the two groups namely C and H using a computer-generated random number table and allocation concealment was done by using sequentially numbered opaque sealed envelopes. Following adequate reversal of neuromuscular blockade, ETT was removed, and patients were shifted to the post-anaesthesia care unit (PACU). Patients in group C received COT via simple face mask, whereas those in group H, HFNO via high frequency nasal cannula (HFNC) with flow rate of 35 to 60 L min for 24 hours.

The FiO_2 was titrated (from 45% to 100%) by the anaesthesiologist to maintain an SpO_2 of 95% or more in both the groups and patients were observed for a period of three days. Standard bedside multipara monitor was used to record the SpO_2, non-invasive blood pressure and HR every 15 minutes for the first 2 hours. Arterial blood gas (ABG) samples were collected in the PACU, at various designated time points i.e. at the end of 2^{nd}, 6^{th}, 12^{th} and 24^{th} hour postoperatively. Additional oxygen was continued beyond 24 hours of the study, if SpO_2 continued to be below 93% after oxygen discontinuation.

The duration and incidence of SpO_2 <90% was noted. The incidence of hypoxemia (defined as P/F ratio ≤ 300 mmHg) was recorded. The management and further ABG sampling were as per the discretion of anaesthesiologist. The differences of PaO_2, $PaCO_2$, P/F and S/F ratios, were noted and compared between the groups.

The proportion of patients who developed PPCs, such as pneumothorax, pleural effusion or suspected pneumonia (defined by at least one of the following criteria: new or changed sputum, new or altered Chest X-ray findings, oral temperature >38.3 °C, and white blood cell count > 12×10^9/L) and atelectasis (as evident on Chest X-ray), were also recorded.[2] Additionally, the proportion of patients who developed acute hypoxemic respiratory failure (AHRF) in both groups was documented. It was defined by meeting any one of the hypoxemic criteria (SpO_2 <92% while on at least 10 L min oxygen, PaO_2 <60 mmHg on room air, or PaO_2 <80 mmHg with supplemental oxygen), along with at least one of the following signs: respiratory rate >25 breaths min, dyspnoea with use of accessory muscles and ABG finding i.e. respiratory acidosis with pH <7.30 or $PaCO_2$ >50 mmHg. The incidence of non-invasive ventilation (NIV) requirement and reintubation, if any, was also noted and compared between the two groups.

Chest X-ray was done as baseline and at the end of day three, any findings suggestive of atelectasis i.e. small volume linear shadows either peripherally or at lung bases, opacification of the lung along with mediastinal shift, elevation of ipsilateral diaphragm, rib crowding etc. was recorded. The Chest X-ray was reported by a senior radiologist who remained blinded to the group allocation. The adverse effects related to HFNC application and COT e.g. throat or nasal pain, air leak, and abdominal distension were also recorded.

Patients were asked to rate the effect of the treatment on their comfort using the following scale: 1 (very poor), 2 (poor), 3 (sufficient), 4 (good), and 5 (very good).[11] Additionally, patient satisfaction scores, Chest X-ray confirmed PPCs, the proportion of PPCs, AHRF, reintubation rates, NIV use, and complications related to the intervention (such as air leaks, nasal or throat pain, and abdominal distension) were also documented.

Statistical Analysis

The sample size calculation was done based on a pilot study of ten patients, where the postoperative P/F ratio on day one was observed to be 356 mmHg [standard deviation (SD) 40.2] with COT in patients undergoing exploratory laparotomy. Considering this SD, a difference of 10% was considered as significant with the alpha error of 0.05 and 80% power of study, a sample size of 40 patients with 20 in each group was calculated. Further, considering a dropout rate of 10%, the final sample size of 50 with 25 patients in each group was decided.

The data was analysed using the statistical software version 20. Quantitative variables were reported with mean (SD) or median [interquartile range] and qualitative variables with number and percentage. The normality was tested using a box-whisker plot and the statistical test Shapiro-Wilk test. The unpaired student t-test was applied for normally distributed variables. The chi-square and Fisher's exact test were applied for the qualitative variables. Linear mixed model with a suitable covariance structure was performed to compare the hemodynamic variables followed by Bonferroni correction to control type I error. The *P* value less than 0.05 was considered as statistically significant.

Results

A total of 110 patients were enrolled; out of which 50 were excluded (Figure 1). Hence, 60 patients were randomised into two groups with 30 in each. Further, five patients in each group were excluded as they required elective mechanical ventilation. Finally, 50 patients with 25 in each group were included.

The demographic parameters i.e. patient's age, weight, gender and ASA physical status were comparable in both groups. Similarly, the duration of surgery and baseline haemodynamic parameters were also comparable between the two groups (Table 1).

The mean P/F ratio at the 24th hour was found to be significantly higher in group H compared to group C i.e. 690.80±79.35 vs. 312.82±29.66, respectively. An unpaired t-test was performed to compare the ratio between the groups and homogeneity of variance assumption was tested using Levene's test, which showed a violation of the normality assumption. So, Welch's corrected *P* value was applied. The mean difference was 377.98 (343.40 to 412.55) i.e. group H ratio was 378 units higher than group C (*P* value: Welch test <0.001). The average P/F ratio between the groups at each observed time point was significantly higher in group H (*P* value: Bonferroni correction <0.001). (Table 2). Similarly, the difference in the incidence of hypoxemia at all designated time points was significant [16% (n = 4) in group C vs. none in H].

Comparison of PaO_2 between the groups at different time points revealed a significant difference in the estimated marginal mean difference (HFNO minus COT at 95% confidence interval) showing higher values in group-H ($P < 0.001$) (Table 3). Similarly, the S/F ratio on comparison showed higher readings at all designated time intervals in the group-H (*P* value of estimated marginal mean $P < 0.001$). The $PaCO_2$ and haemodynamic variables (SBP, DBP, MAP, HR) between the two groups at all designated time points were comparable. The median patient comfort score was elevated with the group H vs group C i.e. 4.0 [3.5-4.0] vs 3.0 [2.0-3.0] ($P < 0.001$) respectively (Table 4).

Five patients in group C had complaints of nasal/throat pain and two patients complained of air leak. Four patients in group H complained of abdominal distension for which the airflows were adjusted accordingly, following which

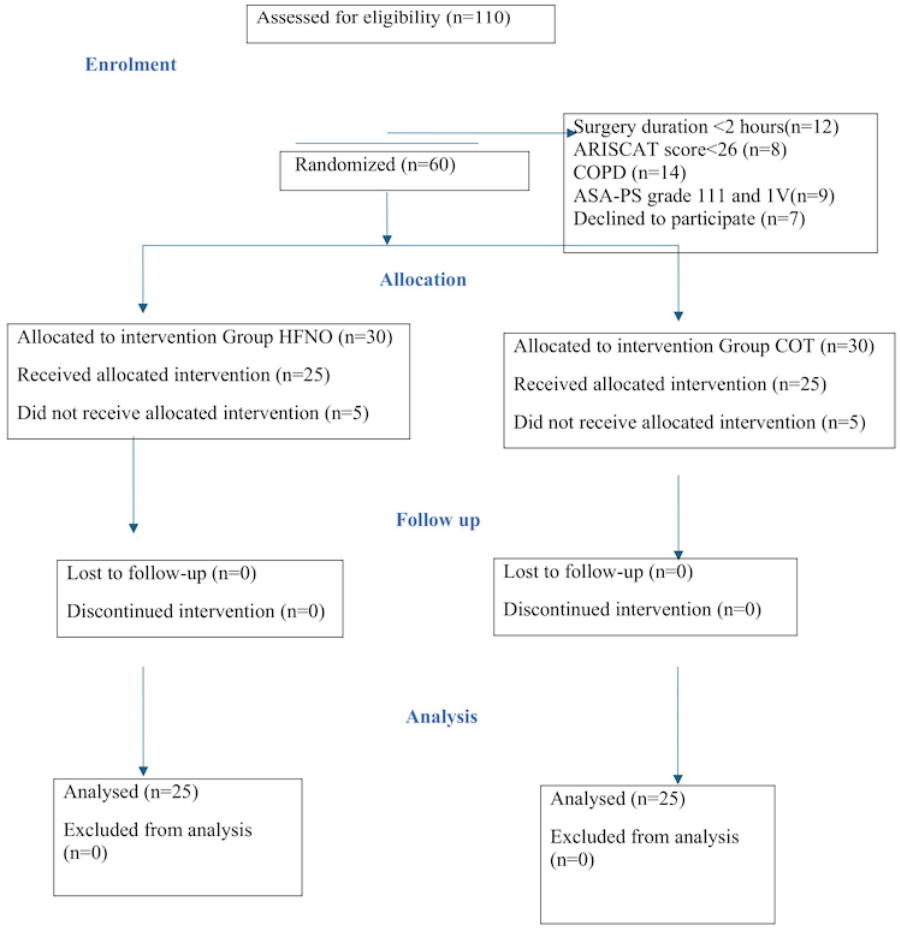

Figure 1. Consort flow diagram of 50 patients who received treatment in two groups, C and H respectively.

Group COT, conventional oxygen therapy; Group HFNO, high frequency nasal oxygenation; COPD, chronic obstructive pulmonary disease; ASA-PS, the American Society of Anaesthesiologist Physical Status.

patients were relieved. Two patients in the group C and one in the group H developed pneumonia postoperatively (Table 4). All these three patients were managed on broad-spectrum antibiotics in the ward and discharged later.

As far as the Chest-X-ray proven PPCs are concerned, two patients in group C and one in H were diagnosed to have atelectasis (Table 3). None of them in either of the groups developed AHRF, neither required NIV or reintubation nor was there any mortality amongst included patients. Therefore, the complications associated with the interventions, Chest-X-ray proven atelectasis, PPCs, AHRF, reintubation, and mortality between the two groups were comparable (Table 3).

Discussion

In the present study we observed a significant improvement in all oxygenation parameters following the use of HFNC for postoperative oxygenation; however, $PaCO_2$, haemodynamic variables, complications, incidence of PPCs/AHRF and atelectasis remained comparable between the two groups.

HFNO has an edge over COT by virtue of its convenient application, providing heated and humidified oxygen at high flows and positive end-expiratory pressure thus improving oxygenation in addition to enhanced patient comfort.[12,13] Amidst the widespread clinical benefits of HFNO, it has become increasingly popular for postoperative oxygenation having been successfully employed for preventing PPCs in obese patients[7,8] and following cardio-thoracic surgical procedures.[14] The risk factors for PPCs are multifactorial, the most common amongst the surgery-related risk factors include upper abdominal procedures accompanied by a long duration.[15] The use of HFNO for postoperative oxygenation in this subset of patients, to prevent hypoxemia and development of PPCs remains an avenue that has not been extensively studied.

Table 1. Demographic Data of Patients with Preoperative Clinical Characteristics and Duration of Surgery According to the Groups

Variable name	Group H (n = 25)	Group C (n = 25)	Mean difference (Group H minus Group C) 95% CI	*P* value
Age (years) - Mean (SD)	36.28±12.10	36.48±15.54	-0.20 (-8.12 to 7.72)	0.960
Gender				
Male	17 (68.0)	15 (60.0)		0.556
Female	8 (32.0)	10 (40.0)		
ASA PS				
ASA1	17 (68.0)	14 (56.0)		0.382
ASA2	8 (32.0)	11 (44.0)		
Weight (kg)	72.24±12.49	68.56±9.29	3.68 (-2.74 to 10.10)	0.255
Duration of surgery (minutes)	316.8±56.18	348.0±54.77	-31.20 (-62.75 to 0.351)	0.053
SBP baseline	130.76±9.27	134.04±12.04	-3.28 (-9.39 to 2.83)	0.286
DBP baseline	84.12±7.44	86.28±7.67	-2.16 (-6.46 to 2.14)	0.317
MBP baseline	99.68±7.50	102.98±7.91	-2.40 (-6.79 to 1.99)	0.277
HR baseline	102.88±12.54	108.64±13.62	-5.76 (-13.2 to 1.69)	0.126

Group C, conventional oxygen therapy; Group H, high frequency nasal oxygenation; SBP, systolic blood pressure; DBP, diastolic blood pressure; ASA PS, American Society Anaesthesiologists Physical Status; CI, confidence interval; MBP, mean blood pressure; HR, heart rate; SD, standard deviation

Table 2. Mean P/F ratio and P/F Ratios at Different Time Intervals Between the Groups

Variable name (P/F ratios at different time intervals)	Mean (SD)		Estimated marginal mean		Estimated marginal mean difference (HFNO minus COT) (95% CI)	*P* value (with Bonferroni correction)
	Group H (n = 25)	Group C (n = 25)	Group H (n = 25)	Group C (n = 25)		
P/F: 2nd hr	683.4±76.62	310.0±31.70	683.4 (11.83)	310.0 (11.83)	373.38 (340.02 to 406.75)	< 0.001#
P/F: 6th hr	702.6±82.1	308.99±36.51	702.6 (11.83)	308.99 (11.83)	393.61 (360.24 to 426.97)	< 0.001#
P/F: 12th hr	702.1±89.73	313.16±28.81	702.1 (11.83)	313.59 (11.83)	388.94 (355.58 to 422.31)	< 0.001#
P/F: 24th hr	690.8±79.35	312.86±29.64	690.8 (11.83)	312.86 (11.83)	377.94 (344.58 to 411.31)	< 0.001#

Data are shown as mean±SD; Group C, conventional oxygen therapy; Group H, high frequency nasal oxygenation; P/F ratio, PaO_2/FiO_2; $P < 0.05$, statistically significant#; hr, hour; CI, confidence interval; SD, standard deviation

Table 3. Partial Pressure of Oxygen (PaO_2) Between the Groups

Variable (PaO_2) time	Original mean (SD)				Estimated marginal mean (Standard error)		Estimated marginal mean difference (Group H minus Group C) (95% CI)	*P* value of estimated marginal mean
	Group H		Group C		Group H	Group C		
	n	Mean (SD)	n	Mean (SD)				
2nd hr	25	273.36±30.65	25	135.37±14.10	273.36 (5.22)	135.37 (4.87)	137.99 (124.26 to 151.72)	< 0.001#
6th hr	25	281.04±32.84	25	135.13±17.41	281.04 (5.22)	135.13 (4.87)	145.91 (132.18 to 159.64)	< 0.001#
12th hr	25	280.68±35.97	25	137.18±13.33	280.68 (5.22)	137.18 (4.87)	143.50 (129.77 to 157.23)	< 0.001#
24th hr	25	276.96±31.84	25	136.38±15.23	276.96 (5.22)	136.38 (4.87)	140.58 (126.85 to 154.31)	< 0.001#

Data are shown as mean±SD; Group C, conventional oxygen therapy; Group H, high frequency nasal oxygenation; CI, confidence interval; PaO_2, partial pressure of oxygen; $P < 0.05$, statistically significant#; hr, hour; SD, standard deviation

Table 4. Comfort Score and Complications Between the Groups

Variable name	Group H (n = 25)	Group C (n = 25)	*P* value
Comfort score median [IQR]	4.0 (3.5 to 4.0)	3.0 (2.0 to 3.0)	<0.001#
Complications associated with intervention	5 (20.0)	4 (16.0)	0.733
Chest X-ray proven atelectasis at the end of 3rd day	2 (8.0)	1 (4.0)	1.00
Proportion of PPCs	2 (8.0)	1 (4.0)	1.00

Group C, conventional oxygen therapy; Group H, high frequency nasal oxygenation; IQR, interquartile range; $P < 0.05$, statistically significant#; PPCs, postoperative pulmonary complications

The popular OPERA trial is the only clinical study to have evaluated the effectiveness of HFNO compared with COT for postoperative oxygenation in patients undergoing upper abdominal surgeries.[2] The primary outcome was the proportion of patients developing hypoxaemia which was defined as P/F ratio ≤300, one hour after tracheal extubation. The study did not report any significant reduction in the incidence of postoperative hypoxaemia with HFNO. This result contrasts our study, possibly due to a few reasons. The primary end point in OPERA trial was arbitrary (as reported by them also) which may not have reflected disease severity. The oxygenation parameters were neither measured beyond one hour, nor any radiological method was employed to rule out PPC's. Additionally, the duration of HFNC application in the OPERA trial varied between patients in the postoperative period with a median duration of 15 hours versus 24 hours uniformly for all patients in the present study.

Amongst the available studies evaluating HFNO for postoperative oxygenation, there has not been any defined recommended time duration for its administration. However, a study recently highlighted that its application for 24 hours after tracheal extubation has been found to be sufficient to reduce the re-intubation rate.[16]

The OPERA study aimed to explore the efficacy of HFNO along with intraoperative lung-protective ventilation on postoperative oxygenation. The use of two preventive strategies simultaneously to reduce PPCs could have confounded the results of their study. Further, in their research, no attempt was made to ensure that patients administered HFNC had their mouth closed, which could have led to reduced airway pressure unlike in the present study where closed mouth breathing was ensured in patients receiving HFNO. Previous studies have shown that the high flowrates in HFNO translate into clinically significant airway pressures only when the mouth is closed.[17,18] These aforementioned factors in the OPERA trial could have perhaps led to an insignificant reduction in the incidence of postoperative hypoxemia with the preventive application of HFNO in patients scheduled for abdominal surgery.

We observed a higher comfort score with the HFNO as opposed to the OPERA trial in which comparable results were obtained.[2] In the present study, the complications associated with the interventions namely Chest-X-ray proven atelectasis, PPCs, AHRF, reintubation, and mortality between the two groups were comparable. Our results contrast with the conclusion of a meta-analysis where reintubation rate was observed to be significantly reduced with the use of HFNC; however, like our study the incidence of PPCs and mortality were comparable.[19] Additionally, no difference was observed in haemodynamic parameters between the two groups post operatively, like the OPERA trial.[2]

We determined the sample size based on the P/F ratio as the study aimed to evaluate the efficacy of HFNO for postoperative oxygenation; however, for complications such as PPC, AHRF and reintubation rates, study may not have adequate power. Amongst complications, Chest-X-ray to rule out basal atelectasis was done on day 3. The decision to perform the imaging on day 3 is based on the previous studies which have shown that the high incidence of PPC is seen within 72 hrs.[20,21]

The present study is dealt with few limitations. Firstly, we did not record the long-term outcomes such as length of hospital stay and morbidity. Secondly, a patient-related outcome measure using QoR score could have been assessed. Thirdly, blinding of the treatment arm was not feasible due to the nature of intervention and thus could have been a source of observer bias. Finally, more sensitive, non-ionizing imaging modalities, such as bedside ultrasonography is now the standard tool to detect postoperative atelectasis but not be attempted due to logistic constraints.

Future Recommendations

A well-designed randomized controlled trial is needed to validate the findings of the current study. In addition, studies utilizing complications (e.g. PPCs, AHRF, reintubation rates etc.) and long-term outcomes (e.g. total hospital stay, morbidity etc.) as primary outcomes, in order to confirm the benefits of HFNO are warranted.

