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Artificial Intelligence in Anaesthesiology: Current Applications, Challenges, and Future Directions
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Turkish Journal of Anaesthesiology & Reanimation

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Artificial Intelligence and Large Language Models: Editorial Reflections

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The *Turkish Journal of Anaesthesiology and Reanimation* reflects current developments in anaesthesiology through the scientific work that emerges organically from the field, rather than through predefined thematic or special issues. Each issue therefore represents a snapshot of the academic and clinical interests shaping the discipline at a given time. As a result, certain subjects may assume greater visibility within individual issues. While research on regional anaesthesia featured prominently in a recent issue, artificial intelligence (AI) has attracted similar attention in the present volume. This pattern should be understood as a reflection of evolving priorities within anaesthesiology, rather than as the outcome of editorial direction.

Such convergence allows the editorial board to step back from thematic labeling and instead engage in critical appraisal. Examining emerging trends, placing them in appropriate context, and encouraging scholarly discussion on their relevance to clinical practice and education form a core part of this editorial role. In the present issue, Dost et al.[1] contribute a narrative review that maps the current and potential applications of AI in anaesthesiology and reanimation, offering a broad clinical and conceptual overview. Alongside this, an original study examines the performance of an AI based model in an assessment format modeled on international anaesthesiology examinations.[2] Although distinct in design and scope, both articles provide a forward-looking perspective and invite reflection on the changing role of AI in clinical work and medical training.

The journal's position on the use of AI in scientific publishing, particularly large language models (LLMs), is grounded in transparency, methodological rigor, and scientific responsibility. These tools are neither inherently advantageous nor intrinsically problematic; their value depends on how they are used and reported.[3] Submissions involving LLMs are therefore expected to clearly define their role and limitations, and to meet standards that safeguard academic integrity and reproducibility.

The use of LLMs in defining a research question or shaping study methodology fundamentally undermines the originality of a study, even when the final version of the manuscript is written independently and appears novel in the literature, and is therefore not recommended. Similarly, assigning statistical analyses directly to LLMs is not currently considered appropriate; however, as contemporary models increasingly rely on the infrastructure of established professional statistical software, this perspective may evolve provided that outputs are independently validated. The increasing availability of AI-supported and commercially established online statistical platforms also suggests that AI-assisted data analysis may soon become more common, reinforcing the need for transparency and validation.

By contrast, the use of LLMs for language revision is supported and encouraged, provided that the human character and stylistic integrity of the text are preserved. We do not intend to revive earlier debates on this issue; when transparently declared in the acknowledgements, employing such tools for linguistic refinement may be both practical and beneficial. However, delegating the writing of an entire manuscript to LLMs—an approach we have

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unfortunately encountered in submissions to the journal—may result in hallucinated content, fabricated references, and text that is uniform, repetitive, and lacking the practical reasoning characteristic of human intelligence. In addition, authors should carefully consider issues of data security and confidentiality, as sharing unpublished data, original analyses, or proprietary material with AI platforms may inadvertently expose sensitive information, increase the risk of misuse, or compromise intellectual ownership.

Beyond our views on the use of AI and LLMs in clinical research and reporting, it is also appropriate to address expectations and observations looking ahead. Much like the surge of Coronavirus Disease 2019 (COVID-19)-related publications during the pandemic, studies exploring the use of AI across different areas of medicine have recently attracted considerable attention. This rapid expansion has led to a noticeable inflation within the literature, making critical appraisal and scientific selectivity increasingly important. Just as the readability and clinical relevance of COVID-19-related publications declined once the acute phase of the pandemic subsided, a similar trajectory may await AI-related manuscripts when AI becomes a routine component of daily clinical practice rather than an emerging novelty. For this reason, the journal will not favor studies that merely repeat existing knowledge, lack clear clinical relevance, or represent short-lived trends likely to fade after brief discussion. Instead, priority will be given to work that openly addresses its limitations, offers new perspectives for future research, questions the role of AI, or challenges it to improve. Studies conducted with appropriate methodology and high scientific quality, including those engaging with AI at a conceptual or philosophical level, will be welcomed.

Popularity alone will not justify overlooking scientific standards.

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Review Article
Perioperative Care

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Artificial Intelligence in Anaesthesiology: Current Applications, Challenges, and Future Directions

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Abstract

Artificial intelligence (AI) is rapidly transforming anaesthesiology through advances in machine learning, deep learning, and large language models. AI-driven tools now contribute to nearly every phase of perioperative care, including preoperative risk stratification, intraoperative monitoring, imaging interpretation, airway assessment, regional anaesthesia, and critical care. Applications such as automated American Society of Anesthesiologists classification, prediction of postoperative complications and intensive care unit needs, electroencephalography-based depth-of-anaesthesia estimation, and proactive haemodynamic management are reshaping clinical decision-making. AI-augmented echocardiography enhances chamber recognition and functional measurements, whereas computer vision systems support airway evaluation and ultrasound-guided regional anaesthesia by providing real-time anatomical identification and facilitating training. In critical care, AI models facilitate the early detection of sepsis, organ dysfunction, and haemodynamic instability, while improving workflow efficiency and resource allocation. AI is increasingly used in academic writing, data processing, and medical education, offering opportunities for personalised learning and simulation but raising concerns about accuracy and hallucinations. In this review, we aimed to summarise the current applications of AI in anaesthesiology, highlight the methodological, ethical, and practical challenges that limit its integration, and discuss future directions for its safe and effective adoption in perioperative care.

Keywords: Airway management, artificial intelligence, intensive care, neuroanaesthesia, perioperative care, pharmacology, regional anaesthesia

Main Points

- Artificial intelligence (AI) is increasingly being integrated into all phases of perioperative care, including preoperative assessment, monitoring, airway management, regional anaesthesia, and critical care.
- AI-driven tools can enhance prediction of perioperative risks, estimation of anaesthetic depth, optimisation of haemodynamics, and interpretation of imaging, potentially improving safety and precision.
- AI is becoming widely used in academic writing, education, and clinical decision support, but requires careful oversight to avoid inaccuracies and hallucinated content.
- AI will not replace anaesthesiologists, but is expected to augment clinical judgment and shift the specialty toward a more cognitive, supervisory, and data-informed practice.
- Future progress requires multicentre validation, transparent reporting, robust regulations, and structured AI training for clinicians to ensure safe, ethical, and effective integration.

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Introduction

Artificial intelligence (AI) is a branch of computer science dedicated to developing software and hardware capable of simulating human cognitive functions, such as problem solving, object recognition, reasoning, and decision-making.[1] The term AI was first introduced by John McCarthy in 1956, who defined it as "the science and engineering of making intelligent machines."[2] In 2024, the Nobel Prize in Physics was awarded to John J. Hopfield and Geoffrey E. Hinton for their pioneering work on artificial neural networks, which underpin modern clinical decision support systems, patient-monitoring algorithms, and data-driven anaesthesia technologies.[3] In the same year, the Nobel Prize in Chemistry recognised the transformative impact of AI on computational protein structure predictions. DeepMind's AI-based system, AlphaFold, which accurately predicts the three-dimensional (3D) structure of proteins, has opened new frontiers in biomedical research. This innovation has remarkable potential for anaesthesiology, including identifying novel drug targets (e.g., G-protein-coupled receptors and ion channels), modelling anaesthetic-receptor interactions, accelerating drug discovery, and predicting toxicity or adverse effects.[4]

To understand how these systems operate across diverse domains, it is essential to outline the fundamental concepts that underpin modern AI. Machine learning (ML) refers to systems that learn patterns and relationships from data without being explicitly programmed. Deep learning (DL), a subfield of ML, uses multi-layered artificial neural networks to enable hierarchical feature extraction and complex pattern recognition in data. Natural language processing (NLP) focuses on enabling machines to understand and generate human language. Depending on the learning paradigm, AI models can be trained in different ways: in supervised learning, they learn from labelled data with known outcomes; in unsupervised learning, they identify hidden structures or clusters without prior labels; in reinforcement learning, they improve performance through trial and error by maximizing a defined reward signal.[5]

Since its conceptual origins, AI has evolved across multiple domains; however, the introduction of transformer-based architectures in 2018 (e.g., GPT-1) marked a major turning point in this field. Building on these foundations, the advent of multimodal large language models (LLMs) in 2025 enabled AI systems to process and integrate diverse data modalities, including text, medical images, audio signals, and video recordings, thereby opening a new era of multimodal intelligence. In medicine, such models support imaging interpretation, drug discovery, diagnostic reasoning, treatment optimisation, and even surgical automation.[6] Within anaesthesiology, AI applications are rapidly expanding across the perioperative continuum, prompting the question of whether intelligent systems may complement or even replace human anaesthesiologists.

In this review, we aimed to summarise the current applications of AI in anaesthesiology, to discuss its methodological and ethical challenges, and to explore future directions for its integration into perioperative care.

Preoperative Assessment

The preoperative period represents a critical opportunity to enhance patient safety, anticipate perioperative risks, and optimise healthcare resources. By synthesising data on patient demographics, comorbidities, laboratory findings, and surgical variables, AI-driven systems can assist clinicians in identifying high-risk patients and predicting postoperative complications earlier and more accurately than conventional methods. This growing integration positions AI not only as a supportive analytical tool but also as a potential partner in clinical reasoning, capable of standardising decision-making in a field where subjective variability has long influenced outcomes.

One of the most fundamental risk classification systems used preoperatively is the American Society of Anesthesiologists (ASA) physical status classification. The ASA score has long been used as an important reference for predicting surgical mortality and morbidity. In a prospective study, ChatGPT-4 was evaluated in 2,851 patients and achieved a kappa score of 0.858, indicating almost perfect agreement with anaesthesiologists for ASA classification.[7] In another study, ChatGPT was evaluated in 203 paediatric patients and achieved a kappa score of 0.72, indicating substantial agreement with anaesthesiologists.[8] An algorithm developed using ML, based on data from 12,064 patients, achieved a 70.4% accuracy.[9] These results suggest that AI systems can approximate anaesthesiologists' decision-making in preoperative risk assessment consistently. ASA scoring can vary significantly among anaesthesiologists, which should be taken into account when evaluating the results of these studies.

Depth of Anaesthesia

The optimal depth of anaesthesia is defined as a state in which unconsciousness, analgesia, and immobility are achieved without excessive sedation. Maintaining this equilibrium remains one of the most intricate challenges in contemporary anaesthesiology. Conventional practice continues to rely largely on physiological indicators, such as mean arterial pressure (MAP) and heart rate; however, the neuronal dynamics underlying consciousness extend far beyond the information these parameters can provide.

Electroencephalography (EEG) offers real-time insights into neuronal activity and enables the estimation of anaesthetic depth through characteristic waveform patterns. However, its clinical interpretation remains constrained by interindividual variability, the combined effects of anaesthetic agents, and the non-linear relationship between cortical activity and the level of consciousness.[10,11] In recent years, data-driven AI-based approaches have emerged to overcome these limitations in EEG analysis. Unlike conventional systems, such as the bispectral index, entropy, or patient state index, which rely on predefined mathematical models, ML algorithms can extract complex temporal and spectral features directly from EEG signals. Among these, convolutional neural networks (CNNs) and recurrent neural networks have demonstrated superior accuracy and speed in decoding the multidimensional structure of EEG data, extending well beyond the capabilities of traditional indices.[12,13] For instance, models employing deep residual shrinkage networks have achieved highly accurate predictions of anaesthetic depth by analysing 14 EEG-derived features.[12] Similarly, CNN-based hybrid models have classified patients into four anaesthetic states, namely awake, light, general, and deep, with an accuracy of approximately 89%.[13] These findings suggest that AI can detect subtle neural signatures in EEG activity before clinical or haemodynamic changes become apparent, potentially enabling earlier and more individualised control of anaesthetic depth.

AI-assisted EEG monitoring not only enhances accuracy but also improves interpretability under complex anaesthetic conditions involving multiple agents. Different anaesthetic drugs induce distinct EEG changes owing to their specific mechanisms of action.[14] Because of this variability, single-index systems cannot maintain the same level of sensitivity across all situations. ML models trained on large and multidimensional datasets that incorporate these diverse patterns can adapt to both drug- and patient-specific characteristics.[15] Consequently, anaesthetic titration can be guided on a more physiological basis, reducing the risk of intraoperative awareness or excessive suppression.

Hypotension Prediction Index

Intraoperative hypotension is a silent yet devastating complication of anaesthesia. When MAP falls below 65 mmHg, particularly when the duration of this decline is prolonged, irreversible impairments in the perfusion of the heart, kidneys, and brain may occur, increasing the risk of postoperative organ dysfunction and mortality.[16] However, in clinical practice, intraoperative hypotension is often recognised and treated only after it has developed. However, this reactive approach is often insufficient to prevent physiological injuries.

The hypotension prediction index (HPI) represents a pivotal step toward proactive haemodynamic management. Using an AI algorithm that analyses 23 features derived from the arterial pressure waveform, the system can estimate the likelihood of MAP dropping below 65 mmHg several minutes in advance.[17] Early validation studies have demonstrated that the algorithm can predict hypotension 5, 10, and 15 min before the onset, with sensitivities and specificities exceeding 80%.[18] This early warning capability provides clinicians with a critical window to initiate timely, targeted interventions such as fluid optimisation or vasopressor titration. Recent systematic reviews have shown that this technology may translate not only into physiological benefits but also into measurable clinical outcomes. A meta-analysis evaluating the use of HPI in noncardiac surgery reported that, compared with standard care, HPI-guided management significantly reduced the total hypotension burden (area under the hypotensive threshold, mean difference -60.28 mmHg·min), the incidence of hypotension (mean difference -4.50), and the cumulative duration of hypotension (mean difference -12.8 min).[19] In another contemporary meta-analysis of 19 studies, HPI-guided therapy was associated with a significant reduction in intraoperative hypotension and related major complications (relative risk 0.79; 95% confidence interval 0.69-0.90).[20] These findings suggest that HPI may shift anaesthetic management from a reactive practice to a proactive haemodynamic paradigm.

Nevertheless, the concept of "predictive haemodynamics" embodied by the HPI has been increasingly scrutinised. Analyses of large databases have indicated that although the algorithm demonstrates high technical accuracy, its clinical impact appears to be less pronounced. Recent prospective studies have reported that, despite strong discriminative performance [receiver operating characteristic-area under the curve (AUC) ≈ 0.9], the positive predictive value of HPI remains approximately 30%.[21,22] Furthermore, several investigations have shown that many of these predictions can be replicated by simpler models that rely solely on current MAP trends.[23] Given that MAP is among the dominant features within the 23 parameters analysed by the algorithm, some authors have argued that HPI may primarily reflect the existing haemodynamic state rather than an independent predictive signal.[24] As a result, it remains uncertain whether HPI provides a clinically meaningful advantage over conventional MAP-based monitoring.

Despite these promising features, the cost-effectiveness of HPI-guided monitoring remains a major practical barrier. The technology requires proprietary hardware-software integration and additional disposables, which substantially increase per-patient monitoring costs.

Echocardiography

Echocardiography is the most dynamic reflection of cardiac function, particularly in the setting of cardiac anaesthesia. The clarity of this mirror depends largely on human factors (e.g., operator expertise and speed of interpretation) and on image quality. Under anaesthesia, where haemodynamic conditions can shift within seconds, rapid and accurate assessment of ventricular performance directly influences clinical outcomes. AI aims to redefine this complex equation by transforming echocardiography from a purely visual assessment tool into a quantitative, standardised, and predictive analytical platform.

In recent years, ML and DL algorithms have been developed to automatically identify cardiac chambers and compute left ventricular volumes and ejection fractions within seconds. The AutoLV software introduced by Knackstedt et al.[25] analysed ejection fraction and strain in 255 patients across four centers in just eight seconds, demonstrating a strong correlation with manual measurements. Similarly, Asch et al.[26] evaluated 279 ejection-fraction datasets and showed that DL-based analysis achieved an accuracy comparable to expert interpretation. The AutoVTI function (GE Healthcare, Chicago, IL), which enables real-time and continuous measurement of stroke volume through velocity-time integral analysis, has further facilitated the continuous monitoring of cardiac output trends using echocardiography.[27]

The impact of AI is not limited to the assessment of left ventricular function. Strain analysis evaluates ventricular deformation and provides insights beyond conventional ejection fraction measurements. ML-based algorithms have achieved high accuracy in identifying ventricular dysfunction in patients with heart failure with preserved ejection fraction.[28] Liu et al.[29] demonstrated a strong correlation between AI-assisted strain measurements and manually obtained fractional area change (FAC) in the evaluation of right ventricular function. However, correlations involving TAPSE were weak or nonsignificant when compared with FAC and global longitudinal strain.[29] In mitral valve analysis, 3D echocardiography has significantly improved measurement accuracy and clinical decision support by leveraging its greater data capacity. Jeganathan et al.[30] analysed intraoperative 3D transoesophageal echocardiographic data from four patients undergoing coronary artery bypass grafting, using the eSie Valve software (Siemens Healthcare, Mountain View, CA), which automatically calculated six geometric parameters of the mitral annulus and leaflets. In this study, full-volume mitral valve datasets were obtained over two to three cardiac cycles without R-wave synchronization, including the entire annulus and the coaptation region. The results demonstrated that the mitral valve could be analysed fully automatically and reproducibly throughout systole and diastole, with reduced dependence on user input. Similarly, the "AI in ultrasound" method enhanced diagnostic accuracy and consistency, even among novice users, by enabling semi-automated analysis of annular and leaflet structures to identify mitral valve prolapse.[31] However, this system was designed solely for prolapse detection and remains limited in identifying other pathologies, such as clefts or chordal rupture.

Despite these advances, several important limitations remain in the integration of AI into echocardiography systems. Image quality is the most critical factor directly affecting algorithm performance, and the margin of error increases under conditions such as atrial fibrillation, obesity, and poor acoustic windows.

Airway

The rapid advances in AI and imaging technologies have ushered in a new era in predicting difficult intubation and improving intubation safety. AI has demonstrated significant progress in predicting difficult intubation using models based on facial morphology analysis. Cuendet et al.[32] developed a fully automated system that predicts difficult intubation by evaluating morphological features automatically extracted from facial photographs of 970 patients and applying a random forest algorithm; the system achieved an AUC of 77.9%. Similarly, Connor and Segal[33] classified difficult intubation using a computerized analysis model combining facial ratios and the thyromental distance, achieving high accuracy (90% sensitivity, 85% specificity, AUC=0.899) and significantly outperforming classic clinical tests. These studies demonstrate that AI can be a powerful tool for predicting difficult airways from facial images. Although facial-image-based AI models demonstrate impressive predictive performance, their actual integration into routine preoperative workflow remains questionable. Obtaining standardized facial photographs, ensuring proper lighting and positioning, securing patient consent, and transferring images to an AI introduce additional steps that are often impractical in a busy preoperative clinic. Moreover, variability in camera quality and environmental conditions may undermine model accuracy in real-world settings.

Lakhani[34] used DL models to detect the presence of an endotracheal tube (ETT) on radiographs (AUC, 0.99) and to determine tube position (AUC, 0.81). This study is among the first robust demonstrations of the high performance of X-ray-based AI for ETT detection. Han et al.[35] successfully performed a preoperative assessment of a laryngectomized patient with a difficult airway by creating a 1:1 tracheal

model from computed tomography (CT) images using a 3D printer. The 3D model clearly showed the anatomical changes in the airway, ensuring a safe anaesthesia plan for the patient. This study is one of the early and important examples demonstrating that CT data can be an effective tool for planning difficult airways using 3D printing.

According to a study by Zang et al.[36], video-assisted devices shorten intubation time, increase first-attempt success rate, and improve safety, particularly in difficult airway management. AI has shown promising results in areas such as automatic anatomy identification in laryngoscopy and fibreoptic bronchoscopy videos, filtering unusable frames, vocal cord motion analysis, and tumour and vascular structure segmentation. However, the lack of standardisation of AI applications and the need for large, multicentre clinical studies have been identified as significant gaps in the literature. A retrospective study developed a machine-learning model to predict extubation failure after general anaesthesia in adult patients undergoing head, neck, and maxillofacial surgery.[37] Of the 89,279 patients evaluated between 2015 and 2022, 77 experienced extubation failure; 186 successfully extubated patients were selected as controls matched by surgical procedure. Six different ML algorithms were tested using seven clinical variables identified by stepwise regression; the best performance was achieved with support vector machines and logistic regression (AUCs of 0.74 and 0.71, respectively). This study demonstrates that ML models can contribute to clinical decisions by enabling the early prediction of extubation failure after high-risk airway surgeries. AI algorithms have been trained to automatically identify pharyngeal and tracheal structures in videolaryngoscopy recordings. DL approaches have also been used to detect the laryngeal adductor reflex in laryngeal endoscopy videos, potentially enabling automated assessment of airway reflex integrity.[38]

Hypoxaemia is one of the most important complications of airway management, and clinicians' predictions are often inadequate. Therefore, AI-based predictive models have attracted attention. For example, et al.'s[39] dynamic perioperative hypoxaemia prediction models demonstrated performance far beyond that of clinical assessment by analysing time-varying vital parameters, ventilator settings, and drug doses.