Conclusion

It was observed that the preventive use of HFNO for post operative oxygenation amongst moderate to high-

risk patients scheduled for exploratory abdominal surgery improves oxygenation; however, the incidence of AHRF/PPCs, reintubation rate, Chest-X-ray proven atelectasis, patient comfort score and adverse events remained comparable between the two groups.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Institutional Ethics Committee of Human Research (IEC-HR) University College of Medical Sciences, University of Delhi (approval no.: IECHR-2022-55-71, date: 30.08.2022).

Informed Consent: A written informed consent from each participant was taken prior to their recruitment.

Footnotes

Author Contributions: Surgical and Medical Practices - G.T.C., P.S., M.G.; Concept - G.T.C., M.M.; Design - G.T.C.; Data Collection and/or/ Processing - G.T.C., P.S.; Analysis and/or/ Interpretation - G.T.C., P.S., M.M.; Literature Review - P.S., M.G.; Writing - M.M., M.G.

Declaration of Interests: The authors declare no conflict of interests.

Funding: No funding was received for the study.

References

1. Serpa Neto A, Hemmes SN, Barbas CS, et al. Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. *Lancet Respir Med.* 2014;2(12):1007-1015. [CrossRef]
2. Futier E, Paugam-Burtz C, Godet T, et al. Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA). *Intensive Care Med.* 2016;42(12):1888-1898. [CrossRef]
3. Mauri T, Alban L, Turrini C, et al. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. *Intensive Care Med.* 2017;43(10):1453-1463. [CrossRef]
4. Nishimura M. High-flow nasal cannula oxygen therapy devices. *Respir Care.* 2019;64(6):735-742. [CrossRef]
5. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med.* 2015;41(4):623-632. [CrossRef]
6. Ferrando C, Puig J, Serralta F, et al. High-flow nasal cannula oxygenation reduces postoperative hypoxemia in morbidly obese patients: a randomized controlled trial. *Minerva Anestesiol.* 2019;85(10):1062-1070. [CrossRef]
7. Rosén J, Frykholm P, Fors D. Effect of high-flow nasal oxygen on postoperative oxygenation in obese patients: a randomized controlled trial. *Health Sci Rep.* 2022;5(3):e616. [CrossRef]
8. Li R, Liu L, Wei K, et al. Effect of noninvasive respiratory support after extubation on postoperative pulmonary complications in obese patients: A systematic review and network meta-analysis. *J Clin Anesth.* 2023;91:111280. [CrossRef]
9. Yu Y, Qian X, Liu C, et al. Effect of high-flow nasal cannula versus conventional oxygen therapy for patients with thoracoscopic lobectomy after extubation. *Can Respir J.* 2017;2017:7894631. [CrossRef]
10. Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology.* 2010;113(6):1338-1350. [CrossRef]
11. Ramirez A, Delord V, Khirani S, et al. Interfaces for long-term noninvasive positive pressure ventilation in children. *Intensive Care Med.* 2012;38(4):655-662. [CrossRef]
12. Leeies M, Flynn E, Turgeon AF, et al. High-flow oxygen via nasal cannulae in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *Syst Rev.* 2017;6(1):202. [CrossRef]
13. Chikata Y, Morinishi K, Nishimura M. Humidification in very-high-flow nasal-cannula therapy in an adult lung model. *Respir Care.* 2019;64(7):809-817. [CrossRef]
14. Stéphan F, Barrucand B, Petit P, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA.* 2015;313(23):2331-2339. [CrossRef]
15. Fisher BW, Majumdar SR, McAlister FA. Predicting pulmonary complications after nonthoracic surgery: a systematic review of blinded studies. *Am J Med.* 2002;112(3):219-225. [CrossRef]
16. Hernández G, Vaquero C, Colinas L, et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. *JAMA.* 2016;316(19):2047-2048. [CrossRef]
17. Parke RL, McGuinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. *Respir Care.* 2013;58(10):1621-1624. [CrossRef]
18. Chanques G, Riboulet F, Molinari N, et al. Comparison of three high flow oxygen therapy delivery devices: a clinical physiological cross-over study. *Minerva Anestesiol.* 2013;79(12):1344-1355. [CrossRef]
19. Lu Z, Chang W, Meng SS, et al. Effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis. *BMJ Open.*2019;9(8):e027523. [CrossRef]
20. Kammerer T, Speck E, von Dossow V. [Anesthesia in thoracic surgery]. [Article in German]. *Anaesthesist.* 2016;65(5):397-412. [CrossRef]
21. Tu CC, Hsu PK. Global development and current evidence of uniportal thoracoscopic surgery. *J Thorac Dis.* 2016;8(Suppl 3):S308-S318. [CrossRef]

DOI: 10.4274/TJAR.2025.251902

Original Article
Paediatric Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):249-255

Comparative Analysis of King Vision aBlade Video Laryngoscopy and Direct Laryngoscopy for Endotracheal Intubation in Paediatric Age Group: a Prospective Randomized Study

Mamta Harjai[1], Chaya Devi D[2], Sujeet Rai[2], Shilpi Misra[2], Tanveer Roshan Khan[3]

[1]Dr. Ram Manohar Lohia Institute of Medical Sciences, Department of Anaesthesia and Critical Care, Lucknow, Uttar Pradesh, India
[2]Dr. Ram Manohar Lohia Institute of Medical Sciences, Department of Anaesthesiology, Lucknow, Uttar Pradesh, India
[3]Dr. Ram Manohar Lohia Institute of Medical Sciences, Department of Paediatric Surgery, Lucknow, Uttar Pradesh, India

Cite this article as: Harjai M, Devi D C, Rai S, Misra S, Khan TR. Comparative analysis of King Vision aBlade video laryngoscopy and direct laryngoscopy for endotracheal intubation in paediatric age group: a prospective randomized study. *Turk J Anaesthesiol Reanim.* 2025;53(5):249-255

Abstract

Objective: Paediatric airway management is challenging due to anatomical differences, making effective endotracheal intubation crucial during surgery. While direct laryngoscopy (DL) has been the standard method, video laryngoscopy (VL) has emerged as a promising alternative. This study compared the effectiveness of King Vision aBlade non-channeled VL (KVL) with Miller/Macintosh DL for intubation in children.

Methods: In this prospective, randomized, single-blinded study, 150 children aged 2-10 years undergoing elective surgery were randomly assigned to either Group DL (n = 75) or Group KVL (n = 75). Data was collected on intubation success, time, glottic view, external maneuvers, and hemodynamic parameters [heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), peripheral oxygen saturation (SpO_2)] at various intervals.

Results: The mean age of patients was similar in both groups (P=0.15). The DL group had a higher success rate on the first attempt (P < 0.001) and shorter intubation times (9.97±3.12 sec vs. 14.35±2.99 sec, P < 0.001) compared to KVL. Although KVL provided a better glottic view, this difference was not statistically significant (P=0.059). Hemodynamic parameters (SBP, DBP) were significantly higher in the DL group post-intubation (P < 0.05), with no significant differences in HR or SpO_2 between groups. The DL group required more external maneuvers for intubation (P=0.022).

Conclusion: DL showed a higher success rate, faster intubation times, and greater hemodynamic stability compared to KVL. While KVL offered better glottic views, it had longer intubation times and lower success rates. Further studies with larger sample sizes are recommended to validate these findings.

Keywords: Endotracheal intubation, King Vision aBlade, direct laryngoscopy, paediatric airway management, video laryngoscopy

Main Points

- Direct laryngoscopy (DL) is faster and more successful on the first attempt compared to King Vision aBlade video laryngoscopy (KVL).
- KVL offers better glottic visualization and requires fewer external maneuvers than DL.
- KVL provides better hemodynamic stability during paediatric intubation compared to DL.

Corresponding author: Mamta Harjai, MD, e-mail: mamtaharjaidoctor@yahoo.co.in

Received: February 18, 2025 Accepted: April 25, 2025
Epub: July 14, 2025 Published date: October 14, 2025

Introduction

Airway management is a critical skill for anaesthesiologists, involving techniques such as facemask ventilation, laryngeal mask airway insertion, and endotracheal intubation using direct or video-assisted laryngoscopy.[1] The laryngoscope, originally developed for otorhinolaryngologists, has become an essential tool in anaesthesiology for visualizing the larynx and managing the airway, particularly during endotracheal intubation. Over the past century, advancements in anaesthesia have refined the use of laryngoscopes, making them indispensable in paediatric and adult airway management.[2]

Paediatric airway management poses unique challenges due to anatomical differences, including a larger head, large tongue, cephalad larynx, and anteriorly angulated vocal cords, making laryngoscopy and intubation more difficult.[3] Additionally, paediatric patients are more susceptible to rapid desaturation during apneic events due to lower functional residual capacity and low tidal volume.[4] These physiological factors make securing the airway a priority, and endotracheal intubation remains the gold standard for airway management in children.[5,6]

Direct laryngoscopy (DL), especially with the Miller blade, is the traditional method for paediatric intubation.[7] However, recent advancements in video laryngoscopy (VL) have shown promising results, particularly in adult populations and mannequins, with VL providing better laryngeal views and improved intubation success rates. Although VL is widely used in adults, its application in paediatric airway management is still an emerging area of research.[8-12]

VLs have been shown to improve glottic visualization in children, offering advantages such as superior laryngeal views, reduced force during intubation, and the ability to record and teach.[13] The King Vision aBlade VL (KVL) (Figure 1), specifically designed for paediatric use, is a novel device that has not been extensively studied in the paediatric population aged 2 to 10 years.[14,15]

Given the potential difficulty of intubating paediatric airways, we conducted a prospective, randomized study to compare the KVL with the Miller/Macintosh DL in children aged 2-10 years. As it is a non-channeled device with a Macintosh-like blade curvature, offering better glottic visualization and reduced lifting force. Compared to other VLs like GlideScope or C-MAC, it is portable, battery-operated, and designed to accommodate paediatric airway anatomy, making it suitable for children aged 2-10 years. We hypothesized that the time for successful tracheal intubation with the King Vision aBlade would be equivalent to that of the Miller/Macintosh blades during routine tracheal intubation in paediatric patients.

Figure 1. King Vision aBlade size 1.

Methods

Study Design and Setting

This is a prospective, interventional, randomized controlled study conducted in the Department of Paediatric Surgery at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. The study was performed over 18 months, with 12 months dedicated to interventions and 6 months for data analysis and thesis writing. Paediatric patients aged 2-10 years undergoing elective surgeries under general anaesthesia, which required tracheal tube intubation, were included in the study. The study was approved by the Institutional Ethical Committee of Dr. Ram Manohar Lohia Institute of Medical Sciences (approval no.: 63/19, date: 02.01.2020), and written informed consent was obtained from parents or guardians of all paediatric patients. The trial was registered with CTRI under registration number [CTRI/2020/06/025915].

Study Participants

The inclusion criteria for the study comprised paediatric patients aged 2-10 years who were admitted for elective surgery under general anaesthesia requiring tracheal intubation, with an American Society of Anesthesiologists (ASA) physical status of I or II. Exclusion criteria included cases where parental consent for participation was not provided, patients with an ASA physical status greater than II, those with active urinary tract infections, and patients with congenital anomalies or an anticipated difficult airway. Additionally, any patient in whom tracheal intubation could not be successfully achieved after three attempts using either laryngoscopy method was also excluded from the study (Figure 2).

Sample Size Calculation

Based on the previous study Jagannathan et al.,[15] the difference in the mean duration of time for tracheal tube entry (from the device into device out (sec) (μ1-μ2) was in the Miller group (12.3) and King Vision group (18.2) and

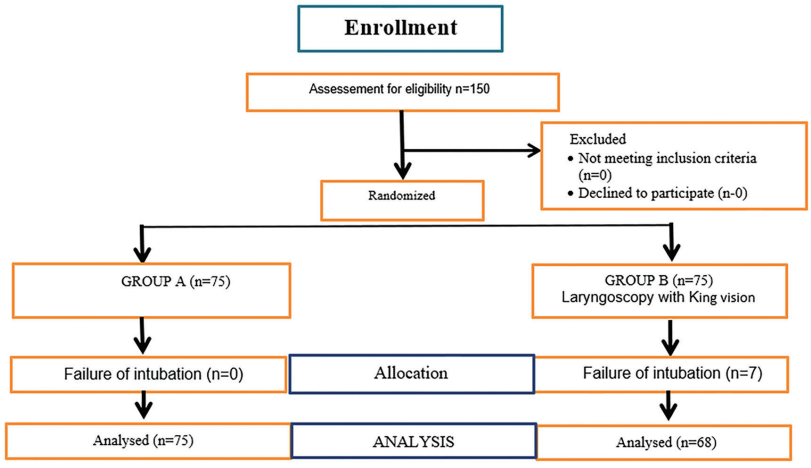

Figure 2. CONSORT diagram representing patient enrolment.

the average population variance (σ2) in 11.9 (Jagannathan et al.,[15]). The sample size (n) = 2 $(Z\alpha/_2 + Z_{[1-\beta]})^2 \times \sigma^2/(\mu 1-\mu 2)^2$, assuming 0.05 level significance ($Z_{\alpha/2} = 1.96$), and 80% power ($Z_{[1-\beta]}$)=0.84) is 63.79 in each group. Considering any dropouts, we will enroll 75 patients in each group:

$n = [2 (Z\alpha/_2 + Z_{[1-\beta]})^2 \times \sigma^2]/(\mu 1-\mu 2)^2$

$n = [2 (1.96 + 0.84)^2 \times 11.9^2]/(18.2-12.3)^2$

$n = 150$

Study Groups

Patients were randomly divided into two groups:

- **Group DL:** Patients intubated using the Miller or Macintosh laryngoscope.
- **Group KVL:** Patients intubated using the King Vision aBlade non-channeled VL.

Hypothesis

Endotracheal intubation with King Vision aBlade non-channeled VL is equivalent to intubation with the DL.

Randomization, Allocation Concealment, and Blinding

Randomization

Sequence generation: A computer-generated random number table was used for randomization into the two study groups. Block randomization with a variable block design was employed to ensure balanced allocation between the groups.

Allocation concealment: Allocation was concealed using sequentially numbered opaque envelopes. Each patient who met the inclusion and exclusion criteria and provided consent for participation was assigned to one of the two groups after their name was entered on the cover of a sequentially numbered envelope. The treatment groups were encoded as Group 1 (DL) and Group 2 (KVL), with the code kept in a sealed envelope in a secure location, only to be opened after the data analysis was complete.

Implementation: The generation of random numbers and the preparation of sealed envelopes were done by a statistician who was not involved in the study. The code for the groups was also kept with the statistician in a sealed envelope until the principal investigator had finished the data analysis.

Blinding

This study was conducted as a single-blind trial, where the outcome assessor was blinded to group allocation. The study groups (DL and KVL) were randomly encoded as Group 1 and Group 2, and the code was hidden from both the patients and the data analyst until the study's completion. However, the anaesthesiologist performing the procedure was aware of the group assignment due to the inherent differences in anatomical positioning required for each intubation technique.

Intervention

Group DL

In Group DL, patients were intubated using either a Miller or Macintosh laryngoscope, with blade sizes 1 or 2 selected based on the patient's anatomy. The Cormack-Lehane grade of the glottic view was recorded during the procedure to assess the visibility of the laryngeal structures. Additionally, the time required for intubation was measured, defined as the interval from the entry of the laryngoscope blade into the mouth to the detection of the first end-tidal CO_2.

Group KVL

In Group KVL, patients were intubated using the King Vision aBlade non-channeled VL, with blade size 2. As in Group DL, the Cormack-Lehane grade of the glottic

view was recorded to assess the visual clarity of the laryngeal aperture. The time to intubation was similarly documented, using the same criteria as in Group DL, from the blade's entry to the detection of the first end-tidal CO_2.

All patients underwent a detailed preoperative airway evaluation, including body mass index, ASA grading, and Modified Mallampati Grading to predict intubation difficulty. The operating room was prepared with all necessary equipment, including laryngoscopes, endotracheal tubes, and emergency drugs, to handle any airway complications. After securing an intravenous line, patients were pre-oxygenated with 100% oxygen for three minutes.

Anaesthesia was induced using sevoflurane (3-6%), fentanyl (2 µg kg^{-1}), and a muscle relaxant, either atracurium (0.5 mg kg^{-1}) or cisatracurium (0.1-0.2 mg kg^{-1}). Hemodynamic parameters, such as heart rate (HR), systolic and diastolic blood pressure, and oxygen saturation, were monitored and recorded at various intervals, including pre-induction, immediately after intubation, and at 1, 3, and 5 minutes post-intubation. The success of intubation, the number of attempts, and the use of any external maneuvers, such as the BURP maneuver, were documented. In cases of failed intubation, corrective actions were taken and recorded. All intubations were performed by a senior anaesthesiology resident in the final year of training (3rd year), under supervision.

Procedures were conducted in accordance with the Helsinki Declaration-2013.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 (Chicago, Inc., USA). Categorical data were analyzed using the chi-square test, while continuous variables were compared using a Student's t-test. For comparisons involving more than two variables, one-way analysis of variance (ANOVA) was employed. The level of statistical significance was set at $P < 0.05$. Mean and standard deviation (SD) were calculated for continuous variables, providing a measure of central tendency and variability, respectively. The chi-square test was utilized to evaluate differences between categorical data, ensuring an assessment of the association between variables. The Student's t-test was used to compare the means of two groups, while the one-way ANOVA test was applied to analyze differences among groups with more than two variables. A *P* value of less than 0.05 was considered statistically significant throughout the study.

Results

This prospective, single blinded, randomised control study was conducted in 150 paediatric patients, undergoing elective surgery under general anaesthesia, to do a comparative analysis of KVL and DL for endotracheal intubation in paediatric population 2-10 years.

The mean age of patients in the DL group was 6.01±2.71 years, while in the KVL group, it was 5.42±2.20 years. This difference is not statistically significant (*P*=0.15), indicating that the age distribution between the two groups is comparable. There was no significant difference in sex distribution (*P*=0.47) or age (*P*=0.15) between the groups. However, the DL group had marginally taller patients, with a borderline significant *P* value of 0.05. The DL group also had significantly heavier patients than the KVL group (*P*=0.01). Both groups consisted entirely of patients with ASA status I, indicating no systemic disease, with no variation in ASA status between them (Table 1).

The DL group had significantly more successful intubations on the first attempt compared to the KVL group ($P < 0.001$). Additionally, the time for intubation was significantly shorter in the DL group (9.97±3.12 seconds) than in the KVL group (14.35±2.99 seconds, $P < 0.001$). Although the Cormack-Lehane glottic view was better in the KVL group, the difference was not statistically significant (*P*=0.059). The need for external maneuvers (e.g., BURP) was significantly higher in the DL group (*P*=0.022). No blade changes were required, and all intubations were performed by a single operator in both groups (Table 2). In the DL group, 64% (48/75) of patients were intubated using the Miller blade and 36% with the Macintosh blade, based on anatomical suitability.

Figure 3 compares the mean time to intubation between the DL and KVL (King Vision Laryngoscopy) groups. The mean time to intubation in the DL group was 9.97±3.12 seconds, whereas in the KVL group, it was significantly higher at 14.35±2.99 seconds. The difference between the two groups was statistically significant ($t = -8.54$, $P < 0.001$), indicating that intubation with the King Vision laryngoscope took longer than with the direct laryngoscope. A preformed stylet was used in all patients in the KVL group to aid in tube navigation due to the curvature of the blade. In the DL

Table 1. Patient Characteristics in Both Groups

Variables		DL (n = 75)	KVL (n = 68)	*P* value
Sex	Female	15	17	0.47
	Male	60	51	
Age (years) Mean ± SD		6.01± 2.71	5.42±2.20	0.15
Height (cm) Mean ± SD		120.39±10.3	116.80±12.02	0.05
Weight (kg) Mean ± SD		22.69±5.78	20.48±4.23	0.01
ASA status	I	75	68	NA
	II	0	0	
	III	0	0	

DL, direct laryngoscopy; KVL, King Vision aBlade video laryngoscopy; SD, standard deviation; ASA, American Society of Anesthesiologists

group, a stylet was used in 18.6% of cases where difficulty was encountered during the first attempt.

The hemodynamic parameters, including HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and oxygen saturation (SpO_2), were assessed at three different time intervals: before intubation, 1 minute after intubation, and 3 minutes after intubation. Significant differences were found in SBP and DBP between the DL and VL groups across all time points, with the DL group consistently showing higher values ($P < 0.05$). Specifically, SBP and DBP were significantly higher in the DL group both after 1 and 3 minutes of intubation compared to the VL group. However, no statistically significant differences were observed in HR or SpO_2 levels at any of the three time intervals between the two groups ($P > 0.05$) (Table 3).

Table 2. Comparative Data During Tracheal Intubation Across Both Groups

		DL (n = 75)	KVL (n = 68)	*P* value
Intubation attempts (n)	1	64	40	<0.001*
	2	11	28	
Time for intubation (s) (Mean ± SD)		9.97±3.12	14.35±2.99	<0.001*
Glottic view (n) Cormack-Lehane	1	25	36	0.059
	2	48	31	
	3	2	1	
	4	0	0	
External manoeuvre	BURP	31	15	0.022*
	None	44	53	
Change of blade		0	0	
Number of operators	1	75	68	

DL, direct laryngoscopy; KVL, King Vision aBlade video laryngoscopy; SD, standard deviation

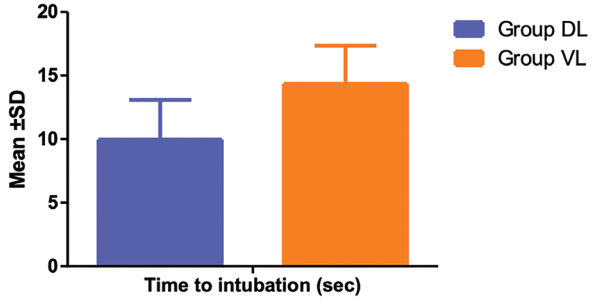

Figure 3. Bar chart shows the comparisons of mean time to intubation (sec) in between group DL and group VL.

DL, direct laryngoscopy; VL, video laryngoscopy; SD, standard deviation.

Table 3. Comparisons of Hemodynamic Parameters in Between Group DL and Group VL at Various Time Intervals (Mean±SD)

Variables		DL (n = 75)	VL (n = 68)	*P* value
Before intubation	HR (Beat/min)	111.87±15.16	115.90±12.59	0.088
	SBP (mmHg)	105.05±9.34	101.76±9.11	0.035
	DBP (mmHg)	65.65±7.91	63.68±8.77	0.159
	SpO_2 (%)	100.00±0.00	100.00±0.00	-
After 1 min intubation	HR (Beat min)	125.13±13.89	126.10±13.97	0.678
	SBP (mmHg)	113.95±9.11	109.24±9.79	0.003
	DBP (mmHg)	73.21±8.72	69.46±8.28	0.009
	SpO_2 (%)	100.00±0.00	100.00±0.00	-
After 3 min of intubation	HR (Beat min)	121.72±14.06	120.85±15.13	0.723
	SBP (mmHg)	110.64±9.52	106.43±10.98	0.015
	DBP (mmHg)	71.52±9.66	65.97±11.63	0.002
	SpO_2 (%)	100.00±0.00	100.00±0.00	-

DL, direct laryngoscopy; KVL, King Vision aBlade video laryngoscopy; VL, video laryngoscopy; SD, standard deviation; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, peripheral oxygen saturation

The success rate for intubation within 10 seconds, using only one attempt and without external maneuvers, between the DL and VL groups was significantly higher in the DL group (54.67%) compared to the VL group (13.24%), with a *P* value of <0.001, indicating a statistically significant difference between the two groups.

Discussion

The main finding in this study is that, the mean time required for tracheal intubation with KVL was found considerably longer (>4 sec) as compared to group DL in 2-10 yrs, of paediatric population. This finding was statistically significant. Although the percentage of success rate for intubation was less with in KVL compared to in DL group which was statistically significantly. KVL provides a better laryngoscopic view of glottis with CL grading in most of paediatric patients than that of DL.

Based on our results KVL time to intubation is longer as compared to DL n significant. The result is in concordance with similar study with KVL in paediatric age group of <2 years the time to intubation was significantly longer in VL

group[7] and also the intubation time with glidoscope was longer compared to conventional DL.[16] Since this finding is in concordance with results of many studies as mentioned above, we can conclude that with VL time to intubation is longer as compared to DL probably because of requirement of additional hand-eye co-ordination for tube manipulation and difficulty in manoeuvring of tracheal tube through the vocal cords. The longer intubation time and lower first-attempt success with KVL may be attributed to the need for hand-eye coordination, less familiarity with the device, and the lack of a channeled blade making tube advancement through the glottis more difficult.

Use of King Vision VL was found associated with better glottic visualisation on laryngoscopy as the glottic view for C-L grade 1, 2, and 3 in our Study. We discovered that the KVL provided a superior view of the glottis than the other groups, although there was no statistically significant difference. These results are similar to other studies with Stortz VL,[17] Glidoscope,[16] Berci-Kaplan VL.[18] Therefore with VL there is improved vision of larynx. External manipulation was necessary for manipulation of larynx for glottic visualisation during intubation in both groups requirement of BURP was more in DL group compared to KVL group, which was statistically significant among both the group similar to other studies.[16-20] We conclude that better visualization of larynx with VL results in less use of external manoeuvres.

Study Limitations

Our study had several limitations. First, the sample size may be considered small, and a larger study is warranted to confirm the findings in this paediatric age group (2-10 years). Second, blinding was not feasible as it was impractical to blind the operator to the device being used. This could introduce bias in favor of the standard device (DL) when comparing the performance of the new device (King Vision aBlade). Third, while the intubations were performed by anaesthesiologists experienced with videolaryngoscopy using devices like True View and Airtraq, their experience with the King Vision aBlade in this paediatric population was limited. Although the blade of the KVL has a shape similar to the Macintosh blade, the intubation technique differs, and the learning curve for advancing the endotracheal tube under various VLs cannot be ignored. This is reflected in our study, as the technique requires adequate training and experience. Additionally, the study only included children with normal airways, so the results cannot be extrapolated to those with abnormal airways. Lastly, we exclusively studied the non-channeled King Vision laryngoscope with a size 2 blade (although younger or smaller patients might benefit from a size 1 blade), and the findings cannot be applied to channeled King Vision blades or other VLs with a similar morphology.

Conclusion

Our hypothesis that KVL is equivalent to conventional DL was not achieved because time to intubation was more in KVL (>4 secs) as compared to DL in 2-10 yrs, of paediatric population. More studies with larger sample size are warranted in future to confirm such findings. KVL provides a better laryngoscopic view of glottis with CL grading in most of paediatric patients than that of DL. Although this study demonstrated that DL outperformed KVL in several key areas of paediatric intubation. DL showed a significantly higher success rate on the first attempt, with faster intubation times compared to KVL. Although KVL provided a better glottic view, the difference was not statistically significant. Hemodynamic parameters, specifically SBP and DBP, were significantly higher in the DL group post-intubation. Additionally, the success rate for intubation within 10 seconds, without external maneuvers, was significantly higher in the DL group. These findings suggest that while KVL offers some advantages in visualization, DL remains more efficient for paediatric intubation in terms of time and ease of procedure.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethical Committee of Dr. Ram Manohar Lohia Institute of Medical Sciences (approval no.: 63/19, date: 02.01.2020).

Informed Consent: Written informed consent was obtained from parents or guardians of all paediatric patients.

Footnotes

Author Contributions: Surgical and Medical Practices - M.H., S.R., S.M.; Concept - M.H., T.R.K.; Design - M.H., S.R.; Data Collection and/or/ Processing - C.R.; Analysis and/or/ Interpretation - M.H., T.R.K.; Literature Review - C.R., S.M.; Writing - M.H., C.R.

Declaration of Interests: The authors declare no conflict of interests.

Funding: No funding was received for the study.

References

1. Harless J, Ramaiah R, Bhananker SM. Pediatric airway management. *Int J Crit Illn Inj Sci.* 2014;4(1):65-70. [CrossRef]
2. Goldmann K. Recent developments in airway management of the paediatric patient. *Curr Opin Anaesthesiol.* 2006;19(3):278-284. [CrossRef]
3. Fiadjoe JE, Nishisaki A, Jagannathan N, et al. Airway management complications in children with difficult tracheal intubation from the Pediatric Difficult Intubation (PeDI) registry: a prospective cohort analysis. *Lancet Respir Med.* 2016;4(1):37-48. [CrossRef]
4. Jagannathan N, Sequera-Ramos L, Sohn L, et al. Randomized comparison of experts and trainees with nasal and oral fibreoptic intubation in children less than 2 yr of age. *Br J Anaesth.* 2015;114(2):290-296. [CrossRef]
5. Passi Y, Sathyamoorthy M, Lerman J, Heard C, Marino M. Comparison of the laryngoscopy views with the size 1 Miller and Macintosh laryngoscope blades lifting the epiglottis or the base of the tongue in infants and children< 2 yr of age. *Br J Anaesth.* 2014;113(5):869-874. [CrossRef]

6. Aziz M, Dillman D, Kirsch JR, Brambrink A. Video laryngoscopy with the macintosh video laryngoscope in simulated prehospital scenarios by paramedic students. *Prehosp Emerg Care.* 2009;13(2):251-255. [CrossRef]
7. Byhahn C, Iber T, Zacharowski K, et al. Tracheal intubation using the mobile C-MAC video laryngoscope or direct laryngoscopy for patients with a simulated difficult airway. *Minerva Anestesiol.* 2010;76(8):577. [CrossRef]
8. Jungbauer A, Schumann M, Brunkhorst V, Börgers A, Groeben H. Expected difficult tracheal intubation: a prospective comparison of direct laryngoscopy and video laryngoscopy in 200 patients. *Br J Anaesth.* 2009 ;102(4):546-550. [CrossRef]
9. Low D, Healy D, Rasburn N. The use of the BERCI DCI® video laryngoscope for teaching novices direct laryngoscopy and tracheal intubation. *Anaesthesia.* 2008;63(2):195-201. [CrossRef]
10. McElwain J, Malik MA, Harte BH, Flynn NM, Laffey JG. Comparison of the C-MAC® videolaryngoscope with the Macintosh, Glidescope®, and Airtraq® laryngoscopes in easy and difficult laryngoscopy scenarios in manikins. *Anaesthesia.* 2010;65(5):483-489. [CrossRef]
11. Ng I, Sim XL, Williams D, Segal R. A randomised controlled trial comparing the McGrath® videolaryngoscope with the straight blade laryngoscope when used in adult patients with potential difficult airways. *Anaesthesia.* 2011;66(8):709-714. [CrossRef]
12. Vlatten A, Aucoin S, Gray A, Soder C. Difficult airway management with the STORZ video laryngoscope in a child with Robin Sequence. *Pediatr Anesth.* 2009;19(7):700-701. [CrossRef]
13. Riveros R, Sung W, Sessler DI, et al. Comparison of the Truview PCDTM and the GlideScope (®) video laryngoscopes with direct laryngoscopy in pediatric patients: a randomized trial. *Can J Anaesth.* 2013;60(5):450-457. [CrossRef]
14. Kim JT, Na HS, Bae JY, et al. GlideScope® video laryngoscope: a randomized clinical trial in 203 paediatric patients. *Br J Anaesth.* 2008;101(4):531-534. [CrossRef]
15. Jagannathan N, Hajduk J, Sohn L, et al. Randomized equivalence trial of the King Vision aBlade videolaryngoscope with the Miller direct laryngoscope for routine tracheal intubation in children< 2 yr of age. *Br J Anaesth.* 2017;118(6):932-937. [CrossRef]
16. Das B, Samanta A, Mitra S, Jamil SN. Comparative evaluation of Airtraq™ optical Laryngoscope and Miller's blade in paediatric patients undergoing elective surgery requiring tracheal intubation: A randomized, controlled trial. *Indian J Anaesth.* 2017;61(4):326-331. [CrossRef]
17. Xu X, Ma H, Zhang Y, et al. Efficacy of bougie first approach for endotracheal intubation with video laryngoscopy during continuous chest compression: a randomized crossover manikin trial. *BMC Anesthesiol.* 2024;24(1):181. [CrossRef]
18. von Hellmann R, Fuhr N, Maia IW, et al. Effect of bougie use on first-attempt success in tracheal intubations: a systematic review and meta-analysis. *Ann Emerg Med.* 2024 ;83(2):132-144. [CrossRef]
19. Vlatten A, Aucoin S, Litz S, Macmanus B, Soder C. A comparison of the STORZ video laryngoscope and standard direct laryngoscopy for intubation in the Pediatric airway–a randomized clinical trial. *Paediatr Anaesth.* 2009;19(11):1102-1107. [CrossRef]
20. Weiss M, Hartmann K, Fischer J, Gerber AC. Video-intuboscopic assistance is a useful aid to tracheal intubation in pediatric patients. *Can J Anesth.* 2001;48:691-696. [CrossRef]

DOI: 10.4274/TJAR.2025.252018

Original Article
Other

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):256-262

Effects of Intravenous Dextrose Timing on Postoperative Nausea, Vomiting and Anxiety

Yusuf Özgüner, Savaş Altınsoy, İsmet Uluhan, Funda Atar, Derya Özkan, Jülide Ergil

University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Anaesthesiology and Reanimation, Ankara, Türkiye

Cite this article as: Özgüner Y, Altınsoy S, Uluhan İ, Atar F, Özkan D, Ergil J. Effects of intravenous dextrose timing on postoperative nausea, vomiting and anxiety. *Turk J Anaesthesiol Reanim*. 2025;53(5):256-262.

Abstract

Objective: Postoperative nausea and vomiting (PONV) is a significant issue encountered in surgical patients. This study aims to investigate the effects of dextrose infusion timing on PONV incidence.

Methods: Ninety patients undergoing laparoscopic cholecystectomy were included in this randomized controlled trial. Patients were assigned to one of three equal groups. In Group I, patients received an infusion of 400 mL of 0.9% saline 2 hours before surgery. In Group D, patients received 400 mL of 5% dextrose at the same infusion rate. Both Groups I and D received 0.9% saline at 10 mL kg^{-1} h^{-1} during the intraoperative period. In Group DD, patients received 200 mL of 5% dextrose preoperatively and 200 mL intraoperatively. To ensure the total maintenance fluid volume was the same as in the other groups, an infusion of 0.9% saline was administered along with the 200 mL dextrose. The primary outcome in our study was PONV incidence. Secondary outcomes were postoperative pain and anxiety levels.

Results: Postoperative PONV incidence, antiemetic consumption, and anxiety levels were lowest in Group DD, while they were highest in Group I ($P < 0.05$).

Conclusion: In this study, we found that dextrose infusion reduced the incidence of PONV, antiemetic consumption, and anxiety levels. We observed that administering the same volumes of dextrose in divided doses during the preoperative and intraoperative periods reduced the incidence of PONV and improved anxiety scores compared to sole preoperative dextrose infusion.

Keywords: Anaesthesia, anxiety, laparoscopic cholecystectomy, postoperative nausea and vomiting

Main Points

- Dextrose infusion is effective in postoperative nausea and vomiting (PONV) prophylaxis.
- There is a relationship between blood glucose levels and PONV.
- In addition to reducing the incidence of PONV, dextrose infusion also decreases anxiety levels.
- Administering dextrose in the same doses preoperatively and intraoperatively results in lower incidence of PONV and anxiety levels compared to administering dextrose alone preoperatively.

Introduction

Pain, postoperative nausea and vomiting (PONV) are significant issues encountered in surgical patients. The incidence of PONV ranges from 30% to 80%.[1,2] Risk factors for PONV include female gender, being under age 50, non-smoking status, motion sickness, laparoscopic cholecystectomy, and gynaecological surgeries.[3] In laparoscopic surgeries, abdominal gas insufflation is thought to increase the risk of PONV by stimulating mechanoreceptors in the intestines, leading to serotonin release and the activation of 5-HT3 receptors.[4,5] Additionally, factors such as anxiety and stress have been reported to cause nausea and vomiting.[6]

Corresponding author: Yusuf Özgüner, MD, e-mail: y.ozguner@hotmail.com

Received: April 06, 2025 Accepted: July 01, 2025
Epub: August 14, 2025 Published date: October 14, 2025

Untreated PONV can lead to dehydration, electrolyte imbalance, aspiration, and bleeding. This results in reduced patient satisfaction, prolonged hospital stays, and increased medical care costs.[3,7] Various pharmacological agents, such as serotonin 5-HT3 receptor antagonists, dopamine receptor antagonists (metoclopramide), antihistamines, and steroids, are used to treat PONV.[5,8] However, these pharmacological agents are associated with side effects, such as extrapyramidal symptoms, sedation, and hyperglycaemia. Many studies have investigated the effectiveness of perioperative fluid therapy in PONV prophylaxis. The infusion of perioperative dextrose at different times and doses reduces the incidence of PONV and the use of antiemetic drugs.[9-11]

The primary aim of our study was to investigate the hypothesis that patients receiving both preoperative and intraoperative dextrose infusions would have a lower incidence of PONV than those receiving only preoperative saline or dextrose infusions. Our secondary aim was to examine the differences in pain scores and anxiety levels between the groups.

Methods

Trial Design

This single-center randomized controlled study complied with the ethical standards of the Helsinki Declaration-2013. Ethics committee approval was obtained from the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (approval no.: 142/07, date: 18.07.2022) and registration with ClinicalTrials.gov were obtained (registration number: NCT05961722-13.07.2023). Written informed consent was obtained from all the participants.

Participants

Female and male patients undergoing laparoscopic cholecystectomy were included in the study. Patients over the age of 18, classified as American Society of Anesthesiologists I-II, who agreed to participate, were included. Patients with a history of PONV or motion sickness, those with diabetes mellitus or hypothyroidism, pregnant women, and individuals receiving opioids, chemotherapy, steroids, or antiemetic treatment, were excluded from the study.