Regional Anaesthesia

AI has also initiated a remarkable transformation in applications of regional anaesthesia, an area that is among the fastest-growing within anaesthesiology. It is widely accepted that one of the areas in which AI can contribute most effectively is regional anaesthesia, particularly through advances in imaging-based technologies.[40] When the historical development of regional anaesthesia is examined, it is observed that neurostimulation techniques were integrated into clinical practice in the 1980s and ultrasound technology in the 2000s. Today, AI technologies have been integrated into this evolution and have begun to transform clinical training.[41]

AI-powered sonographic recognition systems can be integrated with conventional ultrasound devices, enabling AI-based identification of anatomical structures from image output (e.g., HDMI) regardless of image quality. Systems such as ScanNav™ and Nerveblox have pioneered AI-based visual recognition technologies. A study using these systems showed that AI technology provided significant support in the real-time identification of anatomical structures by young anaesthesia physicians using ultrasonography.[42] These findings highlight the increasing importance of AI-based visual recognition technologies in clinical education. In another study, data from 21 different practitioners were analysed; half of the practitioners were instructed to practice with the assistance of AI-supported systems, such as ScanNav™. The results showed significant increases in the success of image acquisition, in the recognition of sonoanatomical structures, and in user satisfaction.[43] Different versions of these systems are becoming increasingly common. It is predicted that NerveTrack, SmartNerve, and cNerve—systems with similar features—will become more widely adopted in clinical practice as software companies release and integrate them directly into ultrasound machines.[44] Although these systems demonstrate substantial promise and have shown clear educational benefits, particularly for novice practitioners, their current role remains primarily supportive in training and skill acquisition. As highlighted in recent evaluations, AI-assisted recognition tools such as ScanNav™ and Nerveblox are not yet capable of replacing expert sonographic judgment in complex or anatomically challenging cases. Instead, they function best as adjuncts that enhance learning and standardize training, rather than as autonomous clinical decision-makers.

The Q-VUM model developed by Wang et al.[45] is a DL-based AI algorithm capable of recognising the quadratus lumborum (QL) muscle and surrounding anatomical structures in real time on ultrasound images. The model has shown potential for increasing the anatomical accuracy of QL blocks and reducing the risk of complications.[45] As in many areas of anaesthesia, the use of AI-based models in clinical decision-making is increasingly widespread in regional anaesthesia. Studies, particularly those conducted using hypothetical patient scenarios, have demonstrated the potential of AI in guiding clinicians. For example, in a study in which hypothetical patient samples with 10 different anticoagulation profiles were presented to AI systems for

neuraxial anaesthesia guidance, the authors observed that LLMs could support some basic clinical decisions, but their accuracy decreased significantly in complex cases.[46] A recent pilot study evaluated the potential of LLMs as clinical decision support tools in regional anaesthesia practice. The ability of four different AI platforms to respond to simple and complex clinical scenarios was evaluated. Significant deficiencies regarding clinical reasoning, justification, and consistency were found in all models, and incorrect responses were particularly evident in complex cases. These findings indicate that current LLM-based systems are not yet ready to provide direct clinical decision support in regional anaesthesia practices, but they do represent a valuable preliminary step for future "e-consult" models to be developed.[47] A recently published study investigated the agreement between clinicians and AI applications in selecting the anaesthesia method for patients undergoing orthopaedic surgery and reported that the Gemini application matched anaesthesiologists' preferences 68.5% of the time. However, the study emphasized that it would be more appropriate to use these systems as decision support tools rather than replacing physicians, due to the AI's inability to fully master clinical guidelines and its inadequate performance in specific patient groups.[48]

The Guidance for Reporting Artificial Intelligence Technology Evaluations for Ultrasound Scanning in Regional Anesthesia (GRAITE-USRA) guideline, published in 2025, is the first international reporting framework developed for the scientific evaluation of AI applications in ultrasound-guided regional anesthesia. This guideline, jointly approved by multiple international associations, aims to standardise elements such as study design, operator experience, ultrasound protocol, and data security through a 40-item checklist. The adoption of GRAITE-USRA will significantly contribute to the quality of academic publications and regulatory processes by increasing the comparability of the clinical validity of different AI-based systems.[49] In parallel, the international Delphi consensus published by Fettiplace et al.[50] emphasises transparency, ethical responsibility, and human oversight in the use of AI for scientific writing and publishing. Both guidelines provide a strong roadmap for integrating AI into regional anaesthesia in a manner that is methodologically sound and ethically aligned.

Critical Care

AI has rapidly become one of the most dynamic frontiers in critical care medicine, with applications in prediction, diagnosis, monitoring, decision support, and operational optimisation. Since the first reports of AI-based intensive care analytics appeared in the late 2010s, its use has expanded from small proof-of-concept algorithms to comprehensive multimodal systems capable of integrating vast amounts of physiological, imaging, and electronic health record data. Its usefulness is paramount, considering that modern intensive care units (ICUs) generate enormous volumes of continuous, heterogeneous data (vital signs, laboratory values, waveform outputs, and clinical notes) that far exceed human cognitive capacity. AI offers a framework to transform these data into clinically actionable insights, thereby augmenting clinical decision-making and potentially improving patient outcomes.[51]

Predictive analytics is one of the most extensively studied domains. ML models have been developed to identify the early signs of deterioration, including sepsis, respiratory failure, and haemodynamic instability. For instance, DL frameworks trained on high-frequency ICU data have been shown to predict the onset of sepsis several hours before traditional diagnostic criteria would allow.[52] Similarly, models integrating electronic health record data and bedside monitor streams have achieved impressive discrimination in predicting mortality and unplanned readmission in both adult and paediatric critical care.[53,54] These predictive systems exemplify AI's potential to act as an early warning adjunct, allowing clinicians to intervene before physiological collapse occurs.

Risk classification and prediction of perioperative complications are central to ensuring surgical safety and informing surgical planning. Hospital records contain rich data, and AI has begun exploiting this potential: in a prospective study, ChatGPT correctly predicted postoperative ICU admission for 65.5% of 406 patients, but performed poorly for other outcomes such as ICU length of stay.[55] In another study using 10 preoperative clinical scenarios, ChatGPT failed to meet minimum clinical standards for perioperative planning, underscoring that current LLMs should be viewed as adjuncts, rather than autonomous decision-makers, in preoperative risk assessment.

AI is also revolutionising clinical decision-making. Algorithms embedded within decision support systems can recommend ventilator settings, antibiotic regimens, and fluid strategies by continuously analysing the evolving patient data. Such systems do not replace the clinician but rather provide dynamic, data-driven suggestions that refine judgment and standardise care.[56] In perioperative and neurocritical care, AI-enhanced monitoring has been used to titrate anaesthetic depth and cerebral perfusion more precisely; in trauma and postoperative management, AI models have guided resuscitation and analgesic dosing.[57] These studies highlight AI's role as an augmentative rather than an autonomous agent, expanding clinicians' situational awareness in data-dense environments.

Another key area is multimodal monitoring and data integration. Intensive care involves the continuous collection of physiological signals, such as ECG, EEG, and arterial pressure waveforms. ML techniques, including convolutional and recurrent neural networks, can process complex time-series data to detect patterns invisible to human observers. For example, predictive algorithms have been used to identify early signs of acute respiratory distress syndrome and to forecast the need for mechanical ventilation.[58,59] In parallel, NLP is increasingly employed to mine unstructured clinical notes and nursing reports, allowing AI to detect subtle clinical shifts or errors that structured data may miss.[60]

Imaging analysis is another promising avenue. DL networks trained on radiographic and ultrasound data can automatically detect pneumothorax, effusion, or ventilator-associated changes, providing near-real-time diagnostic support in settings where expert interpretation may be delayed.[61] Similarly, AI-augmented echocardiography and CT analysis have improved the recognition of cardiac dysfunction and cerebral oedema in critically ill patients.[62] Beyond diagnostics, AI is being used to enhance procedural precision—for example, in needle placement and line insertion—through computer-vision-assisted feedback systems.[63]

Finally, several studies have examined AI's role in resource optimisation and system management. Predictive algorithms can anticipate ICU bed occupancy, model staffing needs, and streamline triage by matching patient severity to appropriate care levels.[64] In multicentre tele-ICU platforms, AI supports remote monitoring and triage prioritisation, improving response times in resource-constrained environments.[65] These operational uses underscore how AI can optimise clinical outcomes and healthcare efficiency.

Academic Literature

AI, particularly LLMs, has rapidly entered the academic ecosystem and is now being used in multiple stages of scholarly activity. These applications include idea generation, literature searching and synthesis, manuscript drafting, methodological assistance, and language refinement.[66,67] Despite the accelerating adoption of these tools and the policies introduced by major publishers and editorial organisations, a universally accepted guideline for the use of AI in academic writing has yet to be established. There is broad consensus in the scientific community that AI tools cannot meet the criteria for authorship. As noted by organisations such as the International Committee of Medical Journal Editors and Committee on Publication Ethics, AI lacks the capacity for accountability, cannot take responsibility for the integrity of the work, and is unable to approve the final version of a manuscript.

Therefore, transparency and human oversight are essential. Any use of AI within the research or writing process must be explicitly disclosed, specifying the tool, version, and precise purpose for which it was used. Importantly, AI should function only as a supportive instrument; the responsibility for scientific accuracy, ethical compliance, interpretation of findings, and data confidentiality remains with the authors. Authors must rigorously verify all AI-assisted outputs to ensure fidelity, methodological soundness, and adherence to ethical standards.[50]

Anaesthesia Education

Specialty training in anaesthesia requires both theoretical knowledge and high-level technical skills. AI has frequently been used to improve and personalise education. A comprehensive review by Komasawa[68] reported that AI can develop student-specific learning paths in anaesthesia education. The study emphasised that simulation-based applications can be personalised. This allows students to gain technical skills as well as awareness of patient safety and decision-making processes. Cai et al.'s[69] study showed that AI-supported image-recognition systems contribute significantly to regional anaesthesia education. In this study, a training platform was developed to automatically identify nerve structures in ultrasound images using a convolutional neural-network-based algorithm. A randomised simulation study showed that the incidence of paraesthesia during puncture and injection was significantly lower among anaesthesia assistants using this system than among those using the traditional method. Such AI-supported tools not only accelerate the learning process but also have the potential to reduce the risk of complications in real-world clinical settings. Sardesai et al.[70] presented an innovative approach using AI-supported virtual patient simulations, particularly for preoperative consultation and training in patient communication. The vast majority of participants found these systems user-friendly, accessible, and realistic, demonstrating that AI can be used not only to develop technical skills but also to develop communication skills. However, the study reported that some responses were incorrect or inadequate. This finding indicates that human oversight remains critical for enhancing the effectiveness of AI-based simulations as educational tools.

A review published by Yu et al.[71] suggested that the integration of AI and virtual reality technologies could be used particularly for patient safety and crisis management training. Such systems enable the repeated practice of high-risk scenarios in a safe environment, thereby improving decision-making skills under stress. However, the authors emphasised that these technologies must be rigorously evaluated for their validity and reliability before being integrated into training programs. Jin et al.[72] evaluated ChatGPT's success in creating learning materials for anaesthesia assistants. Ninety-five prompts derived from Anaesthesia Knowledge keywords (focused information, broad response/

compilation, lesson plan, "biased/incorrect" prompts, and reference prompts) were submitted to ChatGPT-3.5 and ChatGPT-4.0. The responses were scored by two experienced anaesthesiologists on a three-point scale for accuracy and, for long responses, completeness. Ultimately, 55% of the responses were deemed completely accurate by both evaluators, and accuracy and completeness for broad-scope prompts were mostly rated at the "book/expert" level. However, significant errors and fabricated (hallucinated) references were observed in prompts containing incorrect assumptions and in cases where literature references were requested. It was emphasised that some errors could cause harm in clinical practice. The authors suggest that while ChatGPT can be useful and generate consistent content on entry-level topics, it is not reliable on its own in medical education; its outputs need to be verified by expert review, and field-specific (anaesthesiology) knowledge bases and user training are important considerations.

An overview of the major benefits and opportunities of AI in anaesthesiology, along with its current challenges and limitations, is presented in Tables 1 and 2.

Table 1. Benefits and Opportunities of AI Integration in Anaesthesiology and Perioperative Medicine

Enhanced risk predictions	AI enables large-scale data screening to improve risk prediction models, increasing diagnostic accuracy and early warning capabilities. These systems can estimate mortality, postoperative complications, ICU admission, and length of stay. Such predictions support informed consent, perioperative planning, and resource allocation.
Prediction of specific complications	Multimodal AI models synthesizing physiological signals, laboratory data, and imaging can identify early signs of cardiovascular instability, renal dysfunction, and ventilatory disorders before clinical deterioration. Future AI-driven advanced monitoring may integrate haemodynamic, respiratory, and neurophysiological parameters to deliver real-time recommendation-based support.
Personalized risk assessments	AI utilizes patient-specific variables (e.g., ASA class, airway features, comorbidities) to generate individualized risk estimates, facilitating personalized perioperative planning and enhancing risk-benefit discussions with patients.
Precision and decision-making aid	AI algorithms analyze EEG, ECG, and haemodynamic patterns to help clinicians titrate anaesthetic and vasoactive drugs more precisely. Closed-loop systems using AI-derived depth of anaesthesia and haemodynamic indices can autonomously adjust infusion pumps, minimizing variability, reducing adverse effects, and improving outcomes.
Imaging and procedural guidance	AI strengthens image interpretation in echocardiography and regional anaesthesia by assisting with nerve identification and pattern recognition. It improves image acquisition, reduces operator variability, and enables automated calculations (e.g., EF, SV, CO), enhancing speed, accuracy, and reproducibility.
Workflow efficiency and administrative support	AI reduces administrative workload by transcribing clinical conversations, drafting perioperative documentation, and generating discharge summaries. AI-driven predictions of surgical duration, theatre utilization, and patient flow improve operational efficiency. In ICUs, AI assists in forecasting length of stay, readmission risk, and resource needs.
Education and communication	AI supports patient engagement, preoperative education, psychological reassurance, and multilingual communication. In medical training,AI enhances self-directed learning and powers advanced simulation platforms, including virtual OR scenarios, to improve teamwork and crisis management skills.
Acceleration of drug discovery	AI accelerates anaesthetic drug development by enhancing large-scale data analytics, toxicity prediction, and clinical trial optimization. Tools such as AlphaFold help identify protein targets, deepening understanding of anaesthesia mechanisms and enabling faster, more efficient pharmacologic innovation.

AI, artificial intelligence; ICU, intensive care unit; ASA, American Society of Anesthesiologists; EEG, electroencephalography; ECG, electrocardiography; EF, ejection fraction; SV, stroke volume; CO, cardiac output; OR, operating room

Table 2. Challenges and Limitations of AI Integration in Anaesthesiology and Perioperative Medicine	
Technical and methodologic limitations	AI models often function as opaque "black boxes," preventing reverse engineering or clear interpretability. This reduces clinician trust and complicates accountability and medicolegal responsibility. These issues parallel proprietary EEG-based anaesthesia depth monitors, where simplified indices obscure underlying algorithmic processes.
Data quality, volume, and generalizability	AI performance is constrained by the quality and diversity of training data. Many studies rely on small or single-center datasets, limiting external validity. Models perform poorly in rare diseases or complex decisions and remain vulnerable to overfitting, requiring continuous monitoring and retraining.
Clinical safety and judgement risks	AI models may hallucinate, generate factually incorrect or inconsistent outputs, and produce erroneous references, necessitating clinician oversight, especially in high-risk fields like anaesthesia and critical care where tolerance for error is minimal.
Overreliance and automation bias	Dependence on AI may diminish clinical engagement, critical thinking, and interpretive judgement. Automation bias can lead clinicians to uncritically accept AI recommendations, increasing the risk of adverse events.
Data safety and ethical concerns	AI relies on sensitive patient data, raising concerns about consent, privacy, and data security. Cloud-based systems are vulnerable to cyber-attacks, and healthcare settings are high-risk targets. Proposed mitigations include strong encryption, federated learning, and blockchain-based audit trails.
Ethical, regulatory, and professional challenges	Regulatory pathways (e.g., MDR, FDA) require extensive validation and can impose high costs. Hallucination-related errors may create malpractice liability. Clear protocols for responsibility within AI-assisted or closed-loop systems are needed. Ethical issues also include patient data use and the validity of informed consent when AI tools provide unreliable information.
Education and compliance	Many anaesthesiologists lack formal training in AI principles, data governance, algorithmic auditing, or troubleshooting. Without structured AI curricula in residency and continuing education, clinical adoption will face resistance and misuse risks.
Implementation and infrastructure costs	AI deployment requires substantial investment in hardware, software, cybersecurity, cloud storage, governance structures, and dedicated IT personnel. These financial and operational burdens challenge implementation in resource limited healthcare systems.

EEG, electroencephalography; MDR, medical device regulation; FDA, food and drug administration; AI, artificial intelligence; IT, information technology

Conclusion

AI is rapidly reshaping anaesthesiology, offering unprecedented opportunities to enhance perioperative safety, precision, and efficiency. AI-driven tools are increasingly demonstrating their value as augmentative decision-support systems in risk stratification, airway assessment, haemodynamic optimisation, echocardiography, regional anaesthesia, critical care, and medical education. However, significant challenges, including data quality, transparency, algorithmic bias, regulatory uncertainty, medico-legal accountability, and the risk of overreliance, highlight the need for cautious, evidence-based integration. AI will not replace anaesthesiologists; rather, it will redefine the profession toward a more cognitive, supervisory, and data-informed role. The safe and meaningful adoption of AI requires robust validation, interdisciplinary collaboration, clinician training, ethical governance, and transparent human oversight. As AI systems continue to evolve, future research must prioritise clinically relevant outcomes, multicentre evaluations, interpretability, and equitable access.

Footnotes

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Review Article

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The Use of Cisatracurium in Cardiac Surgery

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Abstract

The introduction of neuromuscular blockers (NMBs) has revolutionized the practice of general anaesthesia, ushering in a new era where anaesthesia is conceptualized as a triad comprising narcosis, analgesia, and muscle relaxation. NMBs play a vital role in surgeries by facilitating tracheal intubation, preventing the movement of body and diaphragm, control of ventilation at normal partial pressure of carbon dioxide and counteraction of narcotic-induced truncal rigidity. However, the absence of specific guidelines for the selection and utilization of particular NMBs in various surgical contexts has led to inconsistencies within the healthcare system. Thus, a deep and thorough understanding of pharmacological aspects of NMBs is required for the selection and usage of particular NMB in clinical setting. Ideal NMBs are characterized by rapid onset, non-cumulative effects, independence from renal or hepatic function for elimination, rapid reversibility, and minimal adverse side effects. Among several NMBs, cisatracurium, an isomer of atracurium is a non-depolarizing intermediate-acting with characteristic features of high potency, smaller dosage requirement, no histamine release, no cardiovascular effects and elimination via organ-independent Hofmann reaction. Innumerable clinical experiments and trials suggest cisatracurium as safe, cost-effective, and better molecule with predictable recovery and no postoperative residual paralysis in comparison to other NMBs such as rocuronium, vecuronium, and pancuronium. In this review, we aimed to provide critical insights on the properties of NMBs first and then focused on the use of cisatracurium in cardiac surgeries.

Keywords: Cardiac surgery, cisatracurium, induction, neuromuscular blockers, residual paralysis

Main Points

- Neuromuscular blockers (NMBs) evolved from natural agents to synthetic drugs to induce paralysis and muscle relaxation.
- An ideal NMB should have with characteristic features of high potency, smaller dosage requirement, no histamine release, no cardiovascular effects, and elimination via organ-independent Hofmann reaction.
- In cardiac surgery, cisatracurium is preferred for its minimal circulatory effects and faster recovery.