Interventions

Patients were randomly assigned to one of three groups using sealed envelopes. An anaesthetist, blinded to patient treatment conditions, followed the patients postoperatively. In Group I, patients received an infusion of 400 mL of 0.9% saline over 30 minutes, administered 2 hours before surgery. In Group D, patients received 400 mL of 5% dextrose over 30 minutes, administered 2 hours before surgery. In Group DD, patients received 200 mL of 5% dextrose over 30 minutes, administered 2 hours before surgery. Both Groups I and D received 0.9% saline at 10 mL kg^{-1} h^{-1} during the intraoperative period. In Group DD, patients received 200 ml intraoperatively. To ensure the total maintenance fluid volume was the same as in the other groups, an infusion of 0.9% saline was administered along with the 200 mL dextrose.

Standard Anaesthesia Protocol

For all three groups, anaesthesia induction included 2 mg kg^{-1} of propofol, 1 mg kg^{-1} of lidocaine, 1 µg kg^{-1} of fentanyl, and 0.6 mg kg^{-1} of rocuronium. After anaesthesia induction, patients underwent endotracheal intubation. Anaesthesia maintenance in both groups involved the administration of 0.8-1.2 minimum alveolar concentration sevoflurane and 0.05-0.2 µg kg^{-1} min^{-1} remifentanil. Patients in both groups were monitored during surgery using volume-controlled ventilation mode with 50% oxygen-50% air, a tidal volume of 6 mL kg^{-1}, and a respiratory rate of 12 breaths per minute. Patient monitoring in both groups included pulse oximetry (SpO_2), end-tidal carbon dioxide, heart rate, non-invasive blood pressure, Bispectral index, temperature, and urine output. Blood glucose measurements were taken using a glucometer before preoperative fluid infusion, after intraoperative anaesthesia induction, and when the patient was transferred to the postoperative recovery room. All patients received intravenous 100 mg tramadol and 50 mg dexketoprofen for analgesia at the end of surgery, and 4 mg ondansetron as an antiemetic. At the end of the operation, the reversal of the neuromuscular blockade was achieved using 50 µg kg^{-1} neostigmine plus 10 µg kg^{-1} atropine. Patients were extubated at the end of surgery and transferred to the recovery room. In the first 24 hours postoperatively, all patients routinely received 1 mg kg^{-1} intravenous tramadol and 2 g intravenous paracetamol administered twice for analgesia.

Outcomes

The primary outcome in our study was the 24-hour postoperative incidence of PONV. Secondary outcomes were postoperative pain and anxiety levels.

Evaluation of PONV

PONV score and antiemetic requirements were assessed using the Verbal Descriptive Scale (VDS) at 0, 2, 4, 8, 12, and 24 hours. Patients with VDS of 2 and 3 were treated with 4 mg IV ondansetron. VDS:[12]

• 0= no PONV: patient reports no nausea and has had no emesis episodes;

• 1= mild PONV: patient reports nausea but declines antiemetic treatment;

• 2= moderate PONV: patient reports nausea and accepts antiemetic treatment;

• 3= severe PONV: nausea with any emesis episode (retching or vomiting).

Evaluation of Pain

Pain levels of the patients were assessed using the numeric rating scale (NRS), which ranges from 0 to 10. A score of 0 indicates no pain, while a score of 10 represents the worst possible pain. Pain was assessed using the NRS at 0, 2, 4, 8, 12, and 24 hours. Patients with an NRS score above 4 received 50 mg of dexketoprofen as rescue analgesia.

Evaluation of Anxiety

The State-Trait Anxiety Inventory (STAI) scale is frequently used to assess anxiety. STAI-1 is used to measure state anxiety, reflecting the individual's current level of anxiety, while STAI-2 assesses trait anxiety, indicating the individual's general tendency toward anxiety. The validity and reliability of the scale were established by Oner and LeCompte[13] in Türkiye. High scores indicate high anxiety levels, and low scores indicate low anxiety levels. The scale contains four scores ranging from "never" to "completely".[13,14] Anxiety levels of all patients were evaluated preoperatively using the STAI 1 and 2 anxiety scales before intravenous fluid infusion. The STAI 1 scale was reapplied at 4-6 hours postoperatively.[15]

Statistical Analysis

The sample size was determined assuming an expected prevalence of PONV of 60%, and 29 patients per group were found to be adequate for detecting an absolute 35% reduction in PONV (α=0.05, 1-ß=0.80). According to the preliminary study, the total sample size required was calculated as 87 patients. Taking potential dropouts into account, 96 patients were included in the study. SPSS 21.0 software was used for statistical analysis. The chi-square test (for categorical variables), One-Way ANOVA (for continuous variables with normal distribution), and Kruskal-Wallis test (for continuous variables with non-normal distribution) were employed in this study. A P value of < 0.05 was considered statistically significant. The Tukey test was used for multiple comparisons between the groups.

Results

Ninety-six patients undergoing laparoscopic cholecystectomy were included in the study. From the study, Two patients who experienced severe intraoperative hypotension, three patients who withdrew from the study, and one patient with a drug allergy were excluded. Consequently, a total of 90 patients were included in the final analysis (Figure 1).

The demographic and clinical characteristics (age, gender, ASA classification, body mass index, chronic diseases, average duration of surgery, total intravenous fluid volumes) were similar across the groups (Table 1).

PONV was observed in 19 patients (63.3%) in Group I, 10 patients (33.3%) in Group D, and 3 patients (10%) in Group DD. Postoperative rescue antiemetics were used in 16 patients in Group I, in 8 patients in Group D, and in 2 patients in Group DD. The highest incidence of PONV and postoperative antiemetic use was in Group I, while the lowest was in Group DD ($P < 0.05$) (Table 2).

NRS values and rescue analgesic consumption were similar across all groups at all postoperative time points ($P > 0.05$) (Table 3).

Preoperative blood glucose concentrations were comparable. Intraoperatively, Group I had a mean glucose level of 96.8±5.01, Group D had 149.23±6.41, and Group DD had 130.77±7.72. Postoperatively, Group I had 107.77±6.05, Group D had 151±7.11, and Group DD had 152.93±6.01. The highest intraoperative glucose levels were observed in Group D, while the lowest were in Group I. Postoperatively, there was no significant difference between Group D and Group DD, but Group I had the lowest levels (Table 4).

Preoperatively, STAI-1 and STAI-2 anxiety scores were similar among the three groups ($P > 0.05$). Postoperatively, the highest average STAI-1 score was observed in Group I, while the lowest was in Group DD ($P < 0.05$) (Table 4).

Discussion

In our study investigating the effects of dextrose versus saline infusions on PONV during preoperative and intraoperative periods, we found that the group receiving saline infusion alone had a higher incidence of PONV, increased antiemetic consumption, and higher anxiety scores. In contrast, patients who received dextrose infusions during both the preoperative and intraoperative periods exhibited lower incidences of PONV, reduced need for antiemetic medications, and lower anxiety levels than the other two groups.

Studies investigating the effects of fluid infusion therapy on PONV have reported that the effectiveness of crystalloid and colloid fluids is limited.[16,17] However, other studies have indicated that a dextrose infusion administered during the postoperative period reduces the incidence of PONV.[18,19]

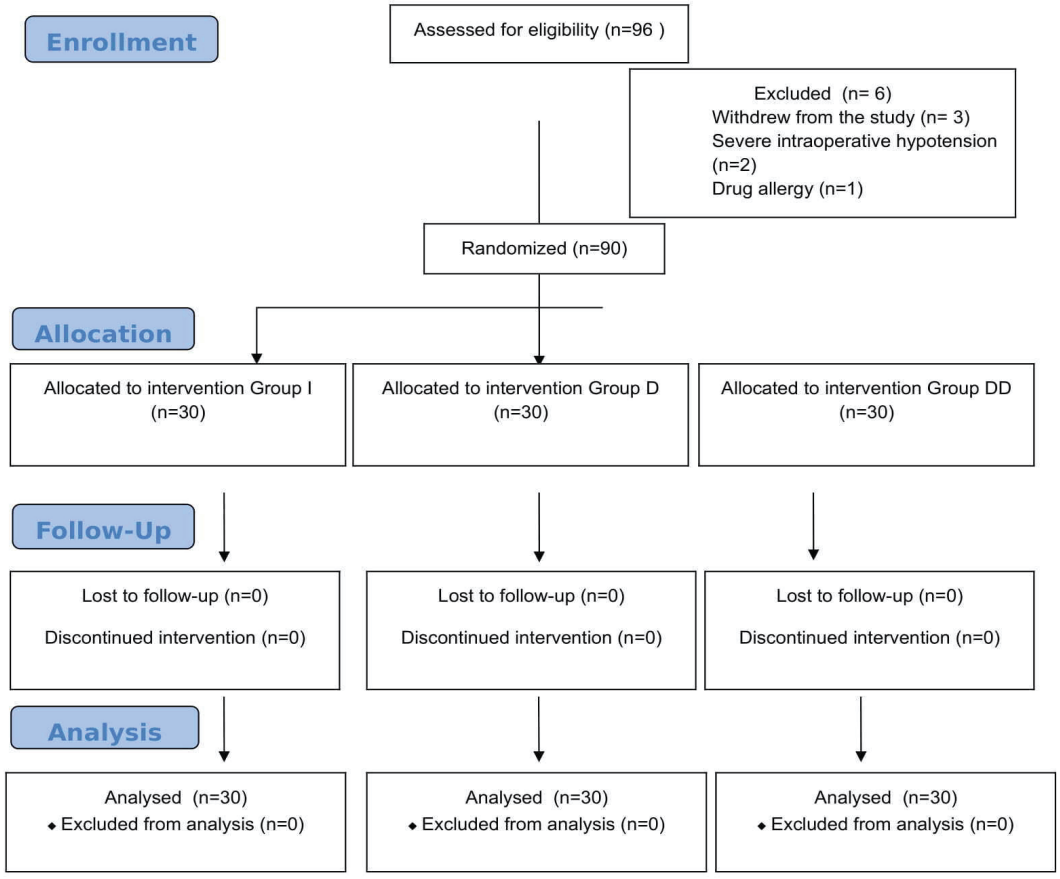

Figure 1. CONSORT diagram of the study.

Table 1. Demographic and Clinical Characteristics of the Study Patients

	Group I n = 30	Group D n = 30	Group DD n = 30	*P* value
Age (year)	48.87±13.48	48.63±7.25	48.13±8.91	0.961
Sex (n) Female/Male	15/15	14/16	14/16	0.956
BMI (kg m^{2-1})	27.59±3.05	27.31±2.77	27.62±3.04	0.902
ASA score (1/2) (n)	13/17	14/16	11/19	0.727
Duration of surgery (minute)	53.5±7.31	56.27±7.46	57.13±9.39	0.200
Volume of fluid administered (mL)	1076.66±127.74	1099.66±142.5	1094.66±122.77	0.776
Comorbidities				
Hypertension	10	9	10	0.950
Smoking	8	7	7	0.943
Asthma	3	2	2	0.856

Values are presented as mean ± standard deviation and numbers. The chi-square test was used for categorical variables, One-Way ANOVA for continuous variables with normal distribution, and the Tukey test for multiple group comparisons.
n, number; BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2. PONV Incidence and Severity

	Group I n = 30	Group D n = 30	Group DD n = 30	*P* value
PONV (n, %)	19 (63.3)	10 (33.3)	3 (10)	**<0.001***
PONV score (n) 0/1/2/3				
0th hour	26/1/1/2	28/1/1/0	30/0/0/0	**<0.001***
2nd hour	9/12/8/1	20/6/3/1	28/1/0/1	**<0.001***
4th hour	15/13/2/0	24/6/0/0	29/1/0/0	**<0.001***
8th hour	24/3/2/1	25/2/2/1	27/2/1/0	0.931
12th hour	26/1/1/2	28/1/1/0	30/0/0/0	0.392
24th hour	29/1/0/0	30/0/0/0	30/0/0/0	0.364
Required antiemetic (n)	16	8	2	**<0.001***

Values are presented as numbers. n, number/percentages. P < 0.05 was considered significant. *There were significant differences among the three groups. The chi-square test was used for categorical variables.
PONV, postoperative nausea and vomiting.

Table 3. Pain Scores (NRS) and Rescue Analgesic Consumption

	Group I n = 30	Group D n = 30	Group DD n = 30	*P* value
NRS 0th	3 (5)	3 (4)	3 (5)	0.464
NRS 2nd	4 (4)	4 (3)	4 (3)	0.481
NRS 4th	3 (4)	3 (3)	2 (4)	0.834
NRS 8th	2.5 (4)	3 (3)	3 (4)	0.987
NRS 12th	3 (3)	3 (3)	2 (3)	0.300
NRS 24th	2 (3)	2 (2)	2 (2)	0.773
Rescue analgesic (n)	6	4	4	0.713

Values are given as median (range) and numbers. *P* < 0.05 was considered significant. The chi-square test was used for categorical variables, while the Kruskal-Wallis test was applied to continuous variables that did not follow a normal distribution.
NRS, numeric rating score.

Table 4. Anxiety Score and Blood Glucose Levels

	Group I n = 30	Group D n = 30	Group DD n = 30	*P* value
Preoperative STAI 1 score	49.23±6.11	49.63±6.62	49.73±6.28	0.949
Preoperative STAI 2 score	42.7±8.45	41.57±6.98	42.83±8.16	0.792
Postoperative STAI 1 score	45.27±6.24	40.87±5.88	36.93±6.5	**<0.001***
Preoperative blood glucose (mg dL^{-1})	87.67±4.7	88.50±5.32	87.47±6.95	0.761
Intraoperative blood glucose (mg dL^{-1})	96.8±5.01	149.23±6.41	130.77±7.72	**<0.001***
Postoperative blood glucose (mg dL^{-1})	107.77±6.05	151±7.11	152.93±6.01	**<0.001#**

Values are given as mean ± standard deviation. *There were significant differences among the three groups. #There is a difference between Group I and the other two groups. One-Way ANOVA was used for continuous variables with normal distribution, and the Tukey test was applied for multiple group comparisons.
STAI, State-Trait Anxiety Inventory.

Mishra et al.[20] reported that intraoperatively administered dextrose infusions decreased the incidence of PONV. Salman et al.[10] compared preoperative and intraoperative dextrose infusions and found that both approaches were effective in preventing PONV. However, preoperative dextrose infusions have resulted in a lower incidence of PONV. Consistent with the literature, we observed a reduced incidence of PONV with dextrose infusions. The relationship between dextrose infusions and PONV is not clearly understood. Hyperglycaemia may lead to reduced gastric acid secretion, which decreases gastric contractions and alleviates nausea.[21] Additionally, dextrose infusions are believed to provide caloric supplementation, reducing catabolism and insulin resistance, thereby decreasing the risk of PONV.[20,22] In line with these findings, we hypothesised that the administration of dextrose infusions would be associated with a reduced incidence of PONV in comparison to those who did not.

In the literature, studies investigating the effect of dextrose infusion on PONV have employed varying dosages, timings, and durations of administration. Furthermore, there is currently no consensus regarding the optimal dextrose infusion protocol. In this study, when comparing two groups that received dextrose infusions at the same volumes, we found that only the patients who received dextrose infusions in the preoperative period had a higher incidence of PONV. Feldbauer et al.[23] reported that infusing glucose at the same dosage for longer durations resulted in fewer fluctuations in blood glucose levels. We observed a rapid increase in intraoperative blood glucose levels in patients in Group D, compared to the preoperative period, while in Group DD, blood glucose levels increased more slowly and gradually. We believe that administering the same volumes of dextrose infusion divided between the preoperative and intraoperative periods resulted in fewer fluctuations in patients' blood glucose levels than infusions administered solely during the preoperative period, potentially contributed to the reduced incidence of PONV. Additionally, we think that continued caloric intake through dextrose infusions during the intraoperative period helped decrease catabolism, thereby contributing to this outcome. Therefore, we consider the timing and rate of dextrose administration to be critical factors in maintaining metabolic stability and promoting postoperative recovery.

The literature has identified the causes of postoperative anxiety. Factors such as gender, age, type of anaesthesia (general or regional), educational status, and type of surgery significantly affect postoperative anxiety. Furthermore, postoperative anxiety has the potential to adversely influence multiple clinical outcomes, such as pain levels and patient comfort.[24,25] We observed that the factors known to influence anxiety were similar among the patient groups. Additionally, a relationship between preoperative fasting duration and postoperative anxiety has been established. Hausel et al.[26] reported in their studies involving patients undergoing abdominal surgery that the preoperative intake of oral carbohydrate-containing solutions reduced anxiety levels. Mousavie et al.[27] also indicated that preoperative oral and intravenous dextrose replacements positively impacted patients' emotional states. Consistent with the literature, our study found that patients receiving dextrose infusions had lower postoperative anxiety levels. Patients receiving both preoperative and intraoperative dextrose infusions exhibited lower anxiety scores than those receiving only preoperative dextrose infusions. Increased blood glucose levels are known to elevate plasma cholecystokinin levels. Cholecystokinin has been reported to play a role in the regulation of pain and anxiety.[11,28] Therefore, we believe that the lower anxiety levels observed in patients receiving dextrose infusions may be attributed to differences in cholecystokinin levels. We also propose that the lower anxiety scores in Group DD, than in Group D may be due to the division of dextrose infusion into preoperative and intraoperative periods with the same total volume. Furthermore, we believe that an ongoing dextrose infusion during the intraoperative period helps to reduce catabolism and the effects of surgical stress. Nonetheless, the potential benefits of dextrose infusion should be balanced with careful monitoring of blood glucose levels to prevent hyperglycemia-related complications. Future research focusing on the optimization of infusion timing and dosage could further enhance patient outcomes and provide clearer guidelines for clinical practice.

Study Limitations

Our study has certain limitations. First, not monitoring hormone levels such as insulin, aside from blood glucose levels, was a limitation. Second, we were unable to evaluate the long-term effects and hospital stay duration as we did not follow patients beyond the first 24 hours postoperatively.

Conclusion

We found that dextrose infusion reduced the incidence of PONV, antiemetic consumption, and anxiety levels. We observed that administering the same volumes of dextrose in divided doses during the preoperative and intraoperative periods positively affected the incidence of PONV and anxiety scores compared to sole preoperative dextrose infusion. Therefore, we believe that dextrose infusion, as a low-cost method, is an effective strategy for PONV prophylaxis in surgical patients during both the preoperative and intraoperative periods.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (approval no.: 142/07, date: 18.07.2022).

Informed Consent: Written informed consent was obtained from all the participants.

Footnotes

Author Contributions: Surgical and Medical Practices - Y.Ö., S.A., İ.U., F.A., D.Ö., J.E.; Concept - Y.Ö., S.A., İ.U., F.A., D.Ö., J.E.; Design - Y.Ö., S.A., İ.U., F.A., D.Ö., J.E.; Data Collection and/or/Processing - Y.Ö., İ.U., F.A.; Analysis and/or/Interpretation - Y.Ö., S.A., F.A., D.Ö., J.E.; Literature Review - Y.Ö., S.A., İ.U., F.A., D.Ö., J.E.; Writing - Y.Ö., S.A., İ.U., J.E.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: No funding was received for conducting this study.

References

1. Gan TJ. Postoperative nausea and vomiting--can it be eliminated? *JAMA.* 2002;287(10):1233-1236. [CrossRef]
2. Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev.* 2006;2006(3):Cd004125. [CrossRef]
3. Apfel CC, Kranke P, Eberhart LHJ, Roos A, Roewer N. Comparison of predictive models for postoperative nausea and vomiting. *Br J Anaesth.* 2002;88(2):234-240. [CrossRef]
4. Liao B, Liao W, Wu X, et al. Analysis of influencing factors and construction of prediction model for postoperative nausea and vomiting in patients undergoing laparoscopic sleeve gastrectomy: a single-center retrospective cohort study. *BMC Anesthesiol.* 2024;24(1):131. [CrossRef]
5. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med.* 2004;350(24):2441-2451. [CrossRef]
6. Pasyar N, Rambod M, Zahedi F, Ramzi M. Pain, fatigue, nausea, and vomiting as the predictors of anxiety in patients undergoing hematopoietic stem cell transplantation: a prospective cohort study. *Support Care Cancer.* 2022;30(7):5871-5879. [CrossRef]
7. Stadler M, Bardiau F, Seidel L, Albert A, Boogaerts JG. Difference in risk factors for postoperative nausea and vomiting. *Anesthesiology.* 2003;98(1):46-52. [CrossRef]
8. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2014;118(1):85-113. [CrossRef]
9. D'Souza RS, Mercogliano C, Ojukwu E, et al. Effects of prophylactic anticholinergic medications to decrease extrapyramidal side effects in patients taking acute antiemetic drugs: a systematic review and meta-analysis. *Emerg Med J.* 2018;35(5):325-331. [CrossRef]
10. Salman N, Aykut A, Sabuncu Ü, Şaylan A, Yağar S, Şekerci S. Dextrose administration may reduce the incidence of postoperative nausea and vomiting after laparoscopic cholecystectomy: a double blind randomized controlled trial. *Minerva Anestesiol.* 2020;86(4):379-86. [CrossRef]
11. Deng R, Huang G, Liu W, Liu X. Effects of perioperative dextrose infusion on preventing postoperative nausea and vomiting in patients undergoing laparoscopic surgery: a meta-analysis of randomized controlled trials. *J Int Med Res.* 2021;49(12):3000605211063264. [CrossRef]
12. Boogaerts JG, Vanacker E, Seidel L, Albert A, Bardiau FM. Assessment of postoperative nausea using a visual analogue scale. *Acta Anaesthesiol Scand.* 2000;44(4):470-474. [CrossRef]
13. Oner N, LeCompte A. Durumluk – Surekli Kaygı Envanteri El Kitabı. 1. Baskı Istanbul: Boğaziçi Üniversitesi Yayını; 1983. s. 1-26. [CrossRef]
14. Topal Hançer A. Prevalence and factors associated with surgery anxiety in hospitalized patients: a point-prevalence study. *Ir J Med Sci.* 2023;192(5):2095-2103. [CrossRef]
15. Akelma FK, Altınsoy S, Nalbant B, Özkan D, Ergil J. Comparison of classical and patient-preferred music on anxiety and recovery after inguinal hernia repair: a prospective randomized controlled study. *Perioper Med (Lond).* 2024;13(1):89. [CrossRef]
16. Dagher CF, Abboud B, Richa F, et al. Effect of intravenous crystalloid infusion on postoperative nausea and vomiting after thyroidectomy: a prospective, randomized, controlled study. *Eur J Anaesthesiol.* 2009;26(3):188-191. [CrossRef]
17. Haentjens LL, Ghoundiwal D, Touhiri K, et al. Does infusion of colloid influence the occurrence of postoperative nausea and vomiting after elective surgery in women? *Anesth Analg.* 2009;108(6):1788-1793. [CrossRef]
18. Dabu-Bondoc S, Vadivelu N, Shimono C, et al. Intravenous dextrose administration reduces postoperative antiemetic rescue treatment requirements and postanesthesia care unit length of stay. *Anesth Analg.* 2013;117(3):591-596. [CrossRef]
19. Rao V, Bala I, Jain D, Bharti N. Effect of intravenous dextrose administration on postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a randomised controlled trial. *Eur J Anaesthesiol.* 2017;34(10):705-707. [CrossRef]
20. Mishra A, Pandey RK, Sharma A, et al. Is perioperative administration of 5% dextrose effective in reducing the incidence of PONV in laparoscopic cholecystectomy?: A randomized control trial. *J Clin Anesth.* 2017;40:7-10. [CrossRef]
21. Agarwal A, Dhiraaj S, Tandon M, Singh PK, Singh U, Pawar S. Evaluation of capsaicin ointment at the Korean hand acupressure point K-D2 for prevention of postoperative nausea and vomiting. *Anaesthesia.* 2005;60(12):1185-1188. [CrossRef]
22. Ljungqvist O, Nygren J, Thorell A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. *Proc Nutr Soc.* 2002;61(3):329-336. [CrossRef]
23. Feldbauer R, Heinzl MW, Klammer C, et al. Effect of repeated bolus and continuous glucose infusion on a panel of circulating biomarkers in healthy volunteers. *PLoS One.* 2022;17(12):e0279308. [CrossRef]
24. Oh J, Lee W, Ki S, Suh J, Hwang S, Lee J. Assessment of preoperative anxiety and influencing factors in patients undergoing elective surgery: an observational cross-sectional study. *Medicina (Kaunas).* 2024;60(3):403. [CrossRef]
25. Uçaner B, Buldanli MZ, Çimen Ş, et al. Investigation of factors that may potentially affect anxiety in patients undergoing esophagogastroduodenoscopy and evaluation of sedation effect. *Medicine (Baltimore).* 2024;103(15):e37801. [CrossRef]
26. Hausel J, Nygren J, Lagerkranser M, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth Analg.* 2001;93(5):1344-1350. [CrossRef]
27. Mousavie SH, Negahi A, Hosseinpour P, Mohseni M, Movassaghi S. The effect of preoperative oral versus parenteral dextrose supplementation on pain, nausea, and quality of recovery after laparoscopic cholecystectomy. *J Perianesth Nurs.* 2021;36(2):153-156. [CrossRef]
28. Mitchell VA, Jeong HJ, Drew GM, Vaughan CW. Cholecystokinin exerts an effect via the endocannabinoid system to inhibit GABAergic transmission in midbrain periaqueductal gray. *Neuropsychopharmacology.* 2011;36(9):1801-1810. [CrossRef]

DOI: 10.4274/TJAR.2025.252054

Original Article

Health Services / Surgical Epidemiology

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):263-276

A 10-Year Analysis of Surgical Interventions Applied to Migrants: A Border Hospital Experience During the Syrian Civil War

Ergün Mendeş[1], Neşet Gümüşburun[2,3]

[1]Koç University Faculty of Medicine Hospital, Department of Anaesthesiology and Reanimation, İstanbul, Türkiye

[2]Medical Park Tokat Hospital, Clinic of Obstetrics and Gynecology, Tokat, Türkiye

[3]İstanbul Aydın University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Türkiye

Cite this article as: Mendeş E, Gümüşburun N. A 10-year analysis of surgical interventions applied to migrants: a border hospital experience during the Syrian civil war. *Turk J Anaesthesiol Reanim.* 2025;53(5):263-276

Abstract

Objective: The Syrian civil war has resulted in one of the largest refugee movements globally, significantly impacting Türkiye due to its geographic proximity. Surgical care represents a critical yet often overlooked aspect of healthcare services required by displaced populations. This study aimed to evaluate the demographic characteristics and surgical procedures performed on migrant patients over a ten-year period at a secondary-level hospital located on Türkiye's southern border.

Methods: A retrospective cohort study was conducted at Kilis State Hospital between March 2010 and January 2020. Surgical procedures were categorized by department, patient nationality, and type of surgery. Patients operated under the "war code" were analyzed separately to identify conflict-related injury patterns.

Results: A total of 52,978 surgical procedures were performed, with 41.76% involving Syrian patients. The mean age was 31.28±20.33 years, and male patients predominated, especially among the war-injured subgroup (91.59%). The most active surgical departments were orthopedics and traumatology (20.63%), gynecology and obstetrics (17.51%), and general surgery (15.67%). Among war-related surgeries, orthopedics, neurosurgery, and plastic surgery departments played major roles.

Conclusion: This study highlights the high surgical demand among migrant populations in border regions, especially in conflict settings. Strengthening healthcare infrastructure, maintaining accurate surgical records, and implementing multidisciplinary approaches are essential for meeting these needs. Our findings can inform future policies aimed at improving surgical care for displaced populations.

Keywords: Border healthcare services, migration, refugees, surgical interventions, war-related trauma

Main Points

- Migration due to armed conflicts has led to a significant surgical burden in border regions.
- Orthopedics, gynecology, and general surgery departments carried the highest surgical load among migrants.
- War-related injuries predominantly affected young males, with orthopedic trauma being the most common.
- Strengthening healthcare infrastructure in border hospitals is essential for managing the surgical needs of displaced populations.

Introduction

Unfortunately, ongoing wars around the world have rendered migration an inevitable phenomenon. As a result, the concept of migration remains a pressing global concern. Over the past two decades, international migration has risen significantly, with approximately 258 million international migrants reported in 2017.[1] If this trend continues, the number of migrants is projected to exceed 400 million by the year 2050.[2]

Due to its geographical location, Türkiye has historically opened its doors and extended assistance to individuals forced to migrate, particularly in response to conflicts in the Middle East. In this context, the Syrian civil war,

Corresponding author: Ergün Mendeş MD, e-mail: erg.mendes@gmail.com

Received: April 29, 2025 Accepted: September 04, 2025
Epub: September 18, 2025 Published date: xxxxx

which has been ongoing since 2011, continues to impact Türkiye-especially its border provinces.[3] Many war casualties were transferred to southern cities such as Hatay and Kilis. Furthermore, due to the prolonged instability in the region, Türkiye's southern border has hosted not only the wounded but also a large number of Syrian migrants. According to United Nations data, Türkiye ranks among the top countries hosting the largest number of refugees, having accommodated more than 3.7 million asylum seekers to date.[4,5]

In general, refugees and migrants-particularly in Türkiye, one of the countries most affected by migration-have faced numerous challenges related to nutrition, shelter, security, and access to healthcare services.[6,7] Among these vulnerable populations, women and children have been disproportionately affected due to the persistent lack of regional stability.[8] Through its healthcare policies targeting migrants-including the "open-door" policy-Türkiye has become the leading provider of humanitarian aid, serving as a model for neighboring countries.[9]

Globally, it is estimated that approximately 3 million surgical procedures are performed on migrants each year.[10] However, only a limited number of countries have conducted studies addressing the surgical needs of migrant populations.[11] A review of the existing literature on Syrian migrant patients in Türkiye reveals a lack of studies focusing specifically on the utilization of surgical services within the healthcare system.

Despite the high number of migrants receiving healthcare services in Türkiye, particularly along the southern border, the surgical needs and utilization patterns of this population remain largely undocumented. We hypothesize that a substantial proportion of surgical interventions in border-region hospitals are associated with migrant populations, reflecting the health burden of conflict-related displacement. Therefore, the aim of our study is to evaluate the surgical procedures performed on migrant patients, along with their demographic, and clinical characteristics, over a ten-year period at a secondary-level hospital located along Türkiye's southern border. By doing so, we seek to address a critical gap in the literature and contribute data that may inform healthcare planning for displaced populations.

Methods

This study was designed as a retrospective and observational cohort study and was conducted at Kilis State Hospital, a secondary-level healthcare facility located near Türkiye's southern border with Syria. Throughout the study period, the hospital played a central role in providing surgical services both to the local Turkish population and to Syrian migrants displaced by the ongoing war in Syria. The study period covered ten years, from March 2010 to January 2020, thus encompassing both pre-conflict and conflict-related migration dynamics. Ethical approval for the study was obtained from the Ethics Committee of Gaziantep University Faculty of Medicine (approval no: 2019/486, date: 05.02.2020). All procedures involving human participants were conducted in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. The requirement for individual informed consent was waived by the Ethics Committee due to the retrospective nature of the study.

Patient data were retrospectively obtained from the hospital's electronic medical record system. All surgical procedures recorded in the operating theater system were reviewed. To maintain data homogeneity, minor interventions performed in the emergency department or outpatient clinics (e.g., superficial wound closure, minor drainage procedures) were excluded. Duplicate records were identified using patients' temporary or permanent identification numbers and were removed from the dataset. Patients with complete information on age, gender, and nationality/ethnicity were included, whereas records with missing data were excluded from the analysis.

For each patient, demographic variables including age (in years), gender (male or female), and nationality/ethnicity (Turkish or Syrian) were recorded. The surgical department performing the operation and the type of procedure were also documented. Wherever possible, procedures were categorized as emergency or elective surgeries based on clinical records. Patients who underwent surgery for conflict-related injuries were identified in the system under the classification "war code" and were analyzed separately.

All surgical procedures were grouped according to the surgical department responsible for the operation. The departments included orthopedics and traumatology, gynecology and obstetrics, general surgery, urology, ear, nose and throat (ENT) surgery, paediatric surgery, plastic and reconstructive surgery, neurosurgery, ophthalmology, cardiovascular surgery, and thoracic surgery. Within each department, the most frequently performed specific procedures [e.g., cesarean section (C/S), appendectomy, orthopedic fixation surgeries, cataract surgery] were also analyzed.

Patients recorded under the "war code" classification were analyzed separately. The intensity of surgical activity by department, the predominant types of trauma, and demographic characteristics (age, gender) were evaluated specifically in this subgroup. Descriptive statistical methods were applied, and the results were presented as frequencies and percentages.

Among patients managed under the war code, injuries were classified into two main categories based on the mechanism.

Direct war injuries resulting directly from combat-related causes such as gunshot, explosive, and shrapnel injuries. Indirect war injuries refer to trauma resulting from secondary effects of the conflict environment, such as being trapped under rubble, injuries sustained during evacuation, or secondary infections. All injuries resulting from either direct or indirect mechanisms were defined collectively as war trauma.

One of the major strengths of the study is that it covers a large patient population over an extended time period in a border region heavily affected by migration, providing a detailed overview of a wide surgical spectrum. However, the study's single-center nature may limit the generalizability of its findings. Furthermore, the retrospective design carries the inherent risk of record errors or missing data, and these limitations were considered when interpreting the study results.

Regarding data security, all patient information was securely stored within the hospital's encrypted electronic record systems, accessible only by authorized research personnel. Data were anonymized prior to analysis to prevent the disclosure of personal identifiers. Patient confidentiality and data protection principles were strictly adhered to throughout the study. The surgical departments performing the operations were grouped, and the types of procedures performed by each department were identified. Minor interventions performed outside the operating room were excluded from the study. Surgical diagnoses were evaluated based on the clinical departments where the patients were admitted and were subsequently referred to the operating room.

Statistical Analysis

Descriptive statistical analyses were performed using IBM SPSS Statistics for Mac OS, version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables (such as gender, surgical department, type of trauma) were summarized as frequencies and percentages [n (%)], while continuous variables (such as age) were evaluated for normality through both visual (histograms, Q-Q plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) and reported as mean ± standard deviation. No data imputation was performed for missing data; incomplete records were excluded from the analysis.

To demonstrate the trends in surgical services over the years, annual surgical volumes by department and ethnicity were visualized using line charts, and the distribution of surgeries among Turkish and Syrian patients was presented in tabular format. A time-series (trend) analysis was used to assess changes in surgical service demands over time. A two-sided p-value of <0.05 was considered statistically significant for comparative analyses. However, as the primary aim of the study was descriptive analysis, inferential statistics were used in a limited scope.

Results

A total of 52,978 surgical procedures were performed over the 10-year period examined at Kilis State Hospital. Of the operated patients, 30,854 (58.24%) were Turkish citizens, while 22,124 (41.76%) were of Syrian nationality. Regarding gender distribution, 31,201 (59.89%) were male and 21,777 (41.11%) were female. Among the Syrian patients, 13,750 (62.15%) were male and 8,374 (37.85%) were female.

The overall mean age of the patients was 31.28±20.33 years. The mean age of Turkish patients was 32.98±21.42 years, while the mean age of Syrian patients was 28.90±18.45 years. The overall mean age of the male patients was 29.04±20.78 years. The mean age of Turkish patients was 30.12±22.39 years, while the mean age of Syrian patients was 27.67±18.44 years. The overall mean age of the female patients was 34.48±19.23 years. The mean age of Turkish patients was 36.71±19.46 years, while the mean age of Syrian patients was 30.92±18.29 years.

When categorized by age groups, 12,454 patients (23.51%) were between 0 and 17 years, 28,030 (52.91%) between 18 and 44 years, 8,225 (15.53%) between 45 and 65 years, and 4,269 (8.06%) were over 65 years of age. Among the Syrian patients, these numbers were 5,650 (25.54%), 12,434 (56.20%), 2,903 (13.12%), and 1,137 (5.14%), respectively.

The age, gender, and ethnicity distribution of the patients included in the study are presented in Table 1.

Distribution of Surgical Procedures by Ethnicity and Department

Over the 10-year study period, the distribution of surgical procedures among Syrian and Turkish patients was analyzed across different surgical departments. The findings reveal considerable variations in service utilization patterns between the two groups. The change in surgeries performed on patients over the years is shown in Figure 1. The distribution of surgical clinics where patients received a service in the last 10 years by ethnic origin is shown in Table 2.

Orthopedics and Traumatology: A total of 10,929 procedures (20.63% of all surgeries) were performed in the orthopedics and traumatology department. Of these, 5,382 (10.16%) were Syrian and 5,547 (10.47%) were Turkish patients. Among Syrian patients, 2,500 surgeries (22.87%) were large bone osteotomy and fixation procedures, while 2,882 (26.37%) consisted of other orthopedic interventions. Turkish patients had a slightly higher proportion of miscellaneous orthopedic surgeries (33.59%) compared to fixation procedures (17.17%).