Introduction

Neuromuscular blockers (NMBs) are the agents that induce paralysis and facilitate profound muscle relaxation and thereby, preventing muscle movement in clinical setting. Muscle relaxation was earlier maintained by deep inhalation of anaesthesia. The introduction and widespread usage of NMBs was a significant milestone for the development of balanced anaesthetic protocols.[1] Historically, natives in South America used "curare", a blocking agent for hunting and killing prey and later used it in specialized surgeries. NMBs were introduced in clinical practice for more than a decade now. From the initial use of naturally occurring tubocurarine, the evolution of NMBs has progressed towards the development of more potent synthetic benzylisoquinoline and amino-steroidal molecules with curare-like effects.[2]

Pharmacologically, NMBs exert their effects by blocking the neuromuscular transmission at the junction, resulting in paralysis of the affected muscle. NMBs may affect both pre- and postsynaptic neuromuscular junctions. Based on their action mechanism, NMBs are categorized as depolarizing and non-depolarizing agents.[3] Depolarizing agent acts as agonist, binding at the acetylcholine receptive sites and causing an end-plate potential/depolarization

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of the muscle fiber. This process initiates two phases of depolarization block: phase I, characterized by muscle fasciculation (twitch), and phase II, or the desensitizing phase, during which the muscle becomes unresponsive to acetylcholinesterase, ultimately leading to neuromuscular blockade. In contrast, non-depolarizing agents act as antagonists, blocking receptor sites and preventing depolarization and neuronal transmission to the muscle.[4]

NMBs are also characterized on the basis of duration of action i.e., short-acting (succinylcholine), intermediate-acting (atracurium, cisatracurium, vecuronium and rocuronium) and long-acting (pancuronium) agents. Innumerable blocking agents with their individualistic features and chemical structures significantly influences factors such as blockage duration, recovery time, and the risk of postoperative residual paralysis in clinical settings.[5] There are several other factors such as abnormal hepatic and renal functions, histamine release and malignant hypothermia that affect the potential and action mechanism of a certain NMBs. Thus, a better understanding of NMBs with effective blockade potential is the need of an hour. However, there are no specific guidelines or consensus data in the literature that could emphasize on the choice of preferrable NMB in a specialized surgery which is highly controversial among clinicians and surgeons.[6] Therefore, this review aimed to provide insights on the different types of NMBs, their characteristic features, and the role of cisatracurium in various cardiac surgeries. By synthesizing existing knowledge and addressing gaps in understanding, this review seeks to offer valuable guidance to healthcare professionals grappling with the complex decision-making process surrounding NMB selection in specialized surgical contexts.

Existing NMBs and Their Pharmacokinetics

The currently available agents are as follow:

Succinylcholine: Succinylcholine is the only depolarizing agent which is currently in use due to its favorable pharmacokinetic profile i.e., rapid onset and short duration of action. Succinylcholine triggers malignant hyperthermia and hyperkalemic response with a transient increase of 0.5-1.0 mEq L in plasma potassium levels.[7]

Pancuronium: Pancuronium was the first steroidal agent that had curare-like effects. It was isolated from the bark of Malouetiabequaertiana. Pancuronium has the ability to block the cardiac muscarinic receptors resulting in tachycardia. Therefore, the usage of pancuronium is discouraged due to slow onset, cardiac effects and prolonged action.[8]

Vecuronium: Vecuronium, an intermediate-acting blocker with stable hemodynamic profile, is metabolized into 3-desacetyl-vecuronium. However, it is not recommended in patients with hepatic or renal dysfunction as it is metabolized in the liver and excreted in bile and urine. The elimination half-life is approximately 45 to 60 minutes.[9]

Rocuronium: Rocuronium, a deacetoxy analogue of vecuronium has shorter onset but an intermediate duration of action depending upon the hepatic or renal functioning. Although rocuronium is not associated with histamine release, it has a little impact on hemodynamic profile and can cause allergic reactions.[10] The half-life of rocuronium elimination is approximately 1-2 hours.

Atracurium: Atracurium is a mixture of ten isomers with intermediate blocking activity. Atracurium is an attractive option to use in patients with renal and/or hepatic dysfunction. However, intubating doses of atracurium (0.5 mg kg^{-1} or $2\times ED_{95}$) can cause histamine release, tachycardia, and hypotension. The half-life of atracurium elimination is approximately 20 to 25 minutes.[11]

Cisatracurium: Cisatracurium, a stereoisomer of atracurium is an intermediate-acting non-depolarizing agent. It constitutes 15% of atracurium. Cisatracurium acts as a competitive antagonist to acetylcholine and binds to the nicotinic cholinergic receptor at the muscular junction. It effectively blocks the motor end-plate potential and inducing paralysis by disrupting the required conformational changes for ion channel opening. Clinically, it is found beneficial because of its duration of action and rate of spontaneous recovery, making it clinically beneficial in anaesthesia management. Notably, it is considered as a "cleaner" molecule with characteristic features of five-fold potency in comparison to atracurium, no histamine release, a smaller dosage requirement for tracheal intubation (0.1 mg kg^{-1} or $2\times ED_{95}$) and elimination via Hofmann method which is independent of renal/hepatic functioning. The metabolization of cisatracurium leads to the formation of mono-quaternary acrylate metabolite and laudanosine. The role of laudanosine metabolite is controversial. Early studies in animal models suggested that laudanosine could induce seizure-like activity at high doses, such adverse effects have not been reported in humans.[12] Importantly, the concentration of laudanosine was significantly lower in cisatracurium infused-surgical patients as compared to atracurium infused-surgical patients. This finding underscores the safety profile of cisatracurium, making it a preferable choice for long-term use in the intensive care unit (ICU) without the concerns associated with adverse effects linked to laudanosine accumulation. Approximately 77% of the drug undergoes degradation reaction and 15% is excreted unchanged in the urine. Its elimination half-life is approximately 20 to 25 minutes.[13] Overall, cisatracurium emerges as a valuable asset in anaesthesia practice, offering effective muscle relaxation with a favorable safety profile and lower risk of laudanosine-related complications compared to other neuromuscular blocking agents.

Ideal NMB as a Drug of Choice

Table 1 shows the comparative analysis of various NMBs in terms of potency, chemical structure variability and pharmacodynamic features, which is as follows:

Chemical structure variability: Most of the NMBs are quaternary ammonium compounds which are structurally similar to acetylcholine. Among them, succinylcholine, pancuronium, atracurium and cisatracurium contain bis-quaternary amines that make them more potent than mono-quaternary NMBs (rocuronium and vecuronium).[14]

Potency: Potency of the drug depends on the potential of the drug to block neuromuscular functions. Potency is inversely proportional to the dose of the drug and onset of time. If the potency of the drug is low, a larger dose is administered which may accelerate onset of action.[15] The ascending order of potency of NMBs initiate from rocuronium with lowest potency followed by atracurium, vecuronium, cisatracurium and pancuronium with highest potency. Rocuronium has four to five times low potency than that of cisatracurium.[10] In a study, Diaz et al.[14] compared the relative potency, onset, duration of action, and reversal characteristics of cisatracurium with pancuronium in rabbits. The authors observed that the clinical time point for reversal and initial recovery was faster in cisatracurium irrespective of same onset.

Pharmacodynamic parameters: Relative efficacy of the agents is measured quantitatively as the ED_{95}. ED_{95} is the average dose needed to produce 95% suppression of the adductor pollicis twitch response to ulnar stimulation. Hemmerling et al.[16] provided an update on the usage of NMBs in cardiac surgery. The authors reported the comparative pharmacodynamic parameters (dose of intubation, onset time, ED_{50}, ED_{95}, elimination, clearance, hepatic/renal failure and histamine release) of widely used NMBs such as cisatracurium, pancuronium, vecuronium and rocuronium. In a study, Jirasiritham et al.[17] compared the effectiveness and characteristics of atracurium and cisatracurium with respect to onset, duration of blockade, intubating conditions and hemodynamic parameters in 150 patients undergoing elective surgeries under general anaesthesia and found cisatracurium as a better NMB.

Cardiac effects/Histamine release: The major adverse events associated with the usage of NMBs include cardiac effects, histamine release and actions at extra-neuromuscular junction of cholinergic receptors. The older agents i.e., curare and succinylcholine and currently available pancuronium and atracurium are found to be causing such adverse effects.[18] However, cisatracurium is a major attraction that shows no such signs of histamine release.

Elimination: The elimination pathway for NMB should be independent from hepatic or renal dysfunction. The metabolization, elimination and prolonged blocking effects of various agents such as pancuronium, vecuronium and rocuronium is dependent on the functioning of kidney and liver. However, atracurium and cisatracurium are considered best in case of multiple-organ failure as their mechanism is based on Hofmann's elimination.[12]

Haemodynamic stability: In case of cardiac surgeries, haemodynamic stability is a must. In a study, Hemmerling et al.[16] have mentioned that cisatracurium has no effect on haemodynamic factors including blood pressure, heart rate and cardiac output whereas other NMBs such as pancuronium, vecuronium and rocuronium have a significant effect on these parameters. Significant hemodynamic changes such as hypotension, tachycardia, and bronchospasm were also evident with the use of various prescribed agents. Particularly, vecuronium and atracurium administration are associated with hypotension and

Table 1. Comparative Features of Various NMBs

NMBs	Action time	Onset of action (min)	Duration of action (min)	Chemical structure variability	Adverse effects/features
Succinylcholine	Short-acting	1	10	Single chemical entity	Malignant hyperthermia, masseter muscle rigidity, bradycardia
	Intermediate-acting	2	43	Mixture of 10 isomers	Release of histamine, toxic metabolite called laudanosine accumulation in individuals with renal failure
Cisatracurium	Intermediate-acting	2-3	45	Stereoisomer of atracurium	Does not cause release of histamine
Vecuronium	Intermediate-acting	3	33		May cause prolonged paralysis and promote muscarinic block
Rocuronium	Intermediate-acting	1-2	33	Deacetoxy analogue of vecuronium	May promote muscarinic block
Pancuronium	Long-acting	3-4	75	Steroidal compound	Tachycardia

NMBs, neuromuscular blockers; min, minutes.

flushing. The use of cisatracurium is preferrable in case of bradycardia and unstable hemodynamic parameters.[11]

Induction and maintenance: Good intubating condition and hemodynamic stability are based on induction. Rocuronium and cisatracurium gives good intubating condition. During maintenance of surgery, muscle relaxation is necessary due to hypothermia, shivering, defibrillation.[19] In addition, malignant hyperthermia is a rare genetic disorder that has shown to be triggered by NMBs administration along with halogenated hydrocarbons anaesthetics. It causes an excessive release of calcium from the sarcoplasmic reticulum of skeletal muscle. The early features include tachycardia, cyanosis, and muscle rigidity and the mortality rate is 80%, if left.[20]

Postoperative residual paralysis: Postoperative residual paralysis is a matter of concern and a great hurdle in cardiac surgery. It is most likely to happen with long-acting NMBs like pancuronium but very less frequent with intermediate-acting NMBs such as cisatracurium.[21]

NMBs in Cardiac Surgeries

The muscle relaxants play an active role in cardiac surgery by facilitating tracheal intubation, preventing pulmonary movement, ventilation control by the partial pressure of arterial carbon dioxide, counteracting narcotic-induced truncal rigidity and prevention of shivering during hypothermic bypass. The choice of muscle relaxant for patients undergoing cardiac surgery may be influenced by the circulatory effects evoked by these agents.[22] The circulatory effects produced by muscle relaxants include release of histamine, autonomic ganglionic block, blockage of cardiac muscarinic effects (vagolytic), noradrenaline release, potassium ion kinetics and drug interaction. The NMB with minimal circulatory effects is desirable in cardiac surgeries. The role of muscle relaxants in cardiac surgery is defined in three phases:

Induction of anaesthesia: Endotracheal airway is inserted using NMB that provides good to excellent intubating conditions in the patients undergoing cardiac surgery. The prime purpose of induction is to provide hemodynamic stability. Generally, rocuronium is used in cardiac surgeries due to early intubation as compared to other NMBs.[23]

Maintenance of NMB during surgery: NMB dosing is titrated to achieve blockade of the core muscles and the blockade is maintained during the surgery to avoid any inadvertent movement of the patient, hypothermia, shivering and defibrillation.[24] Hypothermia alters the distribution and metabolism of NMBs, influences twitch response and increases duration of action of NMB with the reduction of 2 °C in body temperature. Bolus and continuous infusion are two discrete methods of NMB administration. Bolus mode of NMB administration provide sufficient paralysis whereas continuous infusion may cause postoperative residual paralysis. Postoperative residual paralysis is most common with long-acting NMB, pancuronium whereas less frequent with intermediate-acting NMB, cisatracurium. In a study, Van Oldenbeek et al.[25] reported considerable degree of residual block [median: train-of-four (TOF) = 0.23] in 13 of 20 patients with modest dose of pancuronium (median = 0.11 mg kg^{-1} total) after cardiac surgery. In another study, Baillard et al.[26] reported postoperative residual paralysis with vecuronium in 33% of patients undergoing different types of surgery (TOF ratio <0.7). A large bolus of cisatracurium (8X ED_{95}) administration is recommended for initial blockade in peri-operative period and small bolus dose can be used during the surgery, if required to avoid postoperative residual paralysis.[27]

Post-operative period: Recovery from the blockade is a must in post-operative period. Any TOF response of less than 0.9 should be reversed. Though muscle relaxants are not needed post-operatively in stable patients or in case of fast-track surgeries however, if required, cisatracurium is preferred to avoid bradycardia.[28] In a study, Cammu et al.[29] compared the recovery time after continuous infusion of cisatracurium and rocuronium and observed the time interval of 10+9 min for cisatracurium and 18+13 min for rocuronium between end of infusion and reappearance of TOF ratio of 0.9. In some cases, reversal agent such as sugammadex (2 mg kg^{-1} of dose), is also used which is carefully titrated to avoid bradycardia or tachycardia.[29] The following cardiac surgeries are taken into consideration:

Coronary artery disease: Coronary perfusion maintenance and less utilization of myocardium are the pre-requisite goals for the management of patients with coronary artery disease. These factors can be achieved by controlling heart rate and maintaining demand-supply ratio. In this regard, a muscle relaxant providing good intubating condition, hemodynamic stability, prevention from hypothermia and rapid recovery is selected for the patient undergoing cardiac surgery. NMBs with benign circulatory effects include vecuronium, rocuronium and pipecuronium.[30] Atracurium and pancuronium have modest blood pressure and heart rate effects however, pancuronium is extensively being used for many years in patients with coronary artery disease. Pancuronium is useful in offsetting negative inotropic and chronotropic effects of anaesthetic drugs especially in opioid-induced bradycardia. Myocardial ischemia is most likely to occur during tracheal intubation irrespective of NMB choice. In a study, 12 patients with coronary artery disease were administered pancuronium and reported myocardial ischemia in 3 patients due to associated increase in heart rate. Hence, the choice of NMB is dependent on basal heart rate and its maintenance.[31] A paradigm shift from traditional surgical

procedures to fast-track concept highlighted the role of NMBs in cardiac surgeries and demarked the usage of opioid and benzodiazepines. In this regard, NMB agents associated with early recovery, early tracheal extubation and least complications should be used. In a study, Murphy et al.[22] showed a significant delay in tracheal extubation with pancuronium (median, 500 min; range: 240-1305 min) as compared to rocuronium (median, 350 min; range: 210-1140 min). Hence, the selection of NMB relies on the associated circulatory effects and recovery profile.

Valvular heart disease: The patients with mitral stenosis, aortic stenosis, combination of aortic stenosis and mitral stenosis, and other combinations have compromised cardiac filling and contractility.[32] Maintenance of adequate stroke volume is dependent on heart rate and systemic blood pressure in patients with aortic stenosis. Pancuronium promotes forward left ventricular stroke volume and increase cardiac impulse transmission through the atrioventricular node. Short-acting and intermediate-acting muscle relaxants such as rocuronium or cisatracurium are often the logical choices in patients with aortic and mitral stenosis as these agents are associated with minimal changes in heart rate and systemic blood pressure and forward flow maintenance. Further, pancuronium should be preferred in patients with aortic incompetence, mitral incompetence and atrial fibrillation (AF) whereas rocuronium and vecuronium should be used in patients with stenosis to decrease the heart rate. Pancuronium should be avoided in patients with mitral stenosis.[33]

Cardiomyopathies: Cardiomyopathy occurs due to muscle weakness and rigidity. It includes hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic ventricular dysplasia. The treatment protocols include implantable cardioverter defibrillator, ventricular assisted device and cardiac revascularization. The cardiac revascularization practice includes blockage of respiratory movement using NMB for planned intubation and mechanical ventilation.[34] However, prolonged postoperative ventilation is no longer necessary or desirable. The major goal in cardiomyopathy is to minimize negative inotropic effect, maintain preload, prevent increase in afterload causing vasodilation and avoid tachycardia. Pancuronium is associated with increased heart rate and delayed extubation, vecuronium and rocuronium produce positive inotropic effects and vecuronium shortens refractoriness. Based on these facts, vecuronium, rocuronium or cisatracurium should be preferred in patients with myopathy impairment or hypertrophic cardiomyopathy to avoid bradycardia and vasodilation.[35] Pancuronium or cisatracurium should be preferred in patients with restrictive cardiomyopathy to avoid tachycardia and vasodilation. Rocuronium or vecuronium is preferred in patients with no automated implantable cardioverter defibrillator. Cisatracurium is preferred in all types of cardiomyopathies to avoid bradycardia and vasodilatation.[36]

Minimally invasive cardiac surgery: Minimally invasive cardiac surgery (MICS) comprises of minimally invasive direct coronary artery bypass (MIDCAB), robotic-assisted cardiac surgery, AF ablation surgery, and minimally invasive approaches to the mitral valve, left and right atria, and minimal-access aortic valve surgery.[37] The procedure include the necessity of one-lung ventilation, use of cerebral oximetry, additional large-bore jugular vascular access, and advanced skills in transesophageal echocardiography. Several studies highlighted c the benefits of conventional coronary artery bypass grafting and MIDCAB.[38,39] The major benefits of MICS include reduced postoperative pain, shorter hospital stay, better cosmesis, and quicker resumption of normal activities, which form the basis of selection of NMB. Thus, the preferred properties of NMB include no cardiovascular or hemodynamic adverse effects, speedy recovery, highly potent, less inactive metabolites and unaffected by renal/hepatic impairment.

Heart, lung and heart-lung transplant: The heart transplantation procedure preserves the donor sinus node function. Sympathetic and parasympathetic reinnervation is established to improve heart rate and contractile response and to avoid bradycardia. The patients undergoing heart, lung and heart-lung transplantation require hemodynamic stability and post-operative ventilation.[40]

Cardiac patients with renal or hepatic dysfunction: Hepato-biliary disorders are associated with delayed onset of action, delayed metabolism, resistance to drugs. The course of action depends on NMB dosing where repeated dosing causes prolongation of action. Most of the NMBs such as pancuronium, vecuronium, rocuronium are metabolized through bile/liver and excreted through kidney which leads to increase elimination half-life. In diseased condition like cirrhosis, there is increase in volume of distribution, slow onset and prolong duration of action.[41] NMBs like atracurium and cisatracurium have liver and renal-independent elimination. To some extent, vecuronium has renal-independent elimination. Laudanosine is the metabolite of atracurium and cisatracurium. In a clinical study, Zhou et al.[13] suggested the use of atracurium/cisatracurium in patients with renal and hepatic failure.

Cardiac intensive care: NMBs are regularly used in ICUs to facilitate mechanical ventilation, eliminate patient-ventilator dyssynchrony, reducing intra-abdominal pressure and gas exchange by improving chest wall compliance. However, prolonged blockade is associated with ICU-acquired weakness. Succinylcholine is preferred for rapid sequence intubation. In patients with open chest surgery, preferred NMBs are vecuronium, atracurium and cisatracurium.[42]

Innumerable studies in the literature also recommended cisatracurium in cardiac surgeries which are listed in Table 2.

Table 2. Various Studies in Favour of Cisatracurium Administration in Cardiac Surgeries

Study type	Method	Opinion	References
Randomized clinical trial	One hundred patients were randomized to receive succinylcholine or cisatracurium	A strategy of using cisatracurium resulted in better operating conditions	43
Prospective study	Eighty-seven patients were administered with cisatracurium or atracurium	Atracurium or cisatracurium administered in a single dose to facilitate endotracheal intubation does not result in residual postoperative paralysis	44
Prospective study	Twenty adult patients undergoing cardiac surgery received pancuronium	Residual paralysis with Pancuronium was observed. It should be replaced with rocuronium, atracurium or cisatracurium	25
Retrospective study	Seven thousand and one hundred thirteen patients were analyzed in which 3,751 received pancuronium and 3,362 received rocuronium	Both rocuronium and cisatracurium are now considered extremely attractive agents	45
Prospective study	Compared recovery time after continuous infusion of cisatracurium and rocuronium	Cisatracurim should be preferred over rocuronium	46
Review		Cisatracurium or rocuronium is recommended for neuromuscular blockade in modern cardiac surgery	16

Residual Paralysis and Reversal Agents

Muscle relaxation is one of the major elements of the general anaesthesia triad along with the usage of hypnosis and analgesia. However, the reversal procedures at the end of surgery are the matter of concern. Several significant clinical issues including perioperative management of neuromuscular blockade, adequate monitoring and residual neuromuscular blockade have been identified. Because of these concerns, long-acting NMBs are rarely used in the clinical practice. An ideal neuromuscular blocking agent should not only provide profound relaxation but also offer ease of reversal. Thus, ensuring the safety of neuromuscular blockade usage necessitates the availability of agents that can be quickly and reliably reversed.[5] Reversal agents are of great importance in order to restore neuromuscular function in patients and to reduce the risk of postoperative residual paralysis. Several reversal agents hold clinical relevance offering distinct advantages and considerations, which are as follow:

Acetylcholinesterase inhibitors: These inhibitors function by antagonizing the action of NMBs through a mechanism involving the enzyme acetylcholinesterase. Normally, acetylcholinesterase functions to degrade acetylcholine at the neuromuscular junction but acetylcholine accumulates upon inhibition, competing with NMBs for receptive sites on nicotinic receptors.[47] This competition facilitates the reversal of neuromuscular blockade. The median recovery time following administration of acetylcholinesterase inhibitors is typically around 15 minutes, although this timeframe may vary depending on individual patient factors and clinical circumstances. It is imperative to recognize that the increased concentration of acetylcholine resulting from these inhibitors can also affect muscarinic receptors, potentially leading to adverse effects such as bradycardia and bronchoconstriction. To mitigate these risks, the concurrent administration of an antimuscarinic drug like glycopyrrolate is recommended. This adjunctive therapy helps to counteract the muscarinic effects of acetylcholine accumulation, thereby minimizing the occurrence of unwanted side effects and ensuring a smoother recovery from neuromuscular blockade reversal.[48]

Sugammadex: Sugammadex a crucial reversal agent in anaesthesia practice is comprised of a gamma-cyclodextrin compound. It facilitates the encapsulation of NMBs within the plasma. This process results in the formation of a tightly bound, inactive sugammadex-aminosteroidal complex, which is subsequently excreted via the urine.[49] Sugammadex has a remarkable ability to rapidly reverse even deep or profound levels of neuromuscular blockade, swiftly restoring normal muscle function. However, it is important to exercise caution, as its use is contraindicated in patients with a creatinine clearance of less than 30 mL min^{-1}.[50] Furthermore, while hypersensitivity reactions to sugammadex are rare in clinical settings, they remain a potential concern that necessitates vigilance. Despite these considerations, sugammadex remains an invaluable tool in the management of neuromuscular blockade, offering a swift and effective means of reversing its effects.

Conclusion

In conclusion, NMBs serve as valuable adjunctive therapy across a spectrum of surgical procedures, including transplantations and cardiac surgeries. However, the

optimal utilization of a specific NMB necessitates a comprehensive understanding of its intricate properties. Over recent decades, significant strides and breakthroughs have reshaped the landscape of cardiac anaesthesia and surgery. Despite historical preferences, such as the use of pancuronium in cardiac surgery, it has become evident that its pharmacodynamics and pharmacokinetics render it less than ideal. In contrast, cisatracurium emerges as a superior choice for NMB due to its profound properties, highlighting the importance of staying abreast of advancements in pharmacology to optimize patient outcomes and ensure the efficacy and safety of anaesthesia protocols.

Footnotes

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Original Article
Other

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Can Artificial Intelligence be Successful as an Anaesthesiology and Reanimation Resident?

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Abstract

Objective: This study aims to compare the performance of artificial intelligence (AI) chatbot ChatGPT with anaesthesiology and reanimation residents at a major hospital in an exam modelled after the European Diploma in Anaesthesiology and Intensive Care Part I.

Methods: The annual training exam for residents was administered electronically. One day prior to this, the same questions were posed to an AI language model. During the analysis, the residents were divided into two groups based on their training duration (less than 24 months: Group J; 24 months or more: Group S). Two books and four guides were used as references in the preparation of a 100-question multiple-choice exam, with each correct answer awarded one point.

Results: The median exam score among all participants was 70 [interquartile range (IQR) 67-73] out of 100. ChatGPT correctly answered 71 questions. Group J had a median exam score of 67 (IQR 65.25-69), while Group S scored 73 (IQR 70-75) ($P < 0.001$). Residents with less than 24 months of training performed significantly worse across all subtopics compared to those with more extensive training ($P < 0.05$). When ranked within the groups, ChatGPT placed eighth in Group J and 47th in Group S.

Conclusion: ChatGPT exhibited a performance comparable to that of a resident in an exam centred on anaesthesiology and critical care. We suggest that by tailoring an AI model like ChatGPT in anaesthesiology and resuscitation, exam performance could be enhanced, paving the way for its development as a valuable tool in medical education.

Keywords: Anaesthesiology, exam, large language models

Main Points

- Keeping up with the rapid advancements in medical technologies, pharmaceuticals, and interventions, and integrating them into anaesthesiology education is essential.
- Large language models are artificial intelligence systems trained on huge datasets to understand, analyze, and generate text using deep learning techniques and artificial neural networks.
- Comparing trainee physicians in anaesthesiology and reanimation with artificial intelligence models trained on large datasets, can help guide the design of training programs for anaesthesiology and reanimation residents.

Introduction

The science of anaesthesiology and critical care is undergoing a significant digital transformation. This makes it necessary to keep up with the rapid developments in medical technologies, drugs and interventions, and to integrate these into education. Combining traditional knowledge and skills training with cutting-edge digital content, including artificial intelligence (AI), holds great potential for enhancing anaesthesia training.[1]

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Natural language processing (NLP) is a subfield of AI that focuses on understanding, analyzing, and generating human language, often using large language models (LLMs) for advanced capabilities. The most widely used LLM is ChatGPT® (OpenAI, USA). The latest version, ChatGPT-4, has enhanced its ability to understand and generate human language, and it has been reported to provide more accurate, context-appropriate, and effective responses.[2]

ChatGPT has been included in exams with various content and formats. While its responses were found to be sufficient in some cases, it was observed that improvements were needed in others.[3-5] This study aims to test the hypothesis that ChatGPT will outperform anaesthesiology and reanimation residents at a major hospital, in an exam modeled after the European Diploma in Anaesthesiology and Intensive Care (EDAIC) Part I.

Methods

Ethical Statement

The Scientific Research Evaluation and Ethics Board of University of Health Sciences Türkiye, Ankara Etlik City Hospital determined that this singlecentre, cross-sectional study did not require ethical approval (date: 12/06/2024, approval no.: AESHBADEK-2024-546). All participants were informed about the study, and their written consent was obtained.

When writing this article, an AI program was used to correct spelling and grammar (https://chat.openai.com).

Study Design

The study was conducted in the Clinic of Anaesthesiology and Reanimation at University of Health Sciences Türkiye, Ankara Etlik City Hospital. The exam was a standard part of the annual resident training programme, and all residents were informed about its schedule, content and format in advance. However, residents were kept blind to the protocol until informed about the study just before the exam.The study aimed to include all residents trained in the department. Accordingly, the exam date (14 October 2024) and time (9:00 AM, UTC+3) were determined. Residents gathered in the meeting rooms 15 minutes before the exam, and the exam was conducted simultaneously in six different rooms, each overseen by a different proctor. Participants were instructed to log in to the exam via their mobile phones and complete it within the allotted time. Once the exam period expired, the exam was automatically submitted online. At the end of the exam, the questions and answers were shared with all participants. The results were evaluated using e-forms. In the analysis of the results, residents were divided into two groups based on their training duration: those with less than 24 months (Group J) and those with 24 months or more (Group S).

One day before the questions were administered to the participants, they were directed to the ChatGPT application by two consultants (S.F.K., Y.Ö.) in anaesthesia and critical care, who were blind to the study protocol. A new user profile was created to prevent bias. All information and questions were presented in Turkish. Before starting the exam, the question "Which ChatGPT model are we using?" was asked, and it was confirmed that the ChatGPT-4 model was used. Then, the following information was provided to ChatGPT: "You are an anaesthesiology and reanimation resident working in a large hospital". I have prepared an evaluation exam for you. The purpose of the exam is to compare your knowledge with that of anaesthesiology and critical care resident physicians working in a large hospital. The exam topics are as follows: Anaesthesia equipment and monitors, clinical pharmacology, anaesthesia management, regional anaesthesia and pain, and intensive care. The exam consists of 25 questions, with five questions for each topic. Each question has four options. You must answer each option as "True" or "False". The questions will be asked of you one by one. I would like you to complete this exam within 30 minutes. The programme indicated that it was ready to perform its functions after receiving this information. The questions were copied from a word processor document into ChatGPT's chat box for the answers. The first generated answer was taken as the final response, and the option to regenerate the answer was unavailable. The answers were marked on an optical form by the assigned physicians. A total of 100 responses were obtained, with each correct answer scored as one point. There was no penalty for incorrect answers or unanswered questions.

Preparing the Exam

The exam was prepared by two physicians (G.K. and Y.Ö.) who have been specialists in anaesthesiology and resuscitation for at least 10 years. The questions were designed in a manner similar to the EDAIC Part I exam questions. Five main topics were identified: "Anaesthesia equipment and monitors, Clinical pharmacology, Anaesthesia management, Regional anaesthesia and pain, and Intensive care". A total of 25 questions were created, with five questions from each topic. Each question included four statements which were labelled as either "True" or "False". Two primary textbooks were used as references for preparing the questions.[6,7] For topics such as sepsis, acute respiratory distress syndrome, cardiopulmonary resuscitation, and nutrition, the most recent guidelines adopted by our clinic were utilised.[8-10] An associate professor (S.A.) and a professor (J.E.), who were blinded to the study protocol, reviewed the questions for accuracy and validity. After the ChatGPT exam was completed, the questions were converted into an online form for physicians to answer. The questions did not include tables or figures.

Outcome Measures

The primary outcome of the study was the comparison of exam performance among anaesthesiology and reanimation residents and the ChatGPT programme, measured by the total number of correct answers. Secondary outcomes included the relationship between residents' training duration and their exam performance, ChatGPT's performance compared to residents with varying levels of training, and the concordance between ChatGPT and the reference in answering the exam questions.

Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics (version 25.0, IBM Corp., Armonk, NY, USA). Descriptive statistical methods [frequency, percentage, median and interquartile range (IQR 25-75)] were used to evaluate the study data. The normality of the data distribution was assessed using the Shapiro-Wilk test. Non-parametric tests were preferred for the analysis of data that did not follow a normal distribution. The Mann-Whitney U test was employed to compare the two groups. The level of agreement between the responses provided by ChatGPT and the reference answers was assessed using Cohen's kappa coefficient. The Kappa values were interpreted based on the classification proposed by Landis and Koch: <0, poor agreement; 0-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, almost perfect agreement.[11] Additionally, McNemar's test was performed to determine whether there was a statistically significant difference between ChatGPT's correct and incorrect responses compared to the reference answers. A significance level of $P < 0.05$ was considered for all analyses.

Results

A total of 166 residents worked in the Clinic of Anaesthesiology and Reanimation at University of Health Sciences Türkiye, Ankara Etlik City Hospital. Two residents were unable to participate in the examination as they were on maternity leave, and 24 residents did not consent to the use of their exam results for research purposes. Additionally, one resident did not complete the exam within the required timeframe. Consequently, the exam results of 141 residents were included in the study (Figure 1).

ChatGPT answered all the options of the 25 questions (100 answers) and completed the exam in approximately 18 minutes. Only for the first question did it provide explanations alongside the "true/false" answers. For the other questions, it only provided "true/false" answers. It did not leave any questions unanswered. At the end of the exam, it did not wish to change any of its answers.

The median exam score for all participants was 70 out of 100 (IQR 67-73). ChatGPT's correct answer count was found to be 71 (Table 1). Residents with less than 24 months of training had significantly different exam results, both overall and in all subtopics, compared to those with longer training (Table 1). When ranked by exam results, ChatGPT placed 54th in this sample. The exam performance of the groups is presented in Figure 2, with ChatGPT's score marked by a red line. When the exam results were ranked by group, ChatGPT ranked eighth in Group J. In the ranking within Group S, ChatGPT ranked 47th.

ChatGPT provided correct answers to all options in five out of 25 questions. There were no questions for which all answers were incorrect. However, for two questions, the majority of options (3/4) were answered incorrectly. The first of these questions was related to the anatomy of peripheral nerve blocks, where incorrect answers were given for options related to the anatomical structures of the obturator, femoral, and axillary nerves. The second question was related to resuscitation in a hypothermic patient, where incorrect answers were provided for compression, adrenaline administration, and defibrillation. The highest number of correct answers was found in the "Anaesthesia Management" section (17/20 points). The sections with the most incorrect answers were "Clinical Pharmacology, Regional Anaesthesia-Pain and Intensive Care" (13/20 points for each).

The responses given by the ChatGPT-4 language model were compared with the reference answers in Table 2. Cohen's Kappa value was calculated as κ=0.38 (P=0.000). The significance of McNemar's test was found to be P=0.137.

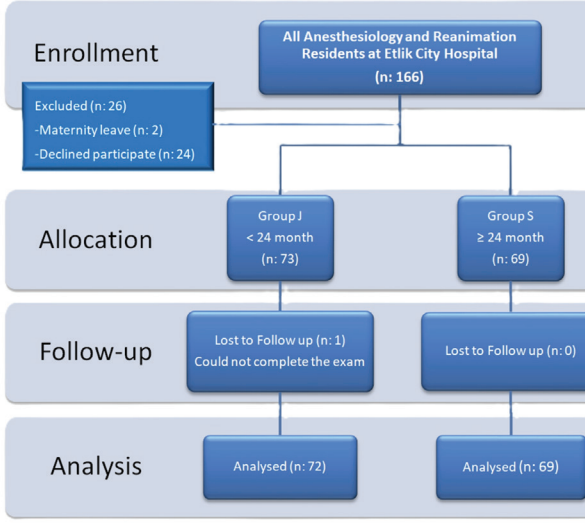

Figure 1. Flowchart of the study

Table 1. Correct Answers of Anaesthesiology and Reanimation Residents and ChatGPT

	Total n=141 Median (IQR 25-75)	Group J (<24 month) n=72 Median (IQR 25-75)	Group S (≥24 month) n=69 Median (IQR 25-75)	*P**	ChatGPT
Anaesthesia equipment and monitors	15 (14-16)	14.5 (14-15)	16 (15-17)	<0.001	15
Clinical pharmacology	12 (11-13)	11 (11-12)	12 (11-14)	0.002	13
Anaesthesia management	16 (15-18)	16 (14-16)	17 (16-18)	<0.001	17
Regional anaesthesia and pain	15 (13-16)	14 (13-15)	15 (14-16)	0.007	13
Intensive care	12 (11-13)	11 (10.25-12)	13 (11-14)	0.001	13
Total score	70 (67-73)	67 (65.25-69)	73 (70-75)	<0.001	71

*It is comparison of Group J and Group S
IQR, interquartile range.

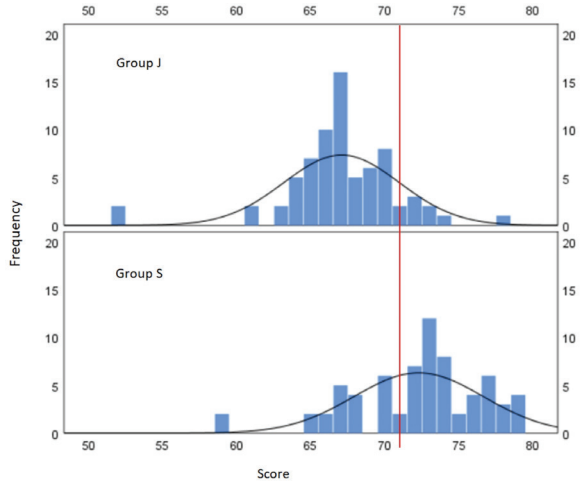

Figure 2. The exam performance of the groups. ChatGPT's score marked by a red line.

Discussion

It is important for physicians and residents working in medicine to recognize NLP models like ChatGPT-4, evaluate their applicability, and examine their limitations.[12] In response to the question, "Is ChatGPT a successful resident?", ChatGPT scored 71 points in a 25-question, 100-point exam similar to the EDAIC Part I, and this score was very close to the median score for all residents. When the residents were divided into two groups based on their training duration, it was observed that ChatGPT provided more correct answers than most of those with less than 24 months of training. However, ChatGPT scored lower than most of those with longer training. ChatGPT's responses to the exam showed a moderate level of agreement with the reference answers and did not reveal any significant differences.

Table 2. Comparison of ChatGPT and Reference Answers

		Reference		Total
		True	False	
ChatGPT	True	49	19	68
	False	10	22	32
Total		59	41	100

ChatGPT has been reported to achieve an accuracy rate of 65-75% on the American Heart Association's Basic Life Support (BLS) and Advanced Cardiovascular Life Support (ACLS) exams. In this study, the authors utilised scenario-based and single-answer questions from the 2016 BLS and ACLS examinations. While the correct answers provided by ChatGPT did not meet the passing threshold of 84%, the results showed a significantly better alignment with resuscitation guidelines compared to previous studies.[13] In another study, ChatGPT demonstrated an accuracy rate of approximately 80% on the 2022 and 2023 National Medical Licensing Examination in Japan, meeting the passing thresholds for these exams.[14] Similarly, in a study evaluating the performance of ChatGPT on an e-Fellowship of the Royal College of Anaesthetists (FRCA) primary exam, it achieved approximately 70% accuracy in multiple choice questions (MCQs). Our results show that ChatGPT can answer Primary FRCA MCQ practice questions at a level close to the 2019 exam pass mark, which was 0.713.[15] However, ChatGPT-4's performance on the Japan Society of Anaesthesiologists (JSA)-certified anaesthesiologist exams was limited, with success rates of 51% and 49% observed for the 2021 and 2022 examinations, respectively.[16] In another study aimed at evaluating ChatGPT's level of anaesthesiology expertise using questions styled after the American Board of Anaesthesiology's (ABA) written examinations, the model achieved a moderate success rate of 56%.[17] In our study, ChatGPT-4 demonstrated a noteworthy performance rate of 71%. This success rate represents a promising indication

of its potential to serve as a reliable resource for passing actual board exams or maintaining certification standards.

It could be anticipated that the participants, divided into two groups based on their years of training, would show differences in the subtopics and in their total scores. It was an expected outcome that individuals with more time spent in professional training would achieve superior performance. However, it was surprising to observe that AI lagged behind many of the senior residents. In a study conducted in medical biochemistry, ChatGPT's performance was compared with that of 100 medical students. The exam included multiple-choice and subjective questions, and it was found that ChatGPT performed better than in the students' responses.[18] In another study, the "Progress Test Medicine" in Germany was administered to ChatGPT. In this multiple-choice exam, ChatGPT outperformed almost all German medical students in the first to third years of a six-year medical programme.[19] In another study, it was noted that ChatGPT achieved better results than both medical students and residents in a written neurosurgery exam consisting of board-like questions.[20] In a study involving histopathological examinations, ChatGPT fell behind pathology residents in all responses.[21] The success of ChatGPT in this study was very close to the performance level of all residents. The fact that the exams were multiple-choice, that they involved images in pathological and radiological evaluations, and that some exams were open-ended and required reasoning will certainly affect the differences in these results. In this study, the exam questions required both knowledge and reasoning. No questions containing images or tables were asked, and there were no open-ended questions.

The agreement between ChatGPT and the reference answers was moderate (κ=0.38), with no significant differences observed between them. This outcome may reflect not only the AI algorithm but also the methodology used in preparing the questions. The questions were developed based on both fundamental textbook knowledge and updated guidelines. The answers were not designed to allow for open interpretation by ChatGPT: they were limited to two options: true/false. Before the questions were shared electronically with participants, they were tested using ChatGPT to check for any prior exposure by the AI. In some studies, evaluations of ChatGPT are carried out using questions from previously administered exams; however, this approach increases the risk of bias.[22] Even a single instance of questions being entered into electronic systems-whether for exam preparation, distribution, printing, or as a result of individuals searching for them online-can familiarize AI applications with these questions, potentially leading to artificially inflated performance scores. In our study, particular care was taken to address this issue, and the questions were saved only in a word processor document and not uploaded to any electronic platform. Another factor that likely influenced the alignment between ChatGPT's responses and the reference answers is the language used. Although this program, developed as a LLM, has a translation feature in many languages, the fact that the exam was conducted in Turkish may have affected the program's performance and its alignment with the reference answers.

This study did not involve open-ended questions-only two options, true or false, were provided. Even under the conditions we set, ChatGPT could not express uncertainty and never responded with "I don't know" or "I don't want to answer". In some studies, ChatGPT has been observed to justify incorrect answers as convincingly as correct ones, a behaviour that is not uncommon in LLMs, sometimes referred to as "hallucination".[19] The question of whether integrating ChatGPT into medical education programs would be beneficial is at the core of this and similar studies. However, its inability to express uncertainty and its tendency to misinterpret information limit its usefulness in medical education.

Study Limitations

The potential benefits of the study include gaining insights into ChatGPT's proficiency in anaesthesiology and critical care topics and generating data to inform future adjustments to the assistant training curriculum related to AI. However, the study had limitations; it only included residents trained in a single clinic, and generalizing the findings may be problematic due to the homogeneous training background of the participants. Although the questions were carefully designed to cover all relevant topics, they may not have encompassed every aspect of anaesthesia, analgesia and critical care procedures. Additionally, the language used in ChatGPT was set to Turkish.

Conclusion

ChatGPT demonstrated an average performance at the level of a resident in an exam focused on anaesthesiology and critical care. While it may provide guidance for beginner-level residents, it generated inadequate responses compared to more experienced residents. By training an AI like ChatGPT in anaesthesiology and resuscitation, it could demonstrate higher exam performance and be developed into an AI that can be utilized in anaesthesiology and reanimation education.

Ethics

Ethics Committee Approval: The Scientific Research Evaluation and Ethics Board of University of Health Sciences Türkiye, Ankara Etlik City Hospital determined that this singlecentre, cross-sectional study did not require ethical approval (date: 12/06/2024, approval no.: AESHBADEK-2024-546).