Table 1. Demographics of Turkish and Syrian Patients

Category	Syrian n (%)	Turkish n (%)	Total n (%)
Number of patients n (%)	22,124 (41.76)	30,854 (58.24)	52,978 (100)
Gender			
Gender - male n (%)	13,750 (62.15)	17,451 (56.57)	31,201 (59.89)
Gender - female n (%)	8,374 (37.85)	13,403 (43.43)	21,777 (41.11)
Age			
Mean age mean ± SD	28.90±18.45	32.98±21.42	31.28±20.33
Mean age - male mean ± SD	27.67±18.44	30.12±22.39	29.04±20.78
Mean age - female mean ± SD	30.92±18.29	36.71±19.46	34.48±19.23
Age groups			
0-17 n (%)	5,650 (25.54)	6,804 (22.06)	12,454 (23.51)
18-44 n (%)	12,434 (56.20)	15,596 (50.55)	28,030 (52.91)
45-65 n (%)	2,903 (13.12)	5,322 (17.25)	8,225 (15.53)
>65 n (%)	1,137 (5.14)	3,132 (10.14)	4,269 (8.06)

*n (%) - Mean ± SD, mean ± standard deviation

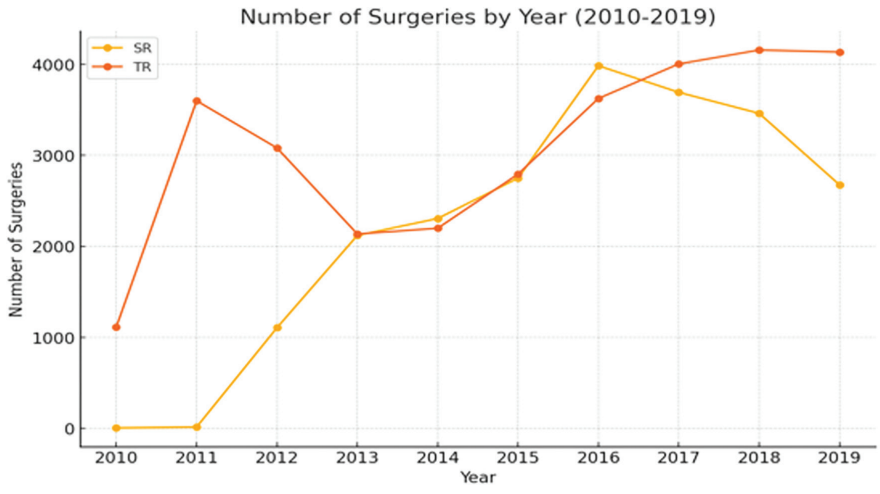

Figure 1. Number of surgeries by year.

SR, Syrian; TR, Türkiye

Table 2. Distribution of Surgical Clinics Where Patients Received Services in the Last 10 Years by Ethnicity			
Department of surgery	**Syrian n (%)**	**Turkish n (%)**	**Total n (%)**
Orthopedics and traumatology surgery			
Large bone osteotomy and fixation	2,500 (22.87)	1,876 (17.17)	4,376 (40.04)
Other	2,882 (26.37)	3,671 (33.59)	6,553 (59.96)
Total	**5,382 (10.16)**	**5,547 (10.47)**	**10,929 (20.63)**
Gynecology and obstetrics surgery			
Caesarean section	3,483 (37.56)	4,888 (52.70)	8,371 (90.26)
Other	303 (3.27)	600 (6.47)	903 (9.74)
Total	**3,786 (7.15)**	**5,488 (10.36)**	**9,274 (17.51)**
General surgery			
Appendectomy	267 (3.21)	937 (11.29)	1,204 (14.50)
Emergency (excluding appendectomy)	595 (7.17)	319 (3.84)	914 (11.01)
Non-emergency	1,338 (16.12)	4,846 (58.37)	6,184 (74.49)
Total	**2,200 (4.15)**	**6,102 (11.52)**	**8,302 (15.67)**
Urology			
Endoscopic surgeries	620 (13.15)	899 (19.07)	1,519 (32.22)
Prostate and bladder surgeries	238 (5.05)	444 (9.42)	682 (14.47)
Varicocele-hydrocele-inguinal and testicular surgery	254 (5.39)	621 (13.17)	875 (18.56)
Circumcision	57 (1.21)	959 (20.34)	1,016 (21.55)
Others	298 (6.32)	324 (6.88)	622 (13.20)
Total	**1,467 (2.77)**	**3,247 (6.13)**	**4,714 (8.90)**
Ear, nose and throat surgery			
Emergency	84 (1.81)	81 (1.75)	165 (3.56)
Tonsil and adenoid surgeries	859 (18.50)	998 (21.50)	1,857 (40.00)
Septum and rhinoplasty surgeries	266 (5.73)	1,246 (26.84)	1,512 (32.57)
Others	331 (7.13)	777 (16.74)	1,108 (23.87)
Total	**1,540 (2.91)**	**3,102 (5.85)**	**4,642 (8.76)**
Pediatric surgery			
Emergency (excluding appendectomy)	188 (4.55)	59 (1.43)	247 (5.98)
Appendectomy	164 (3.97)	286 (6.93)	450 (10.90)
Circumcision	227 (5.50)	1,103 (26.70)	1,330 (32.30)
Non-emergency (excluding circumcision)	1,153 (27.92)	950 (23.00)	2,103 (50.92)
Total	**1,732 (3.27)**	**2,398 (4.53)**	**4,130 (7.80)**
Plastic and reconstructive surgery			
Skin and soft tissue surgeries	700 (22.22)	503 (15.96)	1,203 (38.18)
Others	568 (18.03)	1,066 (33.83)	1,634 (51.86)
Mandibula and maxilla surgery	262 (8.31)	52 (1.65)	314 (9.96)
Total	**1,530 (2.89)**	**1,621 (3.06)**	**3,151 (5.95)**
Neurosurgery			
Emergency	1,138 (39.34)	239 (8.26)	1,377 (47.60)
Non-emergency	732 (25.30)	784 (27.10)	1,516 (52.40)
Total	**1,870 (3.53)**	**1,023 (1.93)**	**2,893 (5.46)**

Table 2. Continued.

Department of surgery	Syrian n (%)	Turkish n (%)	Total n (%)
Ophthalmology			
Emergency	471 (16.80)	52 (1.85)	523 (18.65)
Non-emergency	909 (32.42)	1,372 (48.93)	2,281 (81.35)
Total	**1,380 (2.60)**	**1,424 (2.69)**	**2,804 (5.29)**
Cardiovascular surgery			
Emergency	563 (33.71)	133 (7.96)	696 (41.67)
Non-emergency	301 (18.02)	673 (40.31)	974 (58.33)
Total	**864 (1.63)**	**806 (1.52)**	**1,670 (3.15)**
Thoracic surgery			
Emergency	307 (65.46)	35 (7.46)	342 (72.92)
Non-emergency	66 (14.07)	61 (13.01)	127 (27.08)
Total	**373 (0.70)**	**96 (0.18)**	**469 (0.88)**

Total data are expressed as a percentage of the total number of cases compared to all operations.
Percentage distributions within departments were calculated separately

Gynecology and Obstetrics: The gynecology and obstetrics department accounted for 9,274 operations (17.51%). Of these, 3,786 (7.15%) were Syrian and 5,488 (10.36%) were Turkish. The majority of procedures in this department were C/S's, representing 90.26% of all obstetric surgeries. Specifically, 3,483 Syrian patients (37.56%) and 4,888 Turkish patients (52.70%) underwent C/S's. Other gynecologic surgeries were relatively less, making up 3.27% of their Syrian and 6.47% of their Turkish operations in this department. It has been observed that the number of births to Syrian patients has, over the years, caught up with and even exceeded the number of births to Turkish patients (Figure 2).

General Surgery: In the general surgery department, a total of 8,302 procedures (15.67%) were recorded-2,200 (4.15%) in Syrian and 6,102 (11.52%) in Turkish patients. While appendectomies were more frequent in Turkish patients (11.29%) than in Syrians (3.21%), emergency surgeries other than appendectomies were more common in Syrians (7.17%) than in Turkish patients (3.84%). Non-emergency surgeries dominated the overall caseload, especially among Turkish patients (58.37%).

Urology: The urology department performed 4,714 surgeries (8.90%), including 1,467 (2.77%) in Syrian patients, and 3,247 (6.13%) in Turkish patients. Turkish patients underwent circumcision most frequently (n = 959, 20.34%), whereas Syrian patients most commonly received endoscopic interventions (n = 620, 13.15%). Other frequently performed procedures included varicocele, hydrocele, and inguinal/testicular surgeries.

Ear, Nose, and Throat (ENT): A total of 4,642 surgeries (8.76%) were carried out in ENT, with 1,540 (2.91%) in Syrian and 3,102 (5.85%) in Turkish patients. The most frequent procedures were tonsillectomy and adenoidectomy, accounting for 18.50% of ENT surgeries in Syrians and 21.50% in Turkish patients. Septoplasty and rhinoplasty were also common, particularly among Turkish patients (26.84%).

Paediatric Surgery: In the paediatric surgery department, 4,130 operations (7.80%) were conducted-1,732 (3.27%) in Syrian and 2,398 (4.53%) in Turkish patients. Circumcision was the most common procedure among Turkish children, (n = 1,103, 26.70%), whereas non-emergency surgeries other than circumcision were more frequent in Syrian children, (n = 1,153, 27.92%). Emergency surgeries (excluding appendectomy) were also more common in Syrians.

Plastic and Reconstructive Surgery: A total of 3,151 operations (5.95%) were performed in this department-1,530 (2.89%) in Syrian patients and 1,621 (3.06%) in Turkish patients. Syrian patients underwent more skin and soft tissue surgeries (22.22% of the total surgeries) and maxillofacial procedures (8.31% of the total surgeries) compared to their Turkish counterparts. However, Turkish patients had a higher proportion of surgeries categorized as "others" (33.83%).

Neurosurgery: The neurosurgery department performed 2,893 surgeries (5.46%), with a notable ethnic distribution: 1,870 (3.53%) Syrian and 1,023 (1.93%) Turkish patients. Emergency neurosurgical procedures were significantly more common among Syrian patients, (n = 1,138, 39.34%) compared to Turkish patients, (n = 239, 8.26%).

Ophthalmology: There were 2,804 eye surgeries (5.29%) recorded-1,380 (2.60%) in Syrian and 1,424 (2.69%) in Turkish patients. Non-emergency procedures predominated

for both groups, especially among Turkish patients (48.93%), indicating that this type of procedure constituted nearly half of the cases.

Cardiovascular Surgery: This department accounted for 1,670 surgeries (3.15%), of which 864 (1.63%) were Syrian and 806 (1.52%) were Turkish. Emergency interventions were more frequent among Syrian patients (33.71%), while Turkish patients had a greater proportion of non-emergency cardiovascular surgeries (40.31%).

Thoracic Surgery: Thoracic procedures were the least common, with 469 total operations (0.88%)-373 (0.70%) in Syrian and 96 (0.18%) in Turkish patients. Emergency thoracic surgeries were particularly high among Syrians (65.46%), indicating possible trauma-related indications (Figures 3-6).

Surgical Distribution of Refugees Operated Under "War Code"

Among the migrant patients operated under the "war code" classification, a total of 5,061 surgical procedures were performed across various departments. The distribution of these surgeries by surgical specialty is detailed below. Table 3 shows the surgical distribution of immigrants who were operated on under the war code.

The orthopedics and traumatology department performed the highest number of war-related surgeries, accounting for 1,739 procedures, which represented 34.70% of all operations in this category. These were predominantly related to trauma and fracture management resulting from conflict-related injuries. The second highest surgical load was observed in the neurosurgery department, with

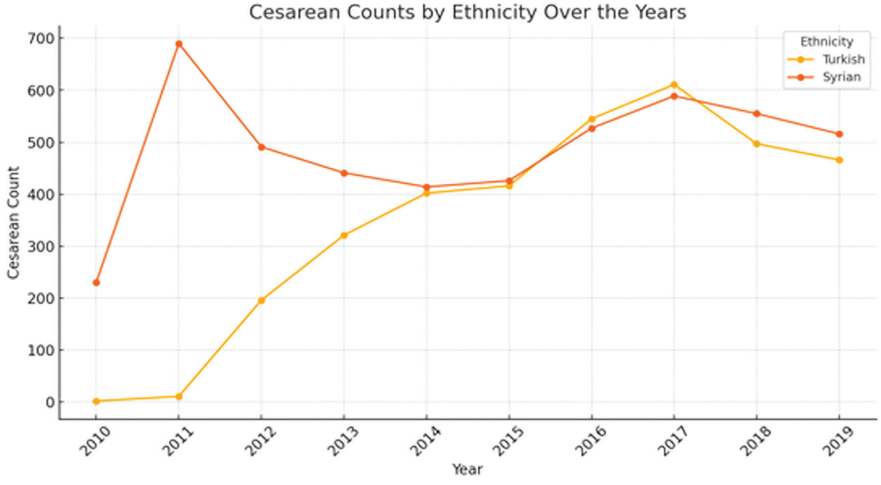

Figure 2. Cesarean counts by ethnicity over the years.

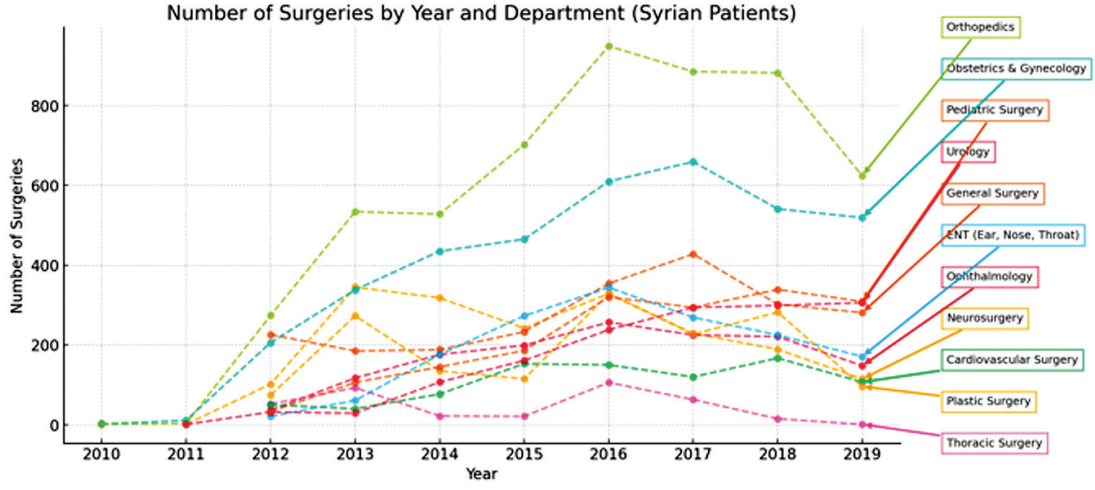

Figure 3. Number of surgeries by year and department (Syrian patients).

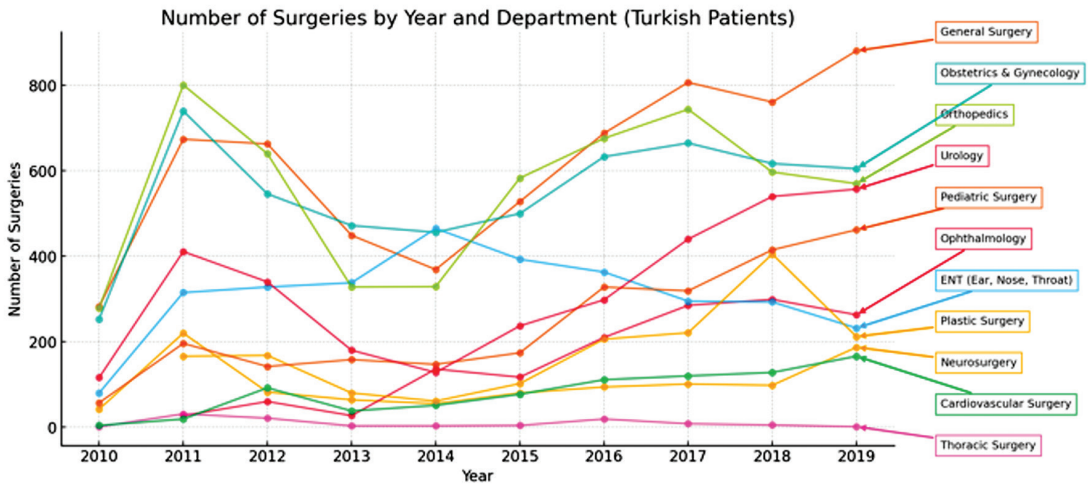

Figure 4. Number of surgeries by year and department (Turkish patients).

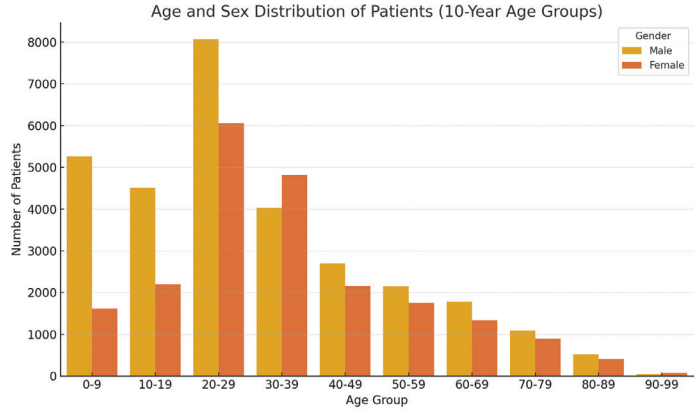

Figure 5. Age and sex distribution of patients (10-year age groups).

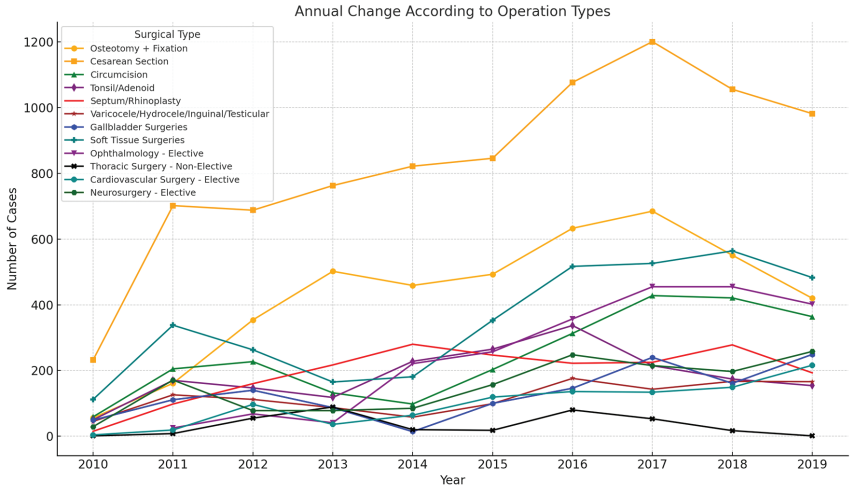

Figure 6. Annual change according to operation types.