Informed Consent: All participants were informed about the study, and their written consent was obtained.

Footnotes

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

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Original Article
Animal Studies

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The Potential Renoprotective Effect of Sugammadex in Renal Ischemia-reperfusion Injury

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Abstract

Objective: We aimed to evaluate the effectiveness of sugammadex on renal tissue for against ischemia-reperfusion injury.

Methods: Twenty-one Wistar albino strain female rats were divided into three groups. The first group functioned as the control cohort for comparison. In Groups 2 and 3, a renal ischemia-reperfusion model was established. Moreover, following the cessation of ischemia, the rats in Group 3 were intravenously administered sugammadex at a dose of 4 mg kg^{-1}. Blood and tissue samples were subsequently collected for analysis.

Results: Biochemical analyses revealed a notable increase in the enzymatic activities of glutathione peroxidase and superoxide dismutase in Group 3 relative to Group 2 ($P < 0.001$ and $P=0.015$, respectively). Additionally, the concentration of malondialdehyde was found to be significantly reduced in Group 3 relative to Group 2 ($P=0.004$). Group 3 exhibited a substantial decrease in tumor necrosis factor-alpha, interleukin 6, and interleukin 1 beta levels when compared to Group 2 ($P=0.021$, $P=0.006$, and $P=0.016$ respectively). Group 2 exhibited the highest concentrations of neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 ($P < 0.001$ and $P=0.015$, respectively). Similarly, the histopathologic tissue damage was the most prominent in Group 2 ($P < 0.001$).

Conclusion: Sugammadex plays a protective role against ischaemia-reperfusion injury in renal tissue.

Keywords: Ischaemia-reperfusion injury, renal, rat, sugammadex

Main Points

- A sudden deterioration in renal function, known as acute renal failure, results in the retention of metabolic waste and disruptions in fluid and electrolyte regulation.
- One of the primary contributors to acute renal failure is renal ischemia-reperfusion injury.
- Sugammadex is a pharmacological agent widely used in general anaesthesia practices to reverse the effects of muscle relaxants.
- Our study's biochemical and histopathological data suggest that sugammadex provides substantial protection against renal ischemia-reperfusion injury.

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Introduction

Acute renal failure is a medical disorder marked by an abrupt decline in kidney function and is commonly encountered in emergencies and intensive care units.[1] Approximately 5% of long-term hospitalized patients suffer from pathologies associated with acute renal failure.[2] One of the primary contributors to acute renal failure is renal ischemia-reperfusion injury.[1] Renal ischemia is defined as a temporary reduction or interruption of renal blood flow. If renal ischemia persists for a long time, cellular integrity is disrupted, and cell death occurs due to excessive accumulation of toxic metabolites. Reperfusion is required to clear toxic metabolites and to maintain tissue viability. Paradoxically, detrimental changes occur much more severely during reperfusion than during ischemic injury. This condition is defined as ischemia-reperfusion injury. The kidneys are quite sensitive to ischemia-reperfusion injury: tubular damage, atrophy, and dilation in tubules are the most common histopathological findings.[3] Several factors, including trauma, shock, infarction, sepsis, aortic dissection, and urologic surgery, contribute to the etiology of reperfusion injury.[1,4] There is limited knowledge about the mechanism of renal ischemia-reperfusion injury. Multiple factors contributing to its pathogenesis, such as oxidative stress, epithelial cell dysfunction, inflammation, cellular necrosis, tubular obstruction, and apoptosis, have been identified by *in vivo* studies as well as by in *in vitro* studies in recent years.[5,6] Furthermore, renal ischemia-reperfusion injury continues to be linked with mortality rates reaching as high as 79%.[7] Renal ischemia-reperfusion is a topic that is intensively studied to minimize the effects on patients.[8]

Sugammadex is a pharmacological agent widely used in general anaesthesia practices to reverse the effects of muscle relaxants, such as rocuronium and vecuronium. This molecule, belonging to the gamma-cyclodextrin group and containing eight sugar rings, is widely used in operating rooms for purposes such as post-operative extubation and reversing newly developed blocks in patients who cannot be intubated or ventilated.[9,10] In addition, recent experimental studies have documented that sugammadex mitigates the damage caused by ischemia-reperfusion injury by suppressing inflammation and enhancing antioxidant enzyme activity.[10,11] The most important advantage of sugammadex is that it can provide fast and effective reversal in anaesthesia practice involving difficult airway ventilation.[9] We thought that evaluating the positive effects of sugammadex, which provides significant advantages to anaesthesia, on tissue oxidative damage from a novel perspective would make important contributions to the literature.

The hypothesis of this study is that sugammedex may reduce renal ischemia reperfusion injury and have nephroprotective effects in a rat renal hypoxia model by showing anti-inflammatory and antioxidant activity. Although the renoprotective effect of sugammadex in renal ischemia-reperfusion injury has been previously evaluated histopathologically, this study aims, for the first time in the English literature, to investigate the potential protective role of sugammadex using both biochemical and histopathological analyses.

Methods

Experimental Animals and Groups

This research involved 21 female albino Wistar rats, each with a weight ranging from 220 to 400 g. The animals were kept in standard cages under strictly controlled conditions, with humidity levels maintained between 45% and 55%, while the ambient temperature was regulated at 20-22 °C. A 12-hour alternating light/dark cycle was applied throughout the study. Vital signs (heart rate, breathing rate, and depth) were stable and similar for all rats throughout the experiment. The experiment adhered to the National Institutes of Health guidelines for animal research and received approval from the Tokat Gaziosmanpaşa University Rectorate, Animal Experiments Local Ethics Committee (approval no.: 2024 HADYEK-13, date: 15.08.2024).

Experimental Method

In the operating room, all experimental animals received an intraperitoneal injection of ketamine hydrochloride (50 mg kg^{-1}) combined with xylazine (7.5 mg kg^{-1}) to induce general anaesthesia. After the appropriate depth of anaesthesia was obtained, the abdominal hairs of all rats were shaved in the supine position, and sterile conditions were met by using povidone-iodine and sterile gauze. Subsequently, all experimental animals underwent laparotomy with a midline incision of 3 cm. The right nephrectomy was performed.[12] Following nephrectomy, this procedure was conducted on all rats, and the experimental animals were allocated into three groups.

Group 1: This cohort functioned as the control cohort. The left renal pedicle was separated, and a left nephrectomy was performed without using any additional surgical intervention or pharmacological agent.

Group 2: This cohort functioned as the ischemia-reperfusion group. The left renal pedicle was separated and subjected to clamping for 45 minutes. A left nephrectomy was performed 6 hours after the clamp was taken out.[12]

Group 3: This cohort functioned as the treatment group. The same procedures applied in Group 2 were applied in Group 3. Additionally, 4 mg kg^{-1} of sugammadex was delivered intravenously to the rats in this group following the termination of ischemia.[10]

Fluid and heat balance was maintained very precisely throughout all interventions. Heparin (100 U kg^{-1}) was

administered intraperitoneally at the beginning of the procedures to prevent renal artery thrombosis.[13] Upon completion of the experiment, blood samples were collected from all rats via the inferior vena cava, followed by a left nephrectomy. Finally, cervical dislocation was applied to all experimental animals to terminate their vital functions.

There were no human subjects in this study and informed consent is not applicable.

Biochemical Analysis

Preparation of Samples

Renal tissues and serum specimens were preserved at -80 °C. Half of the kidney tissue taken was separated for enzyme-linked immunosorbent assay (ELISA) testing and the other half for oxidative stress parameters. Only the supernatant was obtained for ELISA testing from kidney tissue. Kidney tissue specimens were homogenized on ice using a 50 mM Tris-HCl buffer solution (pH=7.4) at a dilution ratio of 1:10. Malondialdehyde (MDA) concentrations were quantified in the homogenized samples. A fraction of the homogenates underwent centrifugation at 3,200×g for about 15 minutes at 4 °C , yielding supernatant fractions. The enzymatic activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were assessed in the collected supernatants. Protein concentrations were evaluated in both homogenized samples and supernatant fractions.

Measurement of GSH-Px and SOD Activity in Kidney Tissue

SOD enzyme activity was evaluated in accordance with the methodology outlined by Sun et al.,[14] while GSH-Px levels were quantified following the protocol proposed by Paglia and Valentine.[15] The enzymatic activities of both were quantified as units per gram of tissue protein (U g protein).

Measurement of MDA Levels in Kidney Tissue

The quantification of MDA levels is based on its reaction with thiobarbituric acid at 90 °C, leading to the formation of a pink chromogen. This reaction product is subsequently measured using spectrophotometry at 532 nm. The obtained values are presented as (nmol g wet tissue) determined through a standard calibration curve generated from serial dilutions of 1,1,3,3-tetramethoxypropane.[16]

Measurement of Protein in Tissues

Tissue protein levels were quantified with bovine serum albumin serving as the standard reference.[17]

Measurement of tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), interleukin-1beta (IL-1beta), kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL).

Measurements were obtained by Thermo Scientific's Multiskan FC photometric microplate reader. Kidney tissue was separated for KIM-1 and NGAL measurement. Kidney tissues were rinsed with ice-cold phosphate buffer solution (PBS) (0.01 N, pH=7.4) to remove excess blood. Kidney tissue specimens were homogenized on ice under cold conditions, using PBS at a rate of 1/10. Kidney injury molecule-1 and NGAL were investigated in supernatants obtained after homogenization. The results are expressed as ng protein.

The concentrations of TNF-alpha, IL-6 and IL-1beta in serum samples were measured through ELISA kits following the manufacturer's guidelines. Results are expressed as ng l^{-1} and pg mL^{-1} respectively.

Histopathological Analysis

Renal tissue specimens were maintained in a 4% buffered neutral formalin solution for 72 hours to facilitate histological examination. Following fixation, the kidneys were continuously rinsed with running water throughout the day, dehydrated through a sequential series of alcohol concentrations, and cleared using xylene baths. Subsequently, paraffin infiltration was performed in three separate paraffin baths at 60 °C. The tissues were then embedded in paraffin in the same orientation, and sectioned into blocks. Consecutive thin serial sections (5 µm thickness) of the paraffin-blocked kidneys were taken using a rotary microtome (Leica RM2135, Germany) and mounted on slides with ground edges for hematoxylin and eosin staining. These slides were then prepared for histopathological analysis.

Histological slides were examined blindly using a light microscope (Nikon Eclipse 200, Japan) at 40× magnification by a single experienced histopathologist. Renal tissue samples were assessed for overall structural integrity, parenchymal and stromal injury, tubular architecture, vascular congestion, and necrotic alterations. The severity of these pathological changes was graded semi-quantitatively on a scale from 1 to 4. Specifically, a score of 1 (none) denotes no detectable damage; a score of 2 (mild) represents minor alterations, including epithelial flattening, tubular dilation, nuclear dropout, and brush border loss; a score of 3 (moderate) signifies moderate injury characterized by focal coagulative necrosis; and a score of 4 (severe) corresponds to infarction or extensive tissue damage.[18]

Statistical Analysis

Descriptive statistical analyses were performed to outline the general characteristics of the study groups. Continuous variables were represented as mean ± standard deviation along with median (minimum-maximum). Intergroup differences in variables were assessed using One-Way Analysis of Variance (ANOVA). Further comparisons were carried out using the post-hoc Tukey HSD test when the variances of the groups are equal (homogeneous variance) or Tamhane's T2 test when the variances of the groups are

not equal (heterogeneous variance). *P* values were deemed statistically significant when below 0.05. Statistical analyses used commercially available software (IBM SPSS Statistics 22, SPSS Inc., an IBM Company, Somers, NY).

Results

Biochemical analysis of blood samples revealed a reduction in pro-inflammatory cytokine levels, including IL-1β, IL-6, and TNF-α, in Group 3 relative to Group 2 (P=0.016, P=0.006, and P=0.021, respectively) (Table 1, Figure 1). Tissue biochemical assessments demonstrated that Group 2 exhibited the lowest levels of GSH-Px and SOD activity ($P < 0.001$ and P=0.003, respectively). However, antioxidant enzyme levels were significantly elevated in Group 3 relative to Group 2 ($P < 0.001$ and P=0.015, respectively). The highest concentrations of NGAL and KIM-1 were observed in Group 2 ($P < 0.001$ and P=0.015, respectively), whereas a significant reduction in these markers was noted in Group 3 relative to Group 2 ($P < 0.001$ and P=0.034, respectively). The mean MDA level in Group 2 was measured at 9.56±1.81, and it significantly decreased in Group 3 (P=0.004) (Table 2, Figure 2).

In Group 2, significant histopathological tissue damage was observed, including epithelial flattening, tubular dilation and irregularities, nuclear detachment/extrusion, loss of the brush border, ischemic and necrotic regions, glomerular deformities, localized tissue infarction areas, extensive hemorrhage, and congestion (Figure 3). The tissue damage score in Group 2 was recorded as 3.13±0.4, which was significantly elevated compared to the other groups ($P < 0.001$). Conversely, Group 3 exhibited notable improvement in renal tissue morphology under microscopic examination, with a recorded damage score of 2.06±0.26 ($P < 0.001$) (Table 3, Figure 4).

Discussion

In this study, the effect of sugammadex on renal ischemia-reperfusion injury was investigated biochemically and histopathologically. Current biochemical results showed that sugammadex significantly suppressed the increase in MDA level and pro-inflammatory cytokine levels, including IL-1beta, IL-6, and TNF-alpha caused by the ischemia-reperfusion injury in renal tissue. Furthermore, it was revealed that sugammadex prevented the decrease in GSH-Px and SOD antioxidants caused by ischemia-reperfusion in renal tissue, and provided a significant improvement in renal function parameters such as NGAL and KIM-1. Sugammadex also exhibited notable recovery in renal tissue morphology under microscopic examination.

Acute kidney injury (AKI) is a medical condition defined by a rapid decline in renal function, occurring within hours to days. This impairment leads to the kidney's an

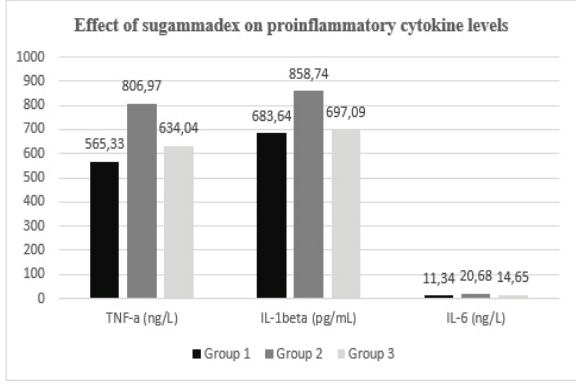

Figure 1. Comparative graphic representation of TNF-alpha, IL-1beta and IL-6 levels.

TNF-alpha, tumor necrosis factor-alpha; IL, interleukin.

Table 1. Effect of Sugammadex on Pro-inflammatory Cytokine Levels

	Groups	N	Mean ± SD	*P* values	η^2 (Partial Eta Sq.)	Post-hoc *P* values
TNF-a (ng/L)	1	7	565.33±152.17	**0.002***	**0.504**	**1-2:0.002***
	2	7	806.97±94.1			**1-3:0.480**
	3	7	634.04±60.2			**2-3:0.021***
IL-1beta (pg/mL)	1	7	683.64±111.51	**0.006***	**0.473**	**1-2:0.009***
	2	7	858.74±99.61			**1-3:0.964**
	3	7	697.09±78.73			**2-3:0.016***
IL-6 (ng/L)	1	7	11.34±1.60	**<0.001***	**0.736**	**1-2:<0.001***
	2	7	20.68±3.65			**1-3:0.059**
	3	7	14.65±1.70			**2-3:0.006***

*: The *P* value is significant at the 0.05 level.
SD, standard deviation; TNF-alpha, tumor necrosis factor-alpha; IL, interleukin.

Table 2. Effect of Sugammadex on Renal Function and Oxidative Stress Levels

	Groups	N	Mean ± SD	*P* values	η² (Partial Eta Sq.)	Post-hoc *P* values
SOD (U g protein)	**1**	7	48.04±13.62	**0.003***	**0.483**	**1-2:0.003***
	2	7	28.54±5.17			**1-3:0.767**
	3	7	44.5±7.55			**2-3:0.015***
GSH-Px (U g protein)	**1**	7	7.27±0.65	**<0.001***	**0.743**	**1-2:<0.001***
	2	7	4.48±0.97			**1-3:0.094**
	3	7	6.39±0.54			**2-3:<0.001***
MDA (nmol g wet tissue)	**1**	7	5.83±0.72	**<0.001***	**0.673**	**1-2:<0.001***
	2	7	9.56±1.81			**1-3:0.091**
	3	7	7.22±0.48			**2-3:0.004***
KIM-1 (ng protein)	**1**	7	6.27±2.19	**0.015***	**0.373**	**1-2:0.024***
	2	7	8.81±1.1			**1-3:0.985**
	3	7	6.41±1.4			**2-3:0.034***
NGAL (ng protein)	**1**	7	24.26±6.07	**<0.001***	**0.685**	**1-2:<0.001***
	2	7	44.91±8.86			**1-3:0.472**
	3	7	28.42±3.55			**2-3:<0.001***

*: The *P* value is significant at the 0.05 level.
SD, standard deviation; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lip

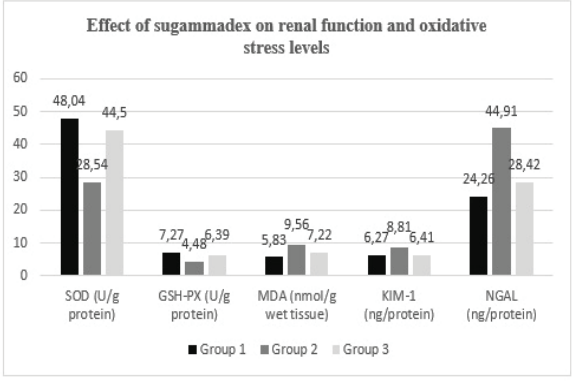

Figure 2. Comparative graphic representation of SOD, GSH-Px, MDA, KIM-1 and NGAL levels.

SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin.

inability to efficiently eliminate nitrogenous waste products and regulate electrolyte and fluid balance. Each year, AKI affects an estimated 13.3 million individuals worldwide, with approximately 1.7 million associated fatalities annually.[19] There are many factors involved in the etiology of acute renal failure, such as urinary stone diseases, infective pathologies, and the use of toxic pharmacological agents; however, renal ischemia–reperfusion injury is shown to be one of the most critical causes.[1]

The phenomenon of ischemia-reperfusion was first observed in the heart by Murry in 1986.[20] However, we still have limited knowledge about the physiopathology of ischemia-reperfusion injury. During the ischemic period, anaerobic metabolism prevails since oxygen levels are quite low in the tissues. In this condition, tissues are not provided with high energy levels as in aerobic metabolism. Acidosis occurs in the cell due to lactate accumulation within the cellular environment.

The Na^+/K^+-ATPase pump is inhibited with decreased adenosine triphosphate (ATP) and pH levels. As a result, Na^+ and Ca^{2+} ion concentrations increase inside the cell. Cellular edema develops because of this change in Na^+ ions. Elevated Ca^{2+} activates protease and phosphatase, causing a cytotoxic effect on the cell. Furthermore, the lysosome membrane is destabilized, leading to the release of enzymes responsible for hydrolysis, which has detrimental effects on the cell in this acidic environment with low levels of energy. With the continuation of the ischemic process, an increase in the level of proinflammatory cytokines and a decrease in antioxidant enzyme levels are observed. This causes the

cell to be highly vulnerable to tissue damage during the reperfusion period.

Low-energy-capacity adenosine monophosphates, and adenosine molecules, which are ATP products, are present in large amounts in the environment during the ischemic period. The breakdown of these molecules leads to elevated levels of hypoxanthine and inosine. When blood flow is reestablished in the tissues, oxygen, which is readily available in the environment, interacts with various molecules, particularly hypoxanthine that accumulates under ischemic conditions, and becomes unstable due to its reaction with oxygen-derived oxidants. This interaction triggers the formation of reactive oxygen species (ROS).[6,21] A rapid surge in ROS levels plays a crucial role in renal ischemia-reperfusion injury. ROS levels are critical to maintaining cell life, affecting components such as membrane lipids, macromolecules, carbohydrates, and cell genomes. They contribute to cell apoptosis and necrosis via reversible or irreversible reactions with these biomolecules. Nevertheless, their ROS stimulate the production of vasoconstrictor mediators, such as endothelin-1 (ET-1). Accordingly, glomerular filtration levels are negatively affected.[4]

Extensive research has been conducted on renal ischemia-reperfusion injury over the past century. Cámara-Lemarroy et al.[5] reported that reperfusion injury led to elevated levels of blood urea nitrogen (BUN), intercellular adhesion molecule-1, TNF-alpha, and ET-1, along with pronounced tubular damage. Similarly, Onem et al.[6] found that renal ischemia-reperfusion injury adversely impacted kidney function, resulting in increased serum urea and creatinine levels. In our study, an increase was observed in NGAL and KIM-1 levels, which are important markers of renal function due to renal ischemia-reperfusion injury. Conversely, our histopathologic examinations showed that edema, inflammatory cell migration, tubular dilatation, and vascularization scores were all adversely affected. Choi et al.[22] indicated that renal ischemia-reperfusion injury was associated with elevated levels of superoxide,

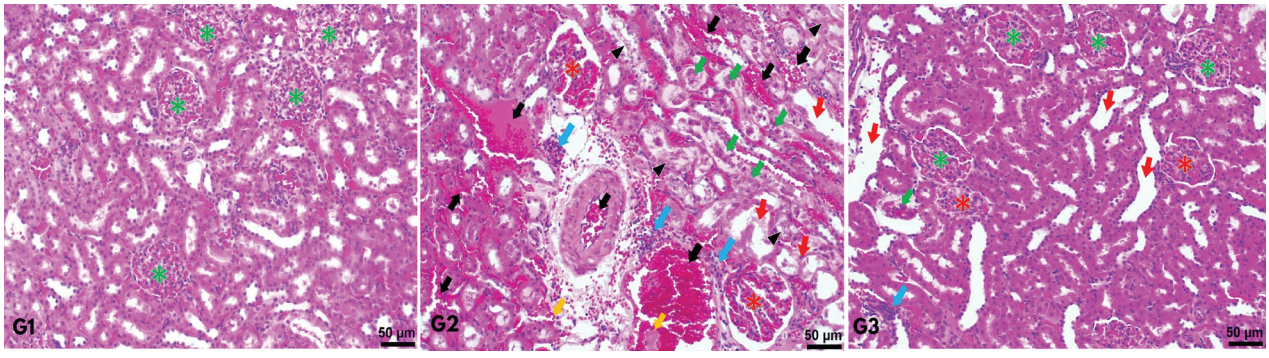

Figure 3. In Group 1, normal histological structures, including glomeruli and surrounding tubular structures, were observed without any tissue damage (G1). In Group 2, kidney tissues exhibited severe damage characterized by deformed glomerular and tubular structures, congestion and extensive hemorrhage, ischemia, parenchymal and stromal tissue infarction areas, intense inflammation, loss of brush borders in most tubules, apoptotic cells, and tubular cell debris (G2). In Group 3, moderate inflammation, tubular dilatation, and minimal glomerular deformities were observed.

Green star: Represents normal glomerular structure. Red star: Represents deformed glomeruli. Red arrow: Represents tubular dilatation. Blue arrow: Represents inflammation. Black arrow: Represents hemorrhage and congestion. Green arrow: Represents apoptotic cells and tubular epithelial debris. Arrowhead: Represents ischemic and necrotic areas (Hematoxylin-eosin, Scale bar: 50 µm).

Table 3. Effect of Sugammadex on Kidney Injury Histopathologically

	Groups	N	Mean ± SD	*P* values	η^2 (Partial Eta Sq.)	Post-hoc *P* values
Tissue damage score	1	7	1.1±0.1	<0.001*	0.912	1-2:<0.001*
	2	7	3.13±0.4			1-3:<0.001*
	3	7	2.06±0.26			2-3:<0.001*

*: The P value is significant at the 0.05 level. Interpretation of partial eta square value:
$0.01<\eta^2<0.06$: Small effect size. The independent variable has a weak effect on the dependent variable.
$0.06<\eta^2<0.14$: Medium effect size. The independent variable has a moderate effect on the variable variable.
$\eta^2>0.14$: Large effect size. The independent variable has a strong effect on the variable variable.
SD, standard deviation.

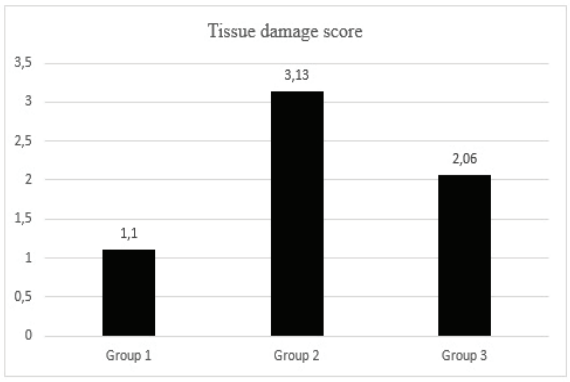

Figure 4. Comparative graphic representation of tissue damage score.

nitric oxide, and peroxynitrite, ultimately contributing to severe renal tissue damage. Similarly, Salahshoor et al.[2] observed an increase in lipid peroxidation following renal ischemia-reperfusion injury. Our analysis demonstrated that ischemia-reperfusion injury induced a prominent increase in MDA levels in experimental animals, alongside a significant decline in SOD and GSH-Px activity.

An acute inflammatory response occurs in ischemia-reperfusion injury. In the renal tissue exposed to oxidative damage, complex changes in the immune system, such as leukocyte activation, invasion, adhesion, and aggregation, are observed. This inflammatory reaction chain is a key contributor to the pathogenesis of renal ischemia-reperfusion injury.[4,20]

Oruc et al.[23] demonstrated in their experimental study that ischemia-reperfusion injury led to a significant rise in neutrophil accumulation, myeloperoxidase enzyme activity, and lipid peroxidation levels. These biochemical and cellular alterations contributed to secondary damage, particularly affecting the glomeruli and renal tubules. Xu et al.[24] reported that ischemia-reperfusion injury in the kidney was associated with elevated levels of BUN, creatinine, MDA, TNF-alpha, IL-1beta and IL-6, while simultaneously leading to a reduction in SOD and catalase activity. Consistent with previous findings, our study revealed a rise in proinflammatory cytokines, including TNF-alpha, IL-1beta and IL-6, after renal ischemia-reperfusion injury. Additionally, extensive inflammatory activity was observed within the renal tissue.

Sugammadex is a drug commonly used in anaesthesia practice that chemically binds aminosteroid neuromuscular blocking agents, providing rapid elimination and reversal of neuromuscular blockade. Residual neuromuscular blockade occurs after surgery, with an estimated 30 to 60% incidence in the recovery room.[25] The low-level neuromuscular blockade (lower than what can be observed with the naked eye) has been linked to supralaryngeal muscle weakness that predisposes to impaired swallowing, upper airway obstruction, hypoxia, and an increased risk for aspiration. Sugammadex is a significant pharmacological agent because it increases the speed of reversal of neuromuscular blockade and thus minimizes all these risks.[26] Sugammadex is not metabolized by the liver; therefore, liver function should not affect the drug's pharmacokinetic profile. By contrast, sugammadex is primarily excreted in an unchanged form via urine within 24 hours at usual clinical doses, which makes it effective for rapid recovery from neuromuscular blockade.[27] Administration of sugammadex in doses ranging from 2 mg kg^{-1} to 16 mg kg^{-1} demonstrates a linear and dose-dependent pharmacokinetic relationship, with an elimination half-life of 100 to 150 minutes and nearly 100% renal clearance.[28,29] The geometric mean time (95% confidence interval) from sugammadex administration to recovery of train-of-four (TOF) ratio to 0.9 increased with age: from 2.3 (2-2.6) minutes for younger adults to 2.6 (2.3-2.9) minutes for elderly adults and 3.6 (3.1-4.1) minutes for older adults.[27] The most important indication for sugammadex in anaesthesia practice is its ability to provide fast and effective reversal in cases of difficult airway ventilation.[9] A systematic review has indicated that the administration of sugammadex is associated with a decreased occurrence of pulmonary complications following surgery.[30] Significant adverse effects with sugammadex have included bradycardia and anaphylaxis, with an incidence of anaphylaxis of 0.039%.[31]

Recent studies suggest that sugammadex serves as a potent pharmacological agent in mitigating oxidative stress in experimental ischemia-reperfusion models applied to different tissue types.[11] However, the molecular mechanism of this situation has not been clearly explained.[32] Sugammadex increases the production of apoptosis-inducing factor, caspase 3 protein, and monoclonal cytochrome c protein in cell cultures. They proposed that this role of sugammadex may be related to changing cholesterol homeostasis alongside oxidative stress and apoptosis.[32,33] On the other hand, it has been documented in many experimental studies that sugammadex prevents tissue damage against ischemia reperfusion injury by maintaining antioxidant levels, preventing polymorphonuclear leucocyte infiltration, reducing myeloperoxidase production, and decreasing inflammatory cytokine levels.[10,11,32]

Koç et al.[32] observed, in a gastric ischemia-reperfusion model, that sugammadex suppressed levels of pro-inflammatory cytokines, such as TNF-alpha and IL-1beta, reduced myeloperoxidase activity-a lysosomal enzyme secreted by leukocytes in response to oxidative stress-and prevented the decline in total GSH levels as a result of ischemia-reperfusion injury. In their experimental study, creating an ovarian ischemia-reperfusion model, Kadioğlu et al.[11] documented that sugammadex inhibited polymorphonuclear leukocyte

infiltration in ovarian tissue, increased levels of antioxidant enzymes, such as GSH, SOD, and catalase, and prevented the increase in MDA levels. Consistent with our findings, MDA levels declined, while GSH and SOD activities increased in rats administered sugammadex. According to Alagöz et al.,[10] sugammadex played a protective role against oxidative stress in a rat model of lower limb ischemia-reperfusion by preventing inflammatory cell formation. Yesiltas et al.[34] also noted that sugammadex mitigated allergic inflammatory responses induced by rocuronium in rat lung tissue. Histopathological analysis in our study demonstrated a marked decrease in inflammation scores among experimental animals receiving sugammadex treatment. Additionally, a marked improvement pattern was observed in other tissue damage parameters, such as tubular dilatation and glomerular deformities, following sugammadex administration.

The optimal dose of sugammadex for the protective effect in ischemia-reperfusion injury is controversial. Although the protective efficacy of sugammadex against ischemia reperfusion injury has been analyzed in different dose ranges in the literature, we observed that the 4 mg kg^{-1} dose (similar to the usual application dose) was preferred frequently. In their experimental studies analyzing unilateral lower extremity ischemia reperfusion injury in rats, Alagöz et al.,[10] observed that a dose of 4 mg kg^{-1} sugammadex protected against oxidative damage more effectively than a dose of 16 mg kg^{-1}. Similarly, Koç et al.[32] documented that 4 mg kg^{-1} sugammadex had effective anti-inflammatory and antioxidant effects in gastric ischemia-reperfusion injury. Kadioglu et al.[11] reported that 4 mg kg^{-1} and 8 mg kg^{-1} doses of sugammadex minimized oxidative and inflammatory damage in ovarian ischemia reperfusion injury; however, 8 mg kg^{-1} was more effective. In the study of Tercan et al.,[35] it was shown histopathologically that a high dose of 100 mg kg^{-1} sugammadex had a renoprotective effect on renal ischemia reperfusion injury. In our study, a 4 mg kg^{-1} sugamedex dose was preferred because its effective protection against oxidative damage at low doses was documented in previous experimental studies.[10,31]

In line with the findings of our experimental study, numerous reports in the literature have highlighted the neuroprotective properties of sugammadex across different ischemia-reperfusion models.[33,36] In the cerebral ischemia-reperfusion model of Ciftci et al.,[36] it is documented that the caspase-3 apopptotic cell numbers that increase due to ischemia-reperfusion damage were significantly reduced by sugammadex application. they reported that sugammadex suppressed the increased MDA and myeloperoxidase levels due to ischemia reperfusion injury. However, no significant difference was found between the groups in terms of SOD levels. In our study, apoptotic indexes are not analyzed. However, in our study, unlike the study by Ciftci et al.,[36] a significant improvement in antioxidant levels was observed after sugammadex administration. In a similar study, Ozbilgin et al.[33], found that the hippocampus *terminal deoxynucleotidyl transferase dUTP nick end labeling*-TUNEL and caspase results in the sugamadex treatment groups were significantly lower than those of the ischemia-reperfusion injury group. However, antioxidant enzyme activity and MDA levels in tissues were not evaluated in their study. In our study, sugammadex provided a significant improvement in kidney tissue morphology in microscopic examination.

Nevertheless, only a single study has specifically investigated the impact of sugammadex on renal ischemia-reperfusion injury. Tercan et al.[35] conducted an experimental study demonstrating the renoprotective properties of sugammadex through histopathological evaluation. However, this study did not analyze antioxidant enzyme activities or assess blood parameters indicative of renal functions.

In our study, for the first time in the literature, sugammadex demonstrated antioxidant enzyme activity in blood and tissue biochemical analyses within a renal ischemia-reperfusion model, significantly improving renal functions while suppressing inflammation. Additionally, histopathological evaluations revealed a marked improvement in tissue condition.

Study Limitations

While our study demonstrates the beneficial effects of sugammadex, a key limitation is the insufficient detail regarding its molecular mechanism and dose-response curve. Additionally, our study is constrained by its primary focus on the early-phase effects of sugammadex treatment. Moreover, the effects of sugammadex on renal tissue could not be demonstrated in healthy rats. For this reason, the intrinsic effects of sugammadex on renal function independent of ischemia-reperfusion injury have not been determined.

Conclusion

Our biochemical and histopathological findings indicate that sugammadex exhibits notable protective effects against renal ischemia-reperfusion injury. We believe that with further comprehensive experimental and randomized large-scale clinical studies, the beneficial use of sugammadex will be observed in cases where renal ischemia-reperfusion injuries can be predicted, such as in kidney surgery and cardiopulmonary bypass. On the other hand, only the short-term effects of sugammadex were analyzed in our study. In this context, we believe that the investigation of the potential long-term effects of sugammadex in the chronic phase of renal recovery will make important contributions to the literature.

Ethics

Ethics Committee Approval: The experiment adhered to the National Institutes of Health guidelines for animal research and received approval from the Tokat Gaziosmanpaşa University Rectorate, Animal Experiments Local Ethics Committee (approval no.: 2024 HADYEK-13, date: 15.08.2024).

Informed Consent: Animal study.

Footnotes

Author Contributions: Surgical and Medical Practices - V.K., M.G.B., A.T.Ş., A.G., V.U., F.F., F.G., A.Y., A.B.G.; Concept - V.K., M.G.B., A.T.Ş., A.G.; Design - V.K., M.G.B., A.T.Ş., A.G., V.U., F.F., F.G., A.B.G.; Data Collection and/or/Processing - V.K., M.G.B., A.T.Ş., A.G., V.U., F.F., F.G., A.Y., A.B.G.; Analysis and/or/Interpretation - V.K., M.G.B., A.T.Ş., A.G., V.U., F.F., F.G., A.Y., A.B.G.; Literature Review - V.K., M.G.B., A.T.Ş., A.G., V.U., F.F., F.G., A.Y., A.B.G.; Writing - V.K., M.G.B., A.T.Ş., A.G., V.U., F.F., F.G., A.Y., A.B.G.

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Comparison of Succinylcholine, Rocuronium, and Rocuronium with Magnesium on Time of Onset of Paralysis in Adult Patients Undergoing Rapid Sequence Induction: A Double Blinded Randomised Control Trial

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Abstract

Objective: We compared magnesium sulphate pre-treatment with rocuronium at a dose of 0.9 mg kg^{-1} to the standard succinylcholine (1 mg kg^{-1}) in rapid sequence induction to see if this combination had an onset of paralysis comparable to succinylcholine.

Methods: This was a prospective, single-centre, double-blinded, parallel-arm, randomized controlled trial on patients aged 18-60 years, either sex, the American Society of Anesthesiologists I and II. Patients received a 100 mL normal saline infusion followed by either succinylcholine at 1 mg kg^{-1} (Group S), or rocuronium 0.9 mg kg^{-1} (Group R), or a 100 mL normal saline infusion containing magnesium sulphate 60 mg kg^{-1}, followed by rocuronium 0.9 mg kg^{-1} (Group MgR). The primary outcome was the time of onset of paralysis evidenced by fading of train-of-four (TOF). Secondary outcomes were the intubation conditions, and the laryngoscopy response.

Results: Data from 135 patients showed TOF fading times differed significantly across the groups, with Group S showing a median (*interquartile range*-IQR) of 65 (61-70) seconds, Group R 102 (98-108) seconds, and Group MgR 82 (79-85) seconds ($P < 0.001$). The ease of laryngoscopy and response to cuff inflation showed no significant difference ($P=1.000$). Analysis of the position of the vocal cords suggested a significant difference ($P < 0.001$). Finally, the total intubating conditions indicated a significant difference among the groups ($P < 0.001$), favouring Group MgR for excellent intubating conditions.

Conclusion: The onset of action was significantly faster with succinylcholine than with magnesium sulphate-rocuronium. Nevertheless, it was significantly faster with magnesium sulphate-rocuronium than with rocuronium alone. However, the intubation conditions were better when magnesium was added to rocuronium.

Keywords: Intubation, laryngoscopy, muscle relaxation, magnesium sulphate, rocuronium, succinylcholine, vocal cords

Main Points

- The onset of action is significantly faster with succinylcholine than that with rocuronium at a dosage of 0.9 mg kg^{-1} alone or with magnesium sulphate added.
- However, the muscle relaxation and intubation conditions are better when magnesium is added to rocuronium in comparison with succinylcholine or rocuronium alone.
- Magnesium sulphate addition provided stable hemodynamic condition, blunting the laryngoscopy response.

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Introduction

Rapid sequence induction (RSI) is usually performed in the emergency department or in specific conditions that require prompt and secure control of the patient's airway.[1] It is commonly used when the patient has a high risk of aspiration, such as when the patient has a full stomach or is pregnant.[2] The choice of drugs is critical, with succinylcholine being the preferred agent due to its rapid onset and short duration, facilitating quick intubation and reducing the risk of aspiration. The recommended dose for RSI is 1-1.5 mg kg^{-1}, which gives an onset time of approximately 45-60 seconds.[3] It even provides excellent intubation conditions, which makes it particularly valuable in emergencies and thereby increases the chances of first-pass success of endotracheal intubation.[4]

However, succinylcholine's adverse effects, such as bradycardia, arrhythmias, and hyperkalaemia, among others, necessitate alternatives in certain patient groups.[5] When succinylcholine is contraindicated or not preferred, rocuronium is commonly used as an alternative non-depolarising muscle relaxant in RSI.[6] However, to achieve a similar speed of onset as succinylcholine, along with excellent intubating conditions, a high dose of rocuronium of 1.2 mg kg^{-1} is typically required.[7] One of the major drawbacks of using a high-dose non-depolarizing muscle relaxant is its prolonged duration of action. This extended effect can be mitigated by sugammadex; however, its high cost is a limitation for its use.[8]

Magnesium sulphate has been extensively studied for its uses in the perioperative period. Known for its perioperative benefits, including reducing the onset time of non-depolarising muscle relaxants and enhancing intubation conditions, magnesium sulphate presents a potential solution.[9] It also offers cardioprotective effects, hemodynamic stability, and neuroprotection. Nalini et al.[10] showed that pretreatment of magnesium sulphate accelerates neuromuscular block as compared to vecuronium with or without priming. Previous research and studies primarily focused on the impact of pretreatment with magnesium on rocuronium in its standard dose (0.6 mg kg^{-1}) in assessing intubating conditions.[11] However, there is still limited evidence regarding the onset time of paralysis of rocuronium at a slightly higher dose of 0.9 mg kg^{-1}, with magnesium sulphate and its use in RSI.

Through this study, we aim to address the gap in evidence by comparing the effects of magnesium sulphate pre-treatment with rocuronium at a dose of 0.9 mg kg^{-1} to the standard treatment with succinylcholine and rocuronium without magnesium sulphate pre-treatment in RSI. We hypothesized that 0.9 mg kg^{-1} rocuronium when preceded by magnesium sulphate could achieve comparable onset times and intubating conditions as succinylcholine at 1 mg kg^{-1}. We have tried to find out if this combination can provide an onset of paralysis comparable to succinylcholine, potentially offering a safer alternative for patients in whom succinylcholine is contraindicated. This research could refine RSI practice by providing an alternative to succinylcholine, thereby enhancing patient safety and care in critical situations.

Methods

The present study was a double-blinded randomized controlled trial and was carried out in the in a tertiary institute, in compliance with the standards outlined in the World Medical Association Declaration of Helsinki after receiving the All India Institute of Medical Sciences, Patna, Institutional Ethics Committee's approval (approval no.: AIIMS/Pat/IEC/PGTh/Jan21/52, and dated: 29th December 2021). Trial Registration was completed (www.ctri.nic.in) with registration no.: CTRI/2022/02/040528, dated February 23, 2022. Patients undergoing elective surgery under general anaesthesia, with an anticipated duration of surgery >60 minutes, of American Society of Anesthesiologists (ASA) physical status I and II, and age group 18-60 years, belonging to either sex with body mass index (BMI) between 18 kg m^{2-1} and 28 kg m^{2-1} were included in the study. The exclusion criteria were patients with contraindications to any of the study drugs, patients with neuromuscular diseases, electrolyte imbalances, anticipated difficult intubation or mask ventilation, and pregnancy.