Table 3. Surgical Distribution of Immigrants Operated with War Code

Department of surgery	Number (n)	Percentage (%)
Orthopedics and traumatology surgery	1739	34.70
Neurosurgery	811	16.18
Plastic and reconstructive surgery	792	15.81
General surgery	474	9.46
Cardiovascular surgery	403	8.04
Ophthalmology	353	7.04
Thoracic surgery	262	5.23
Pediatric surgery	99	1.98
Ear, nose and throat surgery	50	1.00
Urology	26	0.52
Gynecology and obstetrics surgery	2	0.04

811 procedures (16.18%), reflecting the frequency of head injuries and central nervous system trauma among war-injured patients. Plastic and reconstructive surgery ranked third, performing 792 operations (15.81%). These procedures were primarily related to soft tissue repair, burn injuries, and facial trauma commonly seen in war contexts. The general surgery department conducted 474 surgeries (9.46%), many of which likely involved emergency abdominal interventions due to penetrating or blunt trauma. Following this, cardiovascular surgery accounted for 403 interventions (8.04%), underscoring the complexity and severity of vascular injuries seen in war-wounded patients. The ophthalmology department performed 353 surgeries (7.04%), likely addressing globe injuries, orbital trauma, and other ocular complications caused by shrapnel or blast injuries. Thoracic surgery was involved in 262 cases (5.23%), frequently managing thoracic trauma such as rib fractures, hemothorax, or lung lacerations. Paediatric surgery accounted for 99 cases (1.98%), which, though less frequent, still indicates a concerning burden of war-related trauma among children. ENT surgeries were conducted in 50 cases (1.00%), and urology surgeries were conducted in 26 cases (0.52%), likely in response to complex trauma involving the genitourinary tract or head and neck. The gynecology and obstetrics department was the least represented, with only 2 procedures (0.04%), reflecting the trauma-focused nature of war-related surgical needs.

Demographic Characteristics of Patients Operated Under the "War Code"

Among the patients who underwent surgery due to war-related injuries, 91.59% were male and 8.41% were female. The overall mean age of this patient group was 26.45 years. When stratified by gender, the mean age was 26.72 years in males and 23.51 years in females.

In terms of age distribution, 17.84% of the patients were under the age of 18, indicating a notable proportion of paediatric patients affected by war-related trauma. These findings reflect the predominantly young and male profile of individuals exposed to and injured by conflict conditions requiring surgical intervention.

Discussion

Syria is one of the top three countries contributing most significantly to the global refugee population, and due to its geographic location, Türkiye is the country with the highest potential to host these refugees.[12] Following the outbreak of the civil war in 2011, the Syrian healthcare system suffered severe infrastructural damage, rendering it incapable of providing even basic medical services. Consequently, mortality rates in Syria have increased steadily since that year.[13] As a result, a large number of wounded individuals with high mortality risk were transferred to Türkiye, specifically to our hospital, for both surgical intervention and ongoing care.[14] Our hospital, located along Türkiye's southern border, has been significantly affected by the waves of migration since the onset of the Syrian civil war.[15] More than 90% of Syrian refugees living in border camps and approximately 60% of those residing outside the camps, have utilized Turkish healthcare services.[16] Nationwide, an estimated 1.5 million surgical procedures were performed on Syrian refugees during this period.[1] In our hospital, numerous Syrian patients-both from within the province and via cross-border referrals–received surgical treatment.

Over this 10-year period, both Turkish and Syrian patients received equitable access to surgical care in our facility, without any significant differences in the quality or extent of services provided. We attribute this to our hospital being the only center in the province capable of performing surgical procedures. In line with previous studies, our findings confirm that healthcare facilities in border regions serve as the primary providers of medical services for migrant populations.[15,17] Moreover, contrary to the findings of Khalifeh et al.,[18] our study revealed that in our region, migrants received surgical healthcare services to an extent equal to that of the local population. We believe this reflects not only the capacity of the Turkish healthcare system to provide high-quality care to Syrian migrants but also reflects a model that could guide other host countries in the region.

A review of the literature reveals that war affects not only combatants but also civilians. One study reported that 12% of war victims were children, while another indicated that 15% of children were affected by conflict.[19,20] In a study evaluating war victims based on age, the median

age was reported as 19 years.[21] In contrast, Aygün et al.[22] reported a median age of 12.7 years, whereas Babacan et al.[1] documented a median age of 28 years. We believe that these discrepancies in age distribution may be attributed to differences in study design. In our study, the overall mean age of patients was 31.28±20.33 years, which is higher than the average age of Syrian patients (28.90±18.45 years). Additionally, the mean age of Syrian migrants who underwent surgery under the war code was found to be even younger: 26.45 years. This may reflect the fact that younger individuals are more likely to be displaced during armed conflicts, whereas older adults may be less mobile.

A review of the literature suggests that the gender distribution of migrant patients presenting to hospitals is generally balanced.[1,21-23] However, in contrast to these findings, studies by Ağadayı et al.[24] and Tahirbegolli et al.[21] reported that male individuals were disproportionately more affected. In line with these latter findings, our study also revealed a statistically significant male predominance among Syrian migrant patients who underwent surgical procedures in our hospital, with 62.15% of the Syrian cohort being male. Among the war code-operated patients, the male proportion was even higher at 91.59%.

We believe that the primary reason for the observed male predominance among surgically treated Syrian migrants is that our hospital is the closest healthcare facility to both the border camps and active conflict zones. Consequently, many of the injured individuals were brought directly to our hospital for treatment. In addition, due to ongoing security concerns in the region, many migrants have settled permanently near the border, leading to a gradual increase in the number of female patients receiving surgical care over the years. Our findings demonstrated that gynecology and obstetrics emerged as the second most active surgical department, reflecting this shift. Notably, during this period, approximately half of the births in our hospital were among Syrian nationals, and in the later years of the study, the number of births among Syrian women surpassed those of Turkish women's.

One study reported that the pregnancy prevalence among women of reproductive age in migrant populations ranges between 6% and 14%.[10] Another study indicated that approximately 375,394 births occurred among Syrian migrants in Türkiye.[1] Erdoğan and Çorabatır [25] projected that by 2025, around 1.8 million Syrian babies will have been born in Türkiye. Similarly, Özkılıç et al.[26] observed a steady increase in the number of births among Syrian migrants. Consistent with these reports, our study revealed that the number of births among migrant women surpassed that of Turkish women over the study period.

In contrast to the findings of Ibrahim et al.,[27] we observed a decline in C/S rates among Syrian patients in our region. In our previous study, we attributed this trend to the cultural preference of migrants for vaginal delivery over C / S.[28] Globally, it has been reported that approximately 10% of the minimum essential surgical needs are related to obstetric complications, including cesarean delivery, postpartum hemorrhage, and ectopic pregnancy.[10] Furthermore, two previous studies reported that maternal-fetal obstetric procedures accounted for 17% to 43% of all surgical interventions.[29,30] Our study supports these findings by showing that even during periods of intense conflict, the majority of surgeries performed by the gynecology and obstetrics department were obstetric in nature. Additionally, despite the high birth rates and repeated cesarean deliveries among migrant women, we observed a remarkably low number of sterilization procedures such as tubal ligation. We speculate that this reluctance may be related to a desire to preserve fertility in the face of war, as a means of ensuring familial and cultural continuity.

Differences in surgical needs among migrant populations may vary depending on the type of humanitarian crisis encountered, such as natural disasters or armed conflict.[31] Ultimately, each crisis presents unique challenges, and surgical demands are context-specific. In our study, analysis of surgical procedures performed on migrant patients revealed that the three most frequently involved departments were orthopedics, gynecology, and obstetrics, and general surgery, in that order. This ranking was consistent with the data showing orthopedics and traumatology (20.63%), gynecology and obstetrics (17.51%), and general surgery (15.67%) as the most active departments.

It has been previously reported that approximately 5.7% of the refugee population in Türkiye has undergone surgery due to traumatic injuries.[32] Similarly, a recent study by Cakmak et al.[33] conducted in another regional hospital found that orthopedic surgeries were the most frequently performed procedures among Syrian refugees, with 59% related to extremity trauma. This high prevalence may be attributed to the inability of personal protective equipment to adequately shield limbs such as the arms and legs. Moreover, the nature of injuries sustained during wartime differs between civilians and military personnel. While soldiers are more commonly exposed to fatal penetrating injuries, civilians are more likely to experience blunt trauma, often as a result of environmental hazards or occupational accidents.[34,35] These patterns are reflected in our cohort, where orthopedic trauma surgeries constituted a significant proportion of operations among migrants.

Supporting this perspective, a study by Hornez et al.,[36] which shared surgical management experiences from the Syrian conflict, reported that 69% of the most common cases involved extremity surgeries managed by orthopedic departments. Likewise, Biswas et al.[37] in a study from Israel–

another neighboring country affected by the Syrian crisis-also identified extremity-related orthopedic surgeries as the most frequently performed procedures on Syrian migrants during the war period. Taken together, these findings highlight the predominant need for orthopedic surgical care among war-affected populations, both in Türkiye and in other regions. Our study aligns with the existing literature by confirming that orthopedic surgeries-particularly those related to extremity injuries-were the most commonly performed procedures among migrant patients in our hospital. However, unlike the study by Cakmak et al.,[33] which primarily focused on cost analysis, our study aimed to characterize the long-term surgical burden of migrants. This difference in focus may be considered a limitation of our study regarding economic evaluation.

When the general surgery procedures performed on migrants in our study were analyzed, emergency surgeries excluding appendectomy were found to be the most common interventions among Syrian patients, whereas appendectomy was more frequent among Turkish patients. This finding demonstrated that non-appendectomy emergency surgeries were significantly more frequent among Syrian migrants. Despite our hospital being located in a relatively small border province, the local population more than doubled within a year due to the influx of migrants. In the context of this significant demographic shift, it is important to note that prior research has suggested no racial or genetic differences in the incidence of appendicitis.[38] Consistent with this, our findings revealed that the proportion of appendectomy cases for Syrian migrants was lower than among Turkish patients, supporting the notion that ethnicity does not significantly influence the incidence of acute appendicitis.[5]

Children, being in a rapidly developing stage of life, represent one of the most vulnerable age groups–especially in the context of war. In our study, 25.54% of the Syrian migrant patients were under the age of 18, indicating a significant paediatric presence among the surgical cases. This finding is consistent with the study by Bucak et al.[39] While a previous study by Loucas et al.[40] reported that tonsillectomy and circumcision were the most common surgical procedures among migrant children, our study found that non-emergency surgeries, other than circumcision, were the most frequently performed paediatric procedures among Syrian patients. This finding aligns with another study conducted in a Turkish border region, which similarly reported a predominance of non-traumatic elective surgeries among migrant children.[41] Although due to our hospital's proximity to the border, a higher rate of paediatric trauma surgeries might have been expected, we observed a relatively low rate of paediatric trauma cases, likely due to the referral of severe trauma patients to tertiary care centers with specialized services.

Although the American Academy of Otolaryngology has identified hearing loss, thyroid, and parathyroid disorders as the most common conditions requiring surgical intervention in low- and middle-income countries, a review of the literature reveals a lack of studies investigating the surgical needs of migrants within the field of otolaryngology (ENT).[42] Existing data tend to focus on specific ENT-related conditions in migrant populations rather than their overall surgical burden.[43,44] In our study, the most frequently performed ENT procedures among Syrian migrants were tonsillectomy and adenoidectomy. Septorhinoplasty procedures were also performed, but at a lower frequency, reflecting a gradual shift towards quality-of-life-improving surgeries as integration into the host country progressed.

In times of crisis, both adults and children experience an increased need for ophthalmologic care, particularly in relation to visual impairments. One study highlighted that migrants have higher rates of visual impairment and blindness compared to host country populations.[45] The same study also reported that cataract was the most common cause of vision loss among individuals aged 20 to 40 years. Consistent with these findings, our study identified cataract surgery as the most frequently performed ophthalmologic procedure among Syrian migrants over the past decade. Penetrating and sharp object injuries were found to be the second most common cause for ophthalmologic intervention in this population, which we attribute to war-related ocular trauma. Despite the long-term settlement of many migrants in host communities, inadequate nutrition may continue to contribute to the development of cataracts. It is well established that vitamin deficiencies can predispose individuals to cataract formation, and supplementation may help prevent or delay this condition.[46]

Due to the high kinetic energy of bullets and shrapnel during wartime, not only the directly affected organs but also adjacent tissues may sustain significant damage. Saleh et al.[32] reported that 58% of trauma-related surgeries were due to injuries from bombs and firearms. Similarly, in a study by Cakmak et al.,[33] intestinal injuries were found to be the most common outcome of gunshot wounds. Aras et al.,[47] in their study involving 186 patients with firearm-related injuries, emphasized the critical importance of timely and effective surgical intervention. In a previous study conducted in our hospital during the peak of the Syrian civil war, Kocamer Şimşek et al.[48] reported that the neurosurgery department had the highest mortality rate among all surgical units. In our study, the most frequently involved surgical specialties for patients operated under the "war code" were, in descending order, orthopedics, neurosurgery, plastic and reconstructive surgery, general surgery, and cardiovascular surgery. This distribution underscores the severity and complexity of war-related injuries and highlights the indispensable role of multidisciplinary surgical teams.

Given the complexity and severity of such cases, it is essential that border hospitals in countries with high capacity to treat this patient population are equipped not only with advanced medical infrastructure but also with highly trained and experienced personnel. The results of our study support this need. Among patients who underwent surgery under the war code, the mean age corresponded to 26-45 years, reflecting young adulthood; there was a statistically significant male predominance, with 91.59% of these patients being male, which is consistent with previous literature.[49,50] We believe this gender imbalance reflects the fact that many men remained in the conflict zones to fight, resulting in a higher proportion of male casualties requiring surgical care.

Study Limitations

One of the main limitations of this study is its single-center design. As the data were derived from a single public hospital located on the Türkiye-Syria border, the findings may not be fully generalizable to other healthcare settings, regions, or populations with different demographic or institutional characteristics.

This study did not include an economic evaluation of the surgical services provided. As a result, the potential implications regarding the cost-effectiveness or cost-benefit of delivering such healthcare to migrant populations remain unexplored. Future studies incorporating economic assessments would be valuable to guide resource allocation and policy-making in similar high-demand, low-resource healthcare environments.

The most important limitation of our study is that it was conducted at a single tertiary care center, which may limit the generalizability of the findings. There is a pressing need for more comprehensive, multi-center studies evaluating surgical healthcare services provided to migrant and refugee populations in both secondary and tertiary hospitals. Although the retrospective design of our study is a limitation, its strengths include a large sample size, and the fact that, to our knowledge, no other study in Turkiye has addressed this topic in such depth.

In the future, prospective studies are warranted to better assess long-term surgical outcomes and postoperative complication rates. Such studies will contribute valuable data on access to surgical care and the quality of postoperative follow-up for migrant populations, ultimately guiding the improvement of healthcare delivery for displaced individuals.

Conclusion

As a result of global migration movements, the prevalence of surgical conditions is notably high among refugee populations. However, a substantial proportion of displaced individuals are forced to seek medical care in countries with limited surgical capacity. Our study highlights the surgical burden imposed by war-related injuries and prolonged humanitarian crises on migrant populations. In this context, the effective management of surgical healthcare needs among migrants requires experienced medical teams, robust healthcare infrastructure, and a multidisciplinary approach within a well-organized system. For healthcare services in border-region hospitals to be more effectively planned and delivered, it is essential to maintain accurate patient records and analyze the distribution of surgical interventions. These data can help us better understand the surgical needs of migrant populations and serve as a foundation for developing responsive and sustainable health policies. Therefore, strategic efforts should be made to train healthcare professionals working in border areas and to strengthen hospital infrastructure in these high-demand regions. Finally, it is important to note that due to limitations in data accessibility, Turkish patient records for the first quarter of 2010 were unavailable, resulting in a three-month underrepresentation of surgeries performed on Turkish nationals.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of Gaziantep University Faculty of Medicine (approval no: 2019/486, date: 05.02.2020).

Informed Consent: Due to the retrospective nature of the study, an informed consent was not required.

Footnotes

Author Contributions: Surgical and Medical Practices – E.M., N.G.; Concept - E.M., N.G.; Design - E.M., N.G.; Data Collection and/or/Processing - E.M., N.G.; Analysis and/or/Interpretation - E.M., N.G.; Literature Review - E.M., N.G.; Writing - E.M., N.G.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

References

1. Babacan T, Yılmaz TE, Babacan MT, et al. Evaluation of immigrant health services in Turkey: a single-center study. *Journal of Public Health.* 2022;30(10):2491-2498. [CrossRef]
2. T.C. İçişleri Bakanlığı Göç İdaresi Genel Müdürlüğü, 2016 Türkiye Göç Raporu 2016 Available from: https://www.goc.gov.tr/kurumlar/goc.gov.tr/files/2016_yiik_goc_raporu_haziran.pdf [CrossRef]
3. Ören B, Dağcı S, Kızılay V. Socio-demographic characteristics of asylum seekers in Turkey and reasons for referral to the hospital: the İstanbul example. *1.Uluslararası 4.Ulusal Kültürlerarası Hemşirelik Kongresi.* 2018. [CrossRef]
4. Ergin AD, Kader Y. Temporariness in international protection and temporary protection regime: what is "temporary" ? *İnsan Hakları Yıllığı.* 2025;42(2):79-122. [CrossRef]