Patients were allocated to one of three groups with a computer-generated random number table. The study groups were defined as follows:

- Group S received a 100 mL normal saline infusion over 10 minutes followed by succinylcholine at 1 mg kg^{-1}.

- Group R received a 100 mL normal saline infusion over 10 minutes followed by rocuronium at 0.9 mg kg^{-1}.

- The MgR group received a 100 mL normal saline infusion with magnesium sulphate 60 mg kg^{-1} over 10 minutes, followed by rocuronium of 0.9 mg kg^{-1}.

Block randomization with a fixed block size of nine was utilized to assign patients to their respective groups. Concealment of allocation was achieved using the opaque sealed envelope method. The envelopes, prepared by a statistician, were handed over to the anaesthesia team by an operating room technician. The anaesthetist in the operating room opened the envelope to reveal the allocated anaesthesia technique.

The patient was unaware of the infusion given before induction. This involved administering saline or magnesium sulphate in a 100 mL 0.9% normal saline solution, 10 minutes before induction. Secondly, to mitigate the

potential observer bias due to succinylcholine-induced fasciculations, the expert anaesthesiologist, responsible for intubation and assessing the intubating conditions, was called into the operating room once the fasciculations had subsided (at least 45 seconds after the injection of the drug). Both succinylcholine and rocuronium were diluted to 10 mL and prepared by the operating room personnel not involved in the study. This ensured that the study personnel remained unaware of the specific drugs being administered. Additionally, another anaesthesiologist, who was not directly involved in the study, noted down the train-of-four (TOF) values, while a junior anaesthesiologist monitored and recorded the vital signs of the patient.

Written informed consent was obtained from all participants for the study. A detailed pre-anaesthetic check-up was conducted, and informed written consent was obtained. Clinical characteristics such as age, sex, height and weight, and BMI were recorded. In the operating room, standard ASA monitoring devices were attached: pulse oximeter, non-invasive blood pressure, electrocardiogram, temperature monitor. Neuromuscular monitoring was performed using Drager® Infinity® Trident® neuromuscular transmission (NMT) SmartPod®. NMT study was done on the ulnar nerve to adductor pollicis muscle group. Group MgR patients were given 60 mg kg^{-1} magnesium sulphate infusion in 100 mL of 0.9% normal saline over a period of 10 minutes, whereas patients in the other two groups received 100 mL of 0.9% normal saline infusion. Pre-oxygenation was then performed for a period of 3 minutes, to achieve FeO_2 >91%, followed by IV fentanyl 2 µg kg^{-1} and propofol 2 mg kg^{-1}. After induction, according to the randomization, patients were given the respective muscle relaxant. Onset time was then calculated from the end of the muscle relaxant injection to the disappearance of three TOF twitches for rocuronium and the complete disappearance of TOF for succinylcholine. Intubation was then done by an expert anaesthesiologist (with more than 5 years of experience) who was not a part of the study.

Intubation scores (using ease of laryngoscopy, the position of vocal cords, and the reaction to cuff inflation) and the laryngoscopy response (by noting the hemodynamic parameters) were assessed. All the vitals of the patients [heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and SpO_2] were recorded every 3 minutes for the first 10 minutes after the injection of the muscle relaxant. The rest of the surgery continued according to the standard protocol followed by the institute.

TOF measurement settings were as follows:

• Mode - TOF monitoring,

• Measurement interval - 10 seconds,

• Pulse width - 100 microseconds.

The intubation score was based on 3 parameters:

• Ease of laryngoscopy - Easy/Fair/Difficult,

• Position of vocal cords - Abducted/Intermediate/Adducted,

• Response to cuff inflation - None/Slight/Vigorous,

Total intubating score - Excellent/Good/Poor.

Laryngoscopy-easy (jaw relaxed, no resistance to blade insertion), fair (jaw not fully relaxed, slight resistance to blade insertion), difficult (poor jaw relaxation, active resistance of the patient to laryngoscopy)

Response to cuff inflation - Slight (one to two weak contractions and/or movement for <5s),

Vigorous (more than 2 contractions and/or movement for >5s)

Total intubation score - Excellent (all qualities are excellent), Good (all qualities are either excellent or good) and Poor (presence of a single quality listed under "poor")

Any specific complications or adverse events that occurred were also noted.

Primary Outcome

The primary outcome was to compare the time of onset of paralysis as evidenced by fading of TOF between rocuronium (0.9 mg kg^{-1}) with magnesium and succinylcholine (1 mg kg^{-1}), by keeping rocuronium (0.9 mg kg^{-1}) as a control group.

Secondary Outcomes

Secondary outcomes were to compare the intubation conditions between the muscle relaxants and to assess the laryngoscopy response using hemodynamic parameters measured every 3 minutes or until 10 minutes after injection of the muscle relaxant.

To calculate the sample size, a previous study[12] was taken into consideration, and an online calculator was used to determine the minimum number of patients required for each group. Taking alpha as 0.05 and beta as 0.2, and using the difference between the two means and the expected pooled standard deviation, the sample size was calculated to be at least 39 patients for each group. Considering the dropout rate of 10%, a total of 45 patients in each group were enrolled. The control group of the same sample size was added. Therefore, the total sample size was 135.

Statistical Analysis

The collected data were analysed using Jamovi 2.3.26.0, statistical software, Sydney, Australia (open source). Results were expressed as mean ± standard deviation (SD), n

(number), median, or interquartile range (IQR) where appropriate. Data were evaluated to determine whether a normal distribution exists, and the central tendency was appropriately represented. Fisher's exact or chi-square tests were used for categorical variables, and one-way analysis of variance (ANOVA) and repeated measures ANOVA were used for continuous variables. A P value < 0.05 was considered statistically significant. For post-hoc analysis, Bonferroni correction was implemented. As there were three groups, alpha error was corrected for intergroup comparison. The new alpha level would be 0.0167 (0.05/3).

Results

One hundred and thirty-five patients were assessed for eligibility, randomized, and allocated to one of the three groups of forty-five each (Figure 1). None of them were lost to follow-up, and the results of analysis have been described below.

Demographic and Clinical Characteristics of the Patients

The demographic analysis of this study's participants showed the normality of age, weight, height, and BMI, which was confirmed using Q-Q plots. The mean age, BMI, height, and weight across the groups did not show a significant difference among the groups. These findings collectively indicate that there was a uniform distribution of demographic variables across the groups, ensuring a balanced comparison of the study's outcomes (Table 1). Gender distribution has been represented in Table 1. Overall, the study's total sample size had a female representation of 54.8% and a male representation of 45.2%.

Primary Outcome

The primary outcome, i.e., the TOF fading/disappearance times, differed significantly across the groups, with Group S showing a median (IQR) of 65 (61-70) seconds, Group R showing a median (IQR) of 102 (98-108) seconds, and Group MgR showing a median (IQR) of 82 (79-85) seconds (Figure 2). One-way ANOVA (non-parametric Kruskal-Wallis) test showed a χ^2 value of 110 and an overall P value of < 0.001. Post-hoc analysis using Dwass-Steel-Critchlow-Fligner pairwise comparisons showed that there is a significant difference between each pair of groups with a P value of < 0.001. Thus, the onset time of action of the succinylcholine group was significantly faster than that of both other groups. However, the onset of action of the group that received magnesium sulphate pretreatment with rocuronium was significantly faster than the group with rocuronium alone.

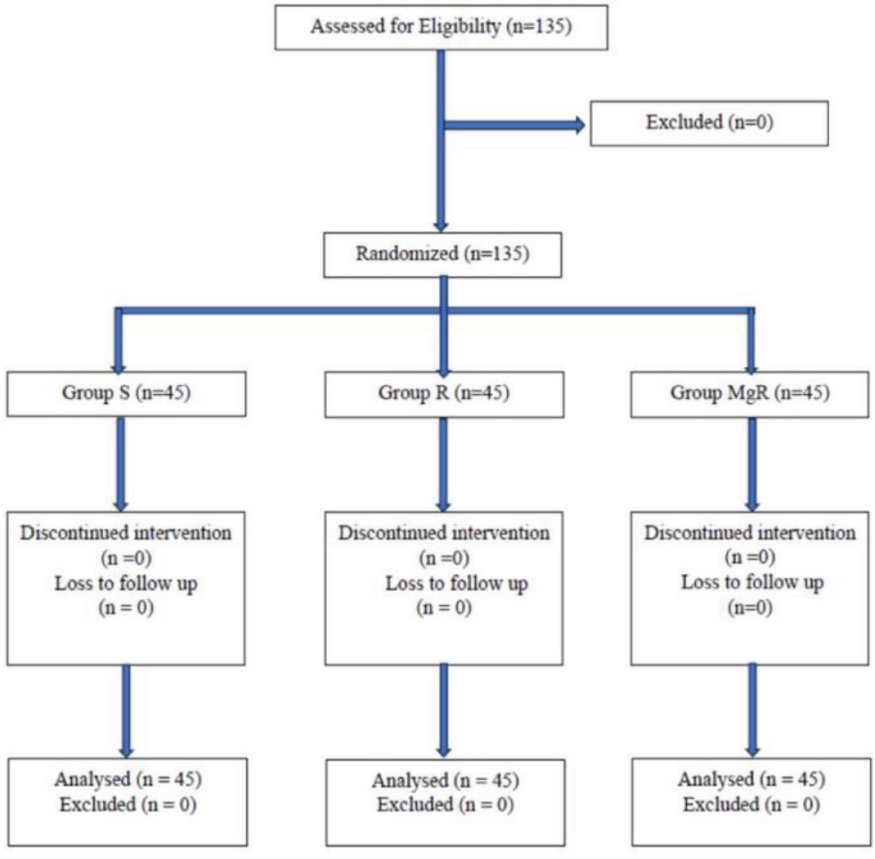

Figure 1. Consort flow diagram.

Secondary Outcomes

In terms of ease of laryngoscopy (Table 2), all groups performed well, with most cases being classified as easy. A *P* value of 1.000 indicated no significant difference in the ease of laryngoscopy between groups.

The position of vocal cords was predominantly open in all groups (Table 2). Fisher's exact test was performed as the expected count was less than 5, which showed a *P* value of < 0.001, suggesting that there is a significant difference among the three groups. Cramer V test for association showed a value of 0.361, which indicates a strong association. A *P* value of less than 0.001 suggested a significant difference, particularly indicating that Group R has more intermediate positions.

Regarding the response to cuff inflation, all groups showed no response in most cases, with a *P* value of 1.000.

Finally, the total intubating conditions were excellent in a high percentage of cases across all groups. A chi-square test of independence was performed for the total intubating conditions in the three groups. The expected frequencies in all the cells were greater than five. Results showed a χ^2 value of 17.9 and a *P* value of < 0.001, suggesting that there is a significant difference between the three groups with a χ^2 value in favour of Group MgR. Cramer V test for association showed a value of 0.364, which is suggestive of a moderate level of association.

Table 3 represents the repeated measures ANOVA, which showed significant changes in HR, systolic blood SBP,

Table 1. Demographic Characteristics of the Participants (Mean ± SD, n or Percent)

Demographic variables	Group S (Mean ± SD)	Group R (Mean ± SD)	Group MgR (Mean ± SD)	*P* value
Age (years)	41.3±12.1	35.7±14.1	37.5±14.1	0.119#
Weight (kg)	59.7±8.01	57.2±7.86	59.4±7.37	0.253#
Height (cm)	159±6.73	159±7.28	159±6.36	0.941#
BMI (kg m^{2-1})	23.7±3.14	22.6±2.98	23.7±2.78	0.166#
Male:Female n (%)	20 (14.8%):25 (18.5%)	18 (13.3%):27 (20.0%)	23 (17.0%):22 (16.3%)	0.567## (χ^2=1.14)

#ANOVA; ##chi-square test; $P < 0.05$ considered as significant.
ANOVA, analysis of variance; BMI, body mass index; SD, standard deviation.

Table 2. Clinical Parameters of the Participants

Clinical parameter	Group S (n = 45)	Group R (n = 45)	Group MgR (n = 45)	*P* value*
Ease of laryngoscopy				
Easy (n)	44	44	45	1.000
Fair (n)	1	1	0	
Difficult (n)	0	0	0	
Position of vocal cords				
Abducted (n)	42	33	45	**<0.001****
Intermediate (n)	3	12	0	
Adducted (n)	0	0	0	
Response to cuff inflation				
None (n)	45	44	45	1.000
Slight (n)	0	1	0	
Vigorous(n)	0	0	0	
Total intubating condition				
Excellent (n)	41	32	45	χ^2 =17.9 **<0.001****
Good (n)	4	13	0	
Poor (n)	0	0	0	

*Fisher's exact test; **$P < 0.05$; n, number.

and DBP in the initial 10 minutes post-administration of muscle relaxants. Violations of sphericity were corrected using Greenhouse-Geisser adjustments (ε values of 0.894 for HR, 0.744 for SBP, and 0.873 for DBP). The findings were statistically significant, with changes in HR ($F = 31.9$, $P < 0.001$), SBP ($F = 12.63$, $P < 0.001$), and DBP ($F = 3.61$, $P=0.003$), demonstrating notable variations in these cardiovascular parameters over time.

Post hoc analyses using Bonferroni adjustments revealed significant cardiovascular differences among the study groups (Table 4). Heart rate, and systolic blood pressure, significantly increased when comparing Group S to MgR and Group R to MgR, while no similar differences were observed between Group S and R. DBP was significantly

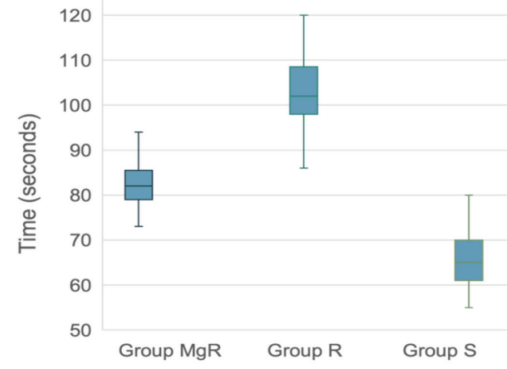

Figure 2. Box-Whisker plot of Train of Four among three groups.

Table 3. Hemodynamic Variables at different Intervals Among Three Groups (Mean ± SD)

Value	Interval	Group S (Mean ± SD)	Group R (Mean ± SD)	Group MgR (Mean ± SD)	F value	*P* value#
HR	Pulse 1	80.8±10.80	82.8±13.63	81.4±9.28	31.9	**<0.001***
	Pulse 4	91.7±9.69	93.5±12.79	77.9±10.88		
	Pulse 7	93.4±9.74	94.0±13.86	78.7±10.48		
	Pulse 10	92.0±9.42	90.8±12.01	80.2±9.40		
SBP	SBP 1	126±12.26	123±13.89	127±10.93	12.63	**<0.001***
	SBP 4	135±15.93	133±18.79	120±10.54		
	SBP 7	134±12.75	132±15.44	123±10.05		
	SBP 10	132±11.53	128±14.12	123±7.82		
DBP	DBP 1	77.9±10.2	79.3±9.43	75.8±10.08	3.58	**0.003***
	DBP 4	80.1±12.45	78.3±12.87	76.3±9.53		
	DBP 7	83.9±9.72	83.3±10.47	75.6±8.55		
	DBP 10	83.2±8.54	80.6±10.59	76.2±8.61		

#Repeated measures ANOVA, *$P < 0.05$.

ANOVA, analysis of variance; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 4. Post-hoc Analysis Between the Hemodynamic Variables

Parameter	Comparison	Mean difference	SE	df	*P* value#
HR	S-R	-0.778	2.18	132	1.000
	S-MgR	9.900	2.18	132	**<0.001***
	R-MgR	10.768	2.18	132	**<0.001***
SBP	S-R	2.82	2.36	132	0.701
	S-MgR	8.59	2.36	132	**0.001***
	R-MgR	5.77	2.36	132	0.047
DBP	S-R	0.917	1.84	131	1.000
	S-MgR	5.409	1.85	131	**0.012***
	R-MgR	4.492	1.85	131	0.050

#Bonferroni correction as post-hoc analysis, *P value < 0.0167 considered statistically significant.

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SE, standard error; df, degrees of freedom.

higher in Group S than in Group MgR, but remained comparable between Group S and R, and Group R and MgR.

Discussion

In our study, succinylcholine showed a significantly faster onset time for muscle paralysis than both rocuronium groups, with and without magnesium sulphate. The median (IQR) TOF fading/disappearance times were notably different, with succinylcholine at 65 (61-70) seconds, rocuronium alone at 102 (98-108) seconds, and rocuronium with magnesium sulphate at 82 (79-85) seconds. These results align with the known rapid action of succinylcholine.[7] However, adding magnesium sulphate to rocuronium did improve intubating conditions significantly, achieving excellent conditions in all subjects within the MgR group. Magnesium sulphate's mechanism of action at the neuromuscular junction, which involves the inhibition of calcium and acetylcholine release, might have contributed to the reduction in the onset time of neuromuscular relaxants when comparing it with rocuronium used alone.

Our study reported a 20% reduction in onset time with magnesium sulphate pre-treatment, as the median-IQR of the TOF value was 102 (98-108) seconds in group R and 82 (79-85) seconds in group MgR. A study done by Czarnetzki et al.[13] on the effect of magnesium sulphate pretreatment 15 minutes, prior to the standard dose of rocuronium (0.6 mg kg^{-1}) showed that the decrease was about 35%. This observed variation in the decrease in onset time could be attributed to the time required for the full effect of magnesium sulphate to manifest, which might not have been realized in our study's protocol, where magnesium sulphate was administered 10 minutes before the start of induction.

In contrast, when comparing the time of onset of muscle paralysis between succinylcholine (1 mg kg^{-1}) and a high dose of rocuronium (1.2 mg kg^{-1}), the high dose of rocuronium showed that the onset time was comparable between the succinylcholine group and the combination of rocuronium and magnesium. This is not in accordance with our findings.[12] The divergent outcomes might be the result of higher rocuronium doses used in the comparative study, which warrants cautious interpretation due to the limited sample size.

A prospective study conducted by Han et al.[14] showed that administering 1.2 mg kg^{-1} of rocuronium did not significantly hasten the onset of neuromuscular block compared to the 0.9 mg kg^{-1} dose, indicating a ceiling effect where the time required for rocuronium to reach the neuromuscular junction may be the limiting factor. However, the duration of the neuromuscular block was extended significantly with the 1.2 mg kg^{-1} dose compared to the 0.9 mg kg^{-1} dose.[14]

Most of the studies have compared intubating conditions. A recent study by Czarnetzki et al.[15] showed that there were comparable intubating conditions using the gold standard succinylcholine (1 mg kg^{-1}) and magnesium sulphate with rocuronium (0.6 mg kg^{-1}). In our study, a dose of rocuronium of 0.9 mg kg^{-1} along with pretreatment of magnesium sulphate resulted in significantly better intubating conditions when compared with succinylcholine of 1 mg kg^{-1}. Thus, our study demonstrated that administration of magnesium as a pretreatment, followed by rocuronium at a comparatively lower dose of 0.9 mg kg^{-1} (compared to the standard 1.2 mg kg^{-1}) yielded more favourable conditions for intubation, compared to the traditional and widely accepted succinylcholine. The difference in our finding compared to the aforementioned study might be due to the different doses of rocuronium used. Czarnetzki et al.[15] did not investigate the onset time of action between succinylcholine and rocuronium. They found that the rate of excellent intubating conditions was significantly higher in women than in men after receiving magnesium-rocuronium. However, we did not investigate this aspect of gender association.

Upon thoroughly analyzing the variables employed to assess the overall intubating conditions, it was observed that the succinylcholine group had more subjects with intermediate positioning of the vocal cords compared to the group receiving magnesium sulphate with rocuronium. This finding implies that the combination of magnesium sulphate and rocuronium potentially reduces the resistance of laryngeal muscles to non-depolarizing muscle relaxants.[16] This suggests that magnesium may have a beneficial effect in enhancing the relaxation of laryngeal muscles when used in conjunction with rocuronium during intubation procedures. Therefore, this combination of rocuronium and magnesium sulphate has the potential to enhance the intubating conditions further and improve overall intubation success.

Our study also revealed that magnesium sulphate provided haemodynamic stability, blunted the laryngoscopy response, and reduced SBP and HR in the initial 10 minutes post-administration when compared with the other groups. These findings are consistent with other studies that have reported similar hemodynamic stability with magnesium sulfate.[17] Czarnetzki et al.[15] observed no significant difference between groups for systolic and diastolic blood pressures; however, mean HR was significantly higher in the magnesium sulphate-rocuronium group. Furthermore, we did not quantitatively measure the prolongation of the duration of action of rocuronium with magnesium pre-treatment. However, it was evident that magnesium sulphate extended the duration of action compared to rocuronium alone, likely due to its inhibitory effect on acetylcholine released at the motor endplate.

While succinylcholine does result in paralysis more quickly according to statistics, the actual significance of this slightly faster action is uncertain when compared to the improved conditions for intubation provided by the combination of magnesium and rocuronium. This benefit becomes even more important in the case of obese patients, who may have difficulties with intubation due to their anatomy and increased adipose tissue. Therefore, it is crucial to ensure that muscle relaxation and intubation conditions are optimal for the successful placement of the endotracheal tube. The study suggests that using magnesium sulphate with rocuronium at a dosage of 0.9 mg kg^{-1}, could be an effective replacement for the usual succinylcholine at 1 mg kg^{-1} RSI.