5. Aksakal İ. Syrian refugees in Turkey: its impact on Turkish social structure and nation state policy. *KAUJISS.* 2022;30, 671-690. [CrossRef]
6. Zeren C, Arslan M, Aydogan A, Ozkalipci O, Karakuş A. Firearm injuries documented among Syrian refugees in Antakya Turkey. *BJASS.* 2012;5(1):1-5. [CrossRef]
7. Döner P, Ozkara A, Kahveci R. Syrian refugees in Turkey: numbers and emotions. *Lancet.* 2013;382(9894):764. [CrossRef]
8. Orhan O, Gündoğar SS. Suriyeli sığınmacıların Türkiye'ye etkileri. *ORSAM-TESEV;* Rapor no: 195, 2015. [CrossRef]
9. Gokalp Aras NE, Sahin Mencutek Z. The international migration and foreign policy nexus: the case of Syrian refugee crisis and Turkey. *Migration Letters.* 2015;12(3):193-208. [CrossRef]
10. Zha Y, Stewart B, Lee E, et al. Global estimation of surgical procedures needed for forcibly displaced persons. *World J Surg.* 2016;40(11):2628-2634. [CrossRef]
11. Meara JG, Leather AJ, Hagander L, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *The Lancet.* 2015;386(9993):569-624. [CrossRef]
12. UNHCR. Refugee data finder. 2021. Available from: https://www.unhcr.org/refugee-statistics
13. Price M, Gohdes A, Ball P. Updated statistical analysis of documentation of killings in the Syrian Arab republic. *HRDAG, Geneva.* 2014:14-15. [CrossRef]
14. Hanedan M, Ketenciler S, Ercişli A, et al. Civil war surgical experience: gun shot or shell fragment injuries.*Turk J Vasc Surg.* 2014;23(1):1-4. [CrossRef]
15. Ekmekci PE. Syrian refugees, health and migration legislation in Turkey. *J Immigr Minor Health.* 2017;19(6):1434-1441. [CrossRef]
16. Duramaz A, Bilgili MG, Bayram B, Ziroğlu N, Bayrak A, Avkan MC. Orthopedic trauma surgery and hospital cost analysis in refugees; the effect of the Syrian civil war. *Int Orthop.* 2017;41(5):877-884. [CrossRef]
17. Kepekci AB. The effects of Syrian immigrants on our health system: Kilis state hospital operating room case profile changes over years. *EJMI.* 2019;3(2):127-131. [CrossRef]
18. Khalifeh R, D'Hoore W, Saliba C, Salameh P, Dauvrin M. experiences of cultural differences, discrimination, and healthcare access of displaced Syrians (DS) in Lebanon: a qualitative study. *Healthcare (Basel).* 2023;11(14):2013. [CrossRef]
19. Helweg-Larsen K, Abdel-Jabbar Al-Qadi AH, Al-Jabriri J, Brønnum-Hansen H. Systematic medical data collection of intentional injuries during armed conflicts: a pilot study conducted in West Bank, Palestine. *Scand J Public Health.* 2004;32(1):17-23. [CrossRef]
20. Hebrang A, Henigsberg N, Golem AZ, Vidjak V, Brnić Z, Hrabac P. Analiza zbrinjavanja vojnih i civilnih ranjenika u ratnoj agresiji na republiku Hrvatsku [care of military and civilian casualties during the war in Croatia]. *Acta Med Croatica.* 2006 Sep;60(4):301-307. [CrossRef]
21. Tahirbegolli B, Çavdar S, Çetinkaya Sümer E, Akdeniz SI, Vehid S. Outpatient admissions and hospital costs of Syrian refugees in a Turkish university hospital. *Saudi Med J.* 2016;37(7):809-812. [CrossRef]
22. Aygün O, Gökdemir Ö, Bulut Ü, Yaprak S, Güldal D. Evaluation of primary health care services which is provided to refugees within a public health center. *TJFMPC.* 2016;10(1):6-12. [CrossRef]
23. Gulacti U, Lok U, Polat H. Emergency department visits of Syrian refugees and the cost of their healthcare. *Pathog Glob Health.* 2017;111(5):219-224. [CrossRef]
24. Ağadayı E, Özer Küçük E, Demir Alsancak A, Gönderen Çakmak S, Kahveci R. Retrospective analysis of electronic medical records of Syrian immigrants admitted to a training and research hospital in Turkey. *TJCL.* 2018;9(4):307-312. [CrossRef]
25. Erdoğan MM, Çorabatır M. Suriyeli mülteci nüfusunun demografik gelişimi, Türkiye'deki eğitim, istihdam ve belediye hizmetlerine yakın gelecekte olası etkileri. *İGAM-UDRA Programme Research Panel.* 2019. [CrossRef]
26. Özkılıç Y, Türe Z, Çelik İ. A single center experience of refugees in a developing country. *JAMER.* 2022;7(3):77-83. [CrossRef]
27. Ibrahim N, Zein M, Abdel Sater AH, El Khatib O, Tayyara L. Syrian refugees seeking hospital care in beirut: a cross-sectional study of reasons for hospital admissions. *Cureus.* 2023;15(7):e42276. [CrossRef]
28. Gumusburun N, Mendes E. The impact of immigrants on the number and type of births. *Makara J Health Res.* 2024;28(3):187-192. [CrossRef]
29. Wong EG, Trelles M, Dominguez L, Gupta S, Burnham G, Kushner AL. Surgical skills needed for humanitarian missions in resource-limited settings: common operative procedures performed at Médecins Sans Frontières facilities. *Surgery.* 2014;156(3):642-649. [CrossRef]
30. Trudeau MO, Baron E, Hérard P, et al. Surgical care of pediatric patients in the humanitarian setting: the médecins sans frontières experience, 2012-2013. *JAMA Surg.* 2015;150(11):1080-1085. [CrossRef]
31. Sharma D, Hayman K, Stewart BT, et al. Care of surgical infections by Médecins Sans Frontières Operations Centre Brussels in 2008-14. *Lancet.* 2015;385(Suppl 2):S31. [CrossRef]
32. Saleh A, Aydin S, Koçak O. A comparative study of Syrian refugees in Turkey, Lebanon, and Jordan: healthcare access and delivery. *OPUS JSR.* 2011;8(14):448-464. [CrossRef]
33. Cakmak F, Ipekci A, Karakus Yilmaz B, Biberoglu S, Akdeniz Y, Ikizceli I. Distribution and cost of Syrian refugees operated on in Southeastern Anatolia, Turkey. *East Mediterr Health J.* 2021;27(12):1137-1141. [CrossRef]
34. Karaarslan B, Uysal C, Celikel A, et al. Evaluation of the death cases occurred as a result of injury during war. Acta Med Mediterr. 2014;30(4):797-800. [CrossRef]
35. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma.* 1995;38(2):185-193. [CrossRef]
36. Hornez E, Ramiara P, Mocellin N, et al. Surgical management of Syria's war casualties: experience from a French surgical team deployed in the Zaatari refugee camp (Jordan). *Eur J Trauma Emerg Surg.* 2015;41(2):143-147. [CrossRef]
37. Biswas S, Waksman I, Baron S, et al. Analysis of the first 100 patients from the Syrian civil war treated in an Israeli district hospital. *Ann Surg.* 2016;263(1):205-209. [CrossRef]
38. Karagöz Eren S, Dönder Y. Comparison of complicated appendicitis rates between refugees and local patients. *Ulus Travma Acil Cerrahi Derg.* 2022;28(1):62-68. [CrossRef]
39. Bucak IH, Almis H, Benli S, Turgut M. An overview of the health status of Syrian refugee children in a tertiary hospital in Turkey. *Avicenna J Med.* 2017;7(3):110-114. [CrossRef]
40. Loucas M, Loucas R, Muensterer OJ. Surgical health needs of minor refugees in Germany: a cross-sectional study. *Eur J Pediatr Surg.* 2018;28(1):60-66. [CrossRef]
41. User IR, Ozokutan BH. Common pediatric surgical diseases of refugee children: health around warzone. *Pediatr Surg Int.* 2019;35(7):803-806. [CrossRef]
42. Jaradeh K, Tang A, Czechowicz JA, Jacobson L, Raphael E. Prevalence of otolaryngological disease in a refugee population compared to US-born patients. *Laryngoscope Investig Otolaryngol.* 2023;8(2):394-400. [CrossRef]
43. Benson J, Mwanri L. Chronic suppurative otitis media and cholesteatoma in Australia's refugee population. *Aust Fam Physician.* 2012;41(12):978-980. [CrossRef]
44. Masters PJ, Lanfranco PJ, Sneath E, et al. Health issues of refugees attending an infectious disease refugee health clinic in a regional Australian hospital. *Aust J Gen Pract.* 2018;47(5):305-310. [CrossRef]

45. Ahmed M, Whitestone N, Patnaik JL, et al. Burden of eye disease and demand for care in the Bangladesh Rohingya displaced population and host community: a cohort study. *PLoS Med.* 2020;17(3):e1003096. [CrossRef]

46. Zhao LQ, Li LM, Zhu H, The epidemiological evidence-based eye disease study research group ey. The effect of multivitamin/mineral supplements on age-related cataracts: a systematic review and meta-analysis. *Nutrients.* 2014;6(3):931-949. [CrossRef]

47. Aras M, Altaş M, Yilmaz A, et al. Being a neighbor to Syria: a retrospective analysis of patients brought to our clinic for cranial gunshot wounds in the Syrian civil war. *Clin Neurol Neurosurg.* 2014;125:222-228. [CrossRef]

48. Kocamer Şimşek B, Dokur M, Uysal E, et al. Characteristics of the injuries of Syrian refugees sustained during the civil war. *Turkish Journal of Trauma and Emergency Surgery.* 2017;23(3):199-206. [CrossRef]

49. Er E, Çorbacıoğlu ŞK, Güler S, et al. Analyses of demographical and injury characteristics of adult and pediatric patients injured in Syrian civil war. *Am J Emerg Med.* 2017;35(1):82-86. [CrossRef].

50. Arafat S, Alsabek MB, Ahmad M, Hamo I, Munder E. Penetrating abdominal injuries during the Syrian war: patterns and factors affecting mortality rates. *Injury.* 2017;48(5):1054-1057. [CrossRef]

DOI: 10.4274/TJAR.2025.241584

Case Report
Thoracic Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2025;53(5):277-279

Anaesthesia Management of a Case with Hereditary Angioedema for Whom Tracheal Dilatation was Planned

Muharrem Uçar[1], Mukadder Şanlı[1], Sezai Aktürk[1], İlham Gülçek[2], Feray Akgül Erdil[1]

[1]İnönü University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Malatya, Türkiye
[2]İnönü University Faculty of Medicine, Department of Thoracic Surgery, Malatya, Türkiye

Cite this article as: Uçar M, Şanlı M, Aktürk S, Gülçek İ, Akgül Erdil F. Anaesthesia management of a case with hereditary angioedema for whom tracheal dilatation was planned. *Turk J Anaesthesiol Reanim.* 2025;53(5):277-279.

Abstract

Hereditary angioedema (HAE) causes recurrent angioedema attacks in the oropharynx, larynx, face, and other regions due to bradykinin overproduction as a result of C1 esterase inhibitor deficiency. Surgical interventions requiring general anaesthesia might trigger HAE attacks. Laryngeal angioedema is the most important cause of perioperative mortality. Tracheal dilatation was performed by rigid bronchoscopy in our patient with type 1 HAE, because of tracheal stenosis due to prolonged intubation, which occurred after the attack. The patient was administered 2x500 IU C1 esterase inhibitor approximately 24 hours before rigid bronchoscopy. No complication developed after the first procedure. Two months later, tracheal dilatation was repeated and 2x500 IU C1 esterase inhibitor was administered. While the patient was followed up in the intensive care unit, significant oedema developed in the facial area, especially the tongue and lips, approximately 10 hours after the procedure. Our patient also had stridor due to airway obstruction. The patient was treated with 1000 IU C1 esterase inhibitor and 3 units of fresh frozen plasma (FFP). After FFP, edema started to regress. The patient was discharged after symptoms improved. The patient should be monitored in the intensive care unit for a minimum of 48 hours to monitor for postoperative laryngeal oedema.

Keywords: Complement C1 inhibitor protein, fresh frozen plasma, hereditary angioedema, tracheal stenoses

Main Points

- Hereditary angioedema causes recurrent angioedema attacks in the oropharynx, larynx, and face.
- Laryngeal angioedema is the most important cause of perioperative mortality.
- Hereditary angioedema may develop even after uneventful anaesthesia and surgery.
- Hereditary angioedema requires good preoperative preparation, careful intraoperative follow-up, and postoperative care.

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by C1 esterase inhibitor deficiency, leading to increased bradykinin production. C1 esterase inhibitor deficiency causes recurrent angioedema attacks in the oropharynx, larynx, face, and other areas via bradykinin. This angioedema can be seen in the larynx during upper airway manipulation such as tracheal intubation. Laryngeal angioedema is the most important cause of perioperative mortality. Its treatments are either the C1 esterase inhibitor or fresh frozen plasma (FFP).[1,2]

In this case report, we aimed to present the anaesthesia management of a patient with HAE, for whom tracheal dilatation was planned due to tracheal stenosis.

Corresponding author: Muharrem Uçar, MD, e-mail: umuharrem@hotmail.com

Received: April 02, 2024 Accepted: August 01, 2025
Epub: September 18, 2025 Published date: October 14, 2025

Case Report

The patient was a 43-year-old female with a weight of 105 kg and a height of 165 cm. The thoracic surgeon planned rigid bronchoscopy under general anaesthesia with the preliminary diagnosis of tracheal stenosis. Our patient was diagnosed with type 1 HAE. In the anamnesis of the case, she had two attacks due to HAE. In the first case, improvement was achieved with medical treatment. After the second attack, the patient was intubated due to spontaneous swelling of the tongue, and then a tracheostomy was opened. She remained intubated for 18 days. Her physical examination revealed no symptoms other than shortness of breath. Laboratory findings were as follows. Glucose: 135 mg dL^{-1}, Hgb: 12.6 g dL^{-1}, Sed: 25, and other parameters were normal. Before rigid bronchoscopy, 2x500 IU C1 esterase inhibitor (CINRYZE 500 IU/5 mL IV) was administered to the patient approximately 24 hours before the procedure. The patient was standard monitored in the operating room and, considering that difficult intubation may develop due to laryngeal edema, it was decided that a C-MAC D blade video laryngoscope, tracheostomy preparation, C1 esterase inhibitor, and FFP were to be kept ready in the room. A 20 G vascular access was established for the patient. 1 mg kg^{-1} lidocaine, 1 µg kg^{-1} fentanyl, 2 mg kg^{-1} propofol, and 0.6 mg kg^{-1} rocuronium were administered IV through the vascular access. The patient was ventilated using a face mask to avoid creating pressure on the face. After muscle relaxation, the thoracic surgeon used a rigid bronchoscope no. 6.5. The vocal cords were traversed and the trachea was entered. The standard anaesthesia circuit was connected to the side inlet of the rigid bronchoscope, and ventilation was provided with 100% oxygen with intermittent positive pressure. Anaesthesia was maintained with intermittent IV pushes of propofol and rocuronium. During the procedure, the patient's mean arterial pressure was between 60-70 mmHg and SpO_2 was between 95-98%. A stenosis of approximately 2 cm in length, 1 cm past the vocal cords, was observed, and dilation was performed with a rigid bronchoscope number no 7.5. After the procedure, the patient was awakened without any problems after applying 2 mg kg^{-1} sugammadex, and was sent to the intensive care unit. The patient's general condition was good during follow-up and she was discharged. Two months later, rigid bronchoscopy was successfully performed again to dilate the trachea. The same prophylactic treatment of 2x500 IU C1 esterase inhibitor was applied before the operation. Approximately 10 hours after the operation, the patient in the intensive care unit developed significant edema in the facial area, primarily the tongue and lips. In addition, our patient had stridor due to airway stenosis. The patient was treated with 1000 IU C1 esterase inhibitor and 3 units of FFP. After FFP, edema started to regress. The patient was discharged after her symptoms improved.

Discussion

Operations requiring general anaesthesia might trigger HAE attacks. The use of inhalation and intravenous anaesthetic drugs in cases with bradykinin-mediated angioedema is not contraindicated.[3] We used propofol as an anaesthetic agent in the induction and maintenance of our patient and did not encounter any problems.

Upper airway manipulation and tracheal intubation may trigger upper airway and laryngeal angioedema. Laryngeal edema is the most serious complication of HAE.[3,4] It was reported that life-threatening airway angioedema attacks are rare, although they may occur in patients receiving short-term prophylaxis and in those who have previously received anaesthesia without problems.[3] We did not encounter any problems in anaesthesia management.

Treatment of HAE: the aim of the treatment includes increasing C1-INH levels and inhibiting the effects of kallikrein, bradykinin, and plasmin.[3,5,6] If concentrate is not available, it is recommended to use plasma treated with solvent/detergent 1-6 hours before the procedure, or if this is not available, it is recommended to use treatment with FFP.[2] One unit of C1-INH concentrate corresponds to the average amount of C1-INH found in 1 mL of fresh normal plasma.[6]

Trigger sensitivity varies among patients with HAE. While triggers vary from patient to patient, common triggers include trauma, medical procedures, and stress. Physical trauma is a prominent and common threat to the larynx.[4] It has been reported that laryngeal oedema may occur more than 2 days later, and therefore postoperative monitoring is important.[2,7-9] Since FFP contains all of the clotting factors and C1 INH, it can be used in the treatment of acute HAE attacks.[4,10,11] FFP is used to treat acute HAE attacks, especially in countries where C1-INH concentrate is not available.[9,11] The recommended dosage for FFP application in the treatment of HAE attacks is 10-20 mL kg^{-1}, with an average use of 1-2 units.[7,10,11] Our patient also developed acute and severe angioedema in the intensive care unit approximately 10 hours postoperatively. The treatment of acute HAE, we administered the second dose of C1 INH and FFP to our patient. Fresh frozen plasma carries the risk of worsening attacks with the addition of contact pathway proteins.[1,3,6,10,11] The FFP we applied to our patient did not worsen the attacks, but instead treated them, and we did not encounter any side effects.

Conclusion

HAE requires caution because of the risk of developing laryngeal edema. It should be anticipated that postoperative HAE may develop even after an uneventful anaesthetic event and surgery. It should be kept in mind that these

cases require thorough preoperative preparation, careful intraoperative follow-up, and postoperative care.

Ethics

Informed Consent: The complete procedure was explained to the patient, and informed consent was obtained.

Footnotes

Author Contributions: Surgical and Medical Practices - İ.G.; Concept - F.A.E.; Design - M.U.; Data Collection or Processing - M.Ş., S.A.; Analysis and/or/Interpretation - M.Ş.; Literature Review - M.U., F.A.E.; Writing - M.U.

Declaration of Interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Dewachter P, Kopac P, Laguna JJ, et al. Anaesthetic management of patients with pre-existing allergic conditions: a narrative review. *Br J Anaesth*. 2019;123(1):e65-e81. [CrossRef]
2. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77(7):1961-1990. [CrossRef]
3. Caballero T. Treatment of hereditary angioedema. *J Investig Allergol Clin Immunol*. 2021;31(1):1-16. [CrossRef]
4. Sinnathamby ES, Issa PP, Roberts L, et al. hereditary angioedema: diagnosis, clinical implications, and pathophysiology. *Adv Ther*. 2023;40(3):814-827. [CrossRef]
5. Barata M, Marques A, Tiago C, Dias-Vaz M, Losa N, Oliveira C. Anesthetic management of a patient with acquired angioedema submitted to broncofibroscopy: a case report. *Braz J Anesthesiol*. 2023;73(4):500-502. [CrossRef]
6. Zafra H. Hereditary angioedema: a review. *WMJ*. 2022;121(1):48-53. [CrossRef]
7. Aroufi W, Pavageau C, Sturque J, Zlowodzki AS, Georgescou G, Denis F. Hereditary angioedema type II and dental extraction: case report and literature review. *J Oral Med Oral Surg*. 2020;26:29. [CrossRef]
8. de Valle MK, Stevenson C, Adkison M, Delaune C, Defilippis N, Murugan S. Hereditary angioedema in pregnancy: a case report and review of obstetric anesthesia management. *A A Pract*. 2024;18(9):e01833. [CrossRef]
9. Williams AH, Craig TJ. Perioperative management for patients with hereditary angioedema. *Allergy Rhinol (Providence)*. 2015;6(1):50-55. [CrossRef]
10. Wentzel N, Panieri A, Ayazi M, et al. Fresh frozen plasma for on-demand hereditary angioedema treatment in South Africa and Iran. *World Allergy Organ J*. 2019;12(9):100049. [CrossRef]
11. Hébert J, Boursiquot JN, Chapdelaine H, et al. Bradykinin-induced angioedema in the emergency department. *Int J Emerg Med*. 2022;15(1):15. [CrossRef]