Some adverse effects due to the drugs were noted. Post-surgery, a few subjects in the succinylcholine group reported having slight muscle pain, which was very much self-limiting and under control by the use of non-steroidal anti-inflammatory drugs. In group MgR, during the administration of magnesium sulphate as a pretreatment, a small number of patients reported experiencing pain at the injection site. Some individuals also reported mild dizziness while the infusion was ongoing. All these side effects were very mild and may not even be considered medically significant. One serious adverse effect that was noted is that one patient in the magnesium group developed bradycardia, which was managed with appropriate medical intervention (immediately corrected by the administration of atropine).

Study Limitations

The study's limitations include a small sample size of 45 patients per group, which challenges the generalizability of the findings, and the potential for a ±10 seconds error in measuring the time onset which was the minimum settings of the monitoring equipment. Additionally, being a single-center study limits the applicability of the results to a broader population.

Conclusion

The onset of action was significantly faster with succinylcholine than with rocuronium at a dosage of 0.9 mg kg^{-1} alone or with magnesium sulphate added. Nevertheless, rocuronium with magnesium sulphate had a significantly faster onset of action compared to rocuronium alone. However, the muscle relaxation and intubation conditions were better when magnesium was added to rocuronium in comparison with succinylcholine or rocuronium alone.

Based on the findings of this study, we recommend the following:

1. Conducting larger studies involving multiple centres to validate and strengthen the evidence which supports the use of magnesium sulphate with rocuronium in RSI.

2. Further evaluating the clinical impact of succinylcholine, considering the minimal observed difference.

3. Monitoring closely for potential side effects such as low blood pressure and slow HR when administering magnesium.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the All India Institute of Medical Sciences, Patna, Institutional Ethics Committee (approval no.: AIIMS/Pat/IEC/PGTh/Jan21/52, and dated: 29th December 2021).

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

Footnotes

Author Contributions: Surgical and Medical Practices - G.P., S.N., U.K.B., N.S., R.K., S.K.; Concept - S.N.; Design - S.N.; Data Collection and/or Processing - G.P., S.N., N.S., R.K., S.K.; Analysis and/or/ Interpretation - G.P., S.N., U.K.B., N.S.; Literature Review - G.P., U.K.B., R.K., S.K.; Writing - G.P., S.N., U.K.B., N.S., R.K., S.K.

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The Relationships Between Patients' Demographic Characteristics, Comorbid Diseases, American Society of Anesthesiologists Scores and Inflammation Indexes: A Retrospective Study

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Abstract

Objective: Parameters that can provide information about patients' current status are very important in preoperative evaluation. The systemic immune inflammation index (SII), and systemic inflammation response index (SIRI) can be easily calculated with a simple hemogram test, and this testing is frequently requested in preoperative preparation. The aim of this research was to examine the relationship between the SII, and SIRI, along with the demographic characteristics and postoperative clinical course of the patient.

Methods: In the study, the records of patients who presented to the anesthesia outpatient clinic for preoperative preparation were retrospectively reviewed. In this study, the relationships between the SII, and SIRI and each patients' demographic characteristics, and the American Society of Anesthesiologists (ASA) score, comorbid disease, and length of hospital stay were examined.

Results: For the SII value, there was a statistically significant difference between the ASA1 and ASA2 groups and between the ASA2 and ASA3 groups there was no significant difference between the ASA3 and ASA4 groups ($P < 0.001$, $P < 0.001$, $P=0.17$, respectively). There were statistically significant differences between the ASA1 and ASA2, ASA2 and ASA3, and ASA3 and ASA4 groups for the SIRI value ($P < 0.001$, $P < 0.001$, $P < 0.001$, respectively).

Conclusion: The findings showed relationships between the SII, SIRI, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio and an increase in patients' ASA scores. In multivariate analysis, some demographic characteristics of the patients, comorbidities, and the postoperative course were found to be independent risk factors predicting SII and SIRI.

Keywords: Comorbidity, inflammation, neutrophils, postoperative period, white blood cells

Main Points

- Systemic immune inflammation index (SII) and systemic inflammation response index (SIRI), which can be easily calculated from the hemogram test, can reflect the clinical condition of the patient.
- As the American Society of Anesthesiologists score increased, SII and SIRI also increased.
- Some comorbid diseases and postoperative clinical courses of the patients were independent risk factors for increased SII and SIRI.

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Introduction

The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune inflammation index (SII = neutrophil X platelet/lymphocyte count) and systemic inflammation response index (SIRI = neutrophil X monocyte/lymphocyte count) can be easily obtained with a simple hemogram test. It has been suggested that these values are a useful parameter regarding the severity of many diseases, but research on this topic is still ongoing.[1] The immunological response and inflammation have important roles in wound formation and healing. However, increased inflammation may cause undesirable conditions such as tissue and organ damage in the postoperative period.

Preoperative identification of patients scheduled for surgery who have a high risk of complications may provide significant benefits in better management of hospital resources, such as intensive care beds.[2] The physical status risk classification of the American Society of Anesthesiologists (ASA) is primarily used to identify these patients. Beyond this classification, biomarkers that provide information about the inflammatory processes present in patients may provide additional benefits to the ASA score in risk estimation.[3] Biomarkers such as B-natriuretic peptide and C-reactive peptide have been used in the past to classify the perioperative risk of patients.[4-6] However, it has been reported that these markers do not provide additional benefits in predicting cardiovascular outcomes in patients without heart failure.[4] Conversely, it has been stated that biomarkers calculated from routine blood tests, such as the NLR and PLR, have better predictive values for death from any cause.[7,8] Using biomarkers that can be measured or derived from routinely taken blood samples during a patient's preoperative preparation phase and have a high predictive value for risk factors is preferable to using biomarkers that require specialized tests.[3]

The NLR is a biomarker that can be used to predict postoperative mortality and morbidity in cardiac and cancer surgeries.[1] Furthermore, it has been shown to predict morbidity and mortality in patients with acute coronary syndrome.[9] A high NLR is also associated with an increased risk of mortality after discharge from the hospital following myocardial infarction.[10] High preoperative values in the elderly have been shown to increase the risk of postoperative cognitive dysfunction.[1] A high preoperative SII has been shown to be significantly associated with an increased risk of perioperative ischemic stroke.[11]

Systemic inflammation is increasingly accepted as initiating and aggravating the pathological process in chronic diseases.[12] The relationship between patients' demographic characteristics and comorbidities and NLR, PLR, SII and SIRI has been investigated in some studies, but conflicting results were obtained. One study showed that the NLR had relationships with hypertension and diabetes mellitus, but no significant relationship was found for asthma, arthritis, age, gender, or obesity.[13] Furthermore, some studies have shown that obesity, age, chronic lung disease, inflammatory diseases, or smoking are related to these inflammation rates.[12,14] It is thought that the use of anti-inflammatory drugs for the treatment of the disease or symptoms, or to prevent pain, may be the cause of these conflicting results.[13]

It is very important to determine the potential risks of patients who are expected to undergo surgery, as well as to implement the necessary perioperative follow-up and treatments.[3] In addition to the ASA score, the NLR, PLR, SII, and SIRI can provide detailed information about a patient's underlying inflammatory processes and are easily obtained and calculated; thus, these parameters can be useful for determining perioperative risks and taking the necessary precautions.[3] In short, these parameters can play a supporting role in preoperative risk estimation and in developing a management plan. The aim of the present study was to investigate the relationship between NLR, PLR, SII and SIRI and chronic diseases, patients' demographic characteristics, ASA score and length of hospital stay.

Methods

Before the study began, approval was obtained from the Clinical Research Ethics Committee of Tokat Gaziosmanpaşa University Faculty of Medicine (approval no.: 24-KAEK-207, date: 27.06.2024). In this study, the records of patients aged 18-85 years who presented to the anesthesia clinic for preoperative preparation between 11/01/2023 and 05/01/2024 were examined. Informed consent was obtained from patients. Demographic characteristics, chronic diseases, the ASA score, and the length of hospital stay; neutrophil, lymphocyte, monocyte, basophil, and eosinophil values in the preoperative hemogram sample; and the NLR, PLR, SII, SIRI, hemoglobin, hematocrit, and platelet counts of the patients were recorded. The aim of the study was to examine the relationships between NLR, PLR, SII and SIRI with patients' demographic characteristics, comorbidities, ASA score, length of hospital stay and outcomes. Patients with any active infection, missing laboratory values, or severe trauma; patients who underwent emergency surgery; and pregnant women were excluded from the study.

Statistical Analysis

The statistical conformity of the data to normal distribution was evaluated using the One-Sample Kolmogorov-Smirnov test. Qualitative data were presented as numbers and percentages, normally distributed quantitative data were presented as mean and standard deviation, and non-normally distributed quantitative data were presented as median [minimum-maximum (min.-max.)] values. Multiple logistic regression analysis was used to determine

the independent predictors of different variables on SII and SIRI. In multiple logistic regression analysis, B (unstandardized coefficient) indicates how much the log-odds of the outcome changes for a one-unit increase in the predictor variable; Beta (standardized coefficient) shows the relative strength of each predictor, allowing comparison across variables measured on different scales; t (test statistic) assess whether the predictor has a statistically significant effect on the outcome. Kruskal-Wallis H test was used to compare SII, SIRI, NLR and PLR values in four ASA groups. When statistically significant differences were found, post-hoc tests with Bonferroni correction were used in pairwise comparisons of groups. The Statistical Package for Social Sciences (version 21.0, SPSS Inc., Chicago, IL, USA) was used to evaluate all data. While analyzing the data, statistical significance was accepted as $P < 0.05$.

Results

A total of 5205 patients were admitted to the anesthesia clinic between 11/01/2023 and 05/01/2024, and after applying the inclusion and exclusion criteria, the records of 3408 patients were reviewed in the current study (Figure 1). The median (min.-max.) age of the patient population was 52 years (18-85), and 53% were female. The demographic data and descriptive characteristics of the patients are detailed in Table 1.

The median (min.-max.) SII values were 394.18 (65.53-1284.72) in ASA1 patients, 456.16 (65.97-2200.83) in ASA2 patients, 801.08 (80.27-4116.8) in ASA3 patients, and 888.76 (224.64-3225.61) in ASA4 patients. There was a statistically significant difference in the SII value between the ASA1 and ASA2, ASA1 and ASA3, ASA1 and ASA4, ASA2 and ASA3, ASA2 and ASA4, but no statistically significant difference was found between the ASA3 and ASA4 groups ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P=0.17$, respectively), (Figure 2).

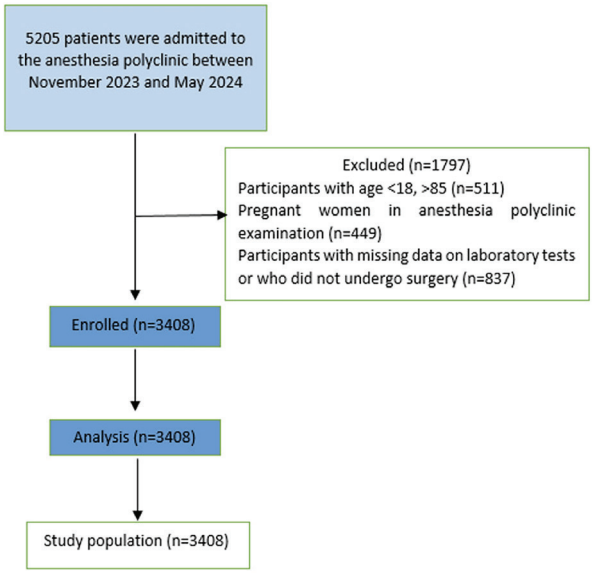

Figure 1. Flow diagram of the study.

The SIRI median (min.-max.) values were 0.84 (0.14-4.46) in ASA1 patients, 1.03 (0.08-6.84) in ASA2 patients, 2.51 (0.18-11.99) in ASA3 patients, and 2.86 (0.23-10.5) in ASA4 patients. There were statistically significant differences in SIRI values between the ASA1 and ASA2, ASA1 and ASA3, ASA1 and ASA4, ASA2 and ASA3, ASA2 and ASA4, and ASA3 and ASA4 groups ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, respectively), (Figure 2).

The NLR median (min.-max.) values were 1.56 (0.53-5.56) in ASA1 patients, 1.78 (0.35-8.01) in ASA2 patients, 3.46 (0.48-9.68) in ASA3 patients, and 4.49 (0.93-10.82) in ASA4 patients. The PLR median (min.-max.) values were 111.21 (18.18-45.08) in ASA1 patients, 113.55 (28.24-420) in ASA2

Table 1. Baseline Characteristics and Clinical Outcomes of the Study Population

Age (years): median (min.-max.)	52 (18-85)
Sex (female/male): n (%)	1791 (53)/1617 (47)
BMI (kg/m^2): median (min.-max.)	27.47 (15.94-52.85)
ASA score: (I/II/III/IV): n (%)	950/1310/1038/110
Hypertension: n (%)	1285 (38)
Diabetes: n (%)	700 (21)
Ischemic heart disease: n (%)	578 (17)
Congestive heart failure: n (%)	212 (6)
Chronic lung disease: n (%)	580 (17)
Thyroid disease: n (%)	269 (8)
Cerebral vascular disease: n (%)	194 (6)
Neoplasm: n (%)	330 (10)
Rheumatic disease: n (%)	165 (5)
Smoking: n (%)	986 (29)
Chronic kidney disease: n (%)	165 (5)
Total hospital stay (day): median (min.-max.)	3 (0-66)
Intensive care unit admission (yes): n (%)	561 (16)
Outcome (death): n (%)	21 (0.6)
SII: median (min.-max.)	507.44 (63.53-4116.2)
SIRI: median (min.-max.)	1.14 (0.08-11.9)
NLR: median (min.-max.)	2.01 (0.35-10.82)
TLR: median (min.-max.)	119.54 (18.18-450.68)

BMI, body mass index; ASA, American Society of Anesthesiologists; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; min.-max., minimum-maximum

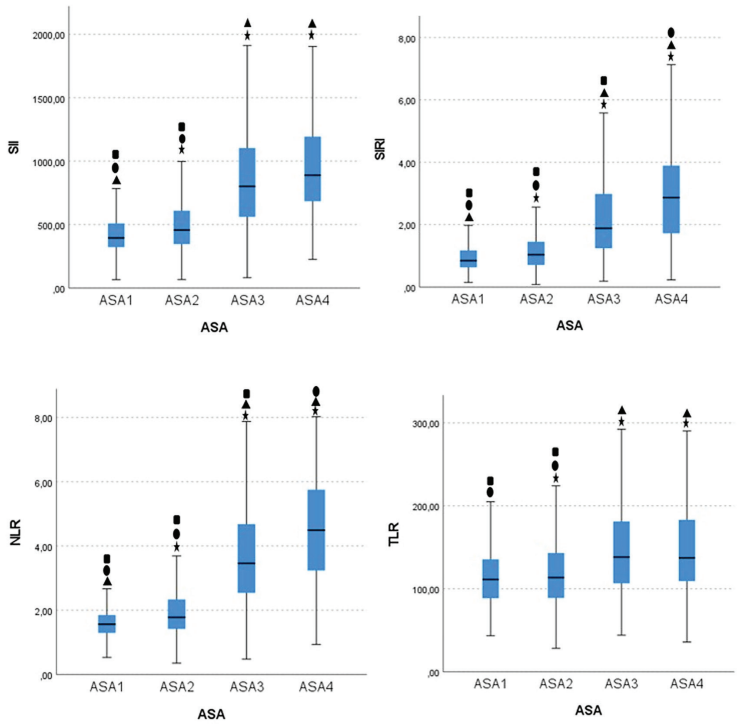

Figure 2. Relationship of the SII, SIRI, NLR and TLR with ASA score. Post-hoc Bonferroni corrected Kruskal-Wallis H test; ✶, statistically significant different from ASA 1; ▲, statistically significant different from ASA 2; ● :, statistically significant different from ASA 3; ■, statistically significant different from ASA 4.

ASA, American Society of Anesthesiologists; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.

patients, 138.25 (44-447.62) in ASA3 patients, and 137.23 (35.80-357.32) in ASA4 patients. There was a statistically significant difference in the NLR values of the ASA1 and ASA2, ASA1 and ASA3, ASA1 and ASA4, ASA2 and ASA3, ASA2 and ASA4, and ASA3 and ASA4 groups ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P=0.02$, respectively), (Figure 2). Whereas there was a statistically significant difference between the PLR values of the ASA1 and ASA3, ASA1 and ASA4, ASA2 and ASA3, ASA2 and ASA4, there was no statistically significant difference between the ASA1 and ASA2 or ASA3 and ASA4 groups ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P=0.1$, $P=1$, respectively), (Figure 2).

The relationship between the SII score and demographic characteristics, comorbidities, and the postoperative course of the patients was evaluated using multivariate regression analysis. In the linear regression analysis, the explanatory power of the model was evaluated using the R^2 value, and it was found that the model explained 37% of the variance in the dependent variable. In addition, the analysis of variance (ANOVA) test result revealed that the model was statistically significant [$F(18.3389)=111.95$, $P < 0.001$]. In the multivariate logistic regression analysis, gender (male); increasing age, body mass index (BMI) and ASA score; presence of comorbid diseases such as hypertension, diabetes, congestive heart failure, neoplasm, chronic kidney disease; the total length of hospital stay, intensive care unit admission, and the outcome (death) were independent risk factors predicting increasing SII (Table 2). However, there was no relationship between SII and ischemic heart disease, chronic lung disease, thyroid disease, cerebral vascular disease, rheumatic disease, or smoking (Table 2).

The relationships between SIRI scores and demographic characteristics, comorbidities, and the postoperative course of the patients were evaluated using multivariate logistic regression analysis. In linear regression analysis, the explanatory power of the model was evaluated with the R^2 value and it was found that the model explained 37% of the variance in the dependent variable. In addition, the ANOVA test result revealed that the model was significantly significant [$F(18.3389)=92.01$, $P < 0.001$]. In the multivariate regression analysis, gender (male); increasing age, BMI, and ASA score; presence of comorbid diseases such as hypertension, congestive heart failure, neoplasm, chronic kidney disease; the total length of hospital stay, and intensive care unit admission were independent risk factors

Table 2. Effect of Patient Characteristics and Clinical Outcomes on SII

	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. error	Beta		
Sex (female/male)	39.018	11.509	0.052	3.390	**<0.001**
Age (years)	2.478	0.413	0.117	5.997	**<0.001**
BMI	4.707	1.085	0.073	4.338	**<0.001**
ASA	63.230	12.307	0.141	5.138	**<0.001**
Hypertension	112.876	15.435	0.145	7.313	**<0.001**
Diabetes	57.271	14.412	0.061	3.974	**<0.001**
Ischemic heart disease	-21.776	19.092	-0.022	-1.141	0.254
Congestive heart failure	178.500	25.901	0.114	6.891	**<0.001**
Chronic lung disease	23.714	16.202	0.024	1.464	0.143
Thyroid disease	3.150	19.857	0.002	0.159	0.874
Cerebral vascular disease	38.192	23.690	0.023	1.612	0.107
Neoplasm	175.775	19.887	0.138	8.839	**<0.001**
Rheumatic disease	-12.193	24.356	-0.007	-0.501	0.617
Smoking	12.129	13.096	0.015	0.926	0.354
Chronic kidney disease	114.655	26.026	0.065	4.405	**<0.001**
Total hospital stay (day)	27.595	2.620	0.223	10.532	**<0.001**
Intensive care unit admission	57.352	20.824	0.056	2.754	**0.006**
Outcome (discharge-death)	199.163	72.646	0.041	2.742	**0.006**

Multiple logistic regression analysis; Sig. (*P*) < 0.05: statistically significant; BMI, body mass index; ASA, American Society of Anesthesiologists; SII, systemic immune inflammation index

predicting increasing SIRI (Table 3). However, there was no relationship between SIRI and diabetes, ischemic heart disease, chronic lung disease, thyroid disease, cerebrovascular disease, rheumatic disease, smoking, or outcome (Table 3).

The primary outcome of the study was to investigate the relationship between ASA score and systemic inflammation indexes. Patients were divided into four groups based on their ASA scores, and differences in SII levels among these groups were assessed. A post hoc power analysis revealed that the statistical power for the comparison among four groups (n = 3408) exceeded 0.95, with an effect size of f = 0.528, indicating that the sample size was sufficient to detect

Table 3. Effect of Patient Characteristics and Clinical Outcomes on SIRI

	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. Error	Beta		
Sex (female/male)	0.096	0.040	0.038	2.396	0.017
Age (years)	0.007	0.001	0.094	4.690	**<0.001**
BMI	0.016	0.004	0.075	4.313	**<0.001**
ASA	0.281	0.043	0.186	6.568	**<0.001**
Hypertension	0.196	0.054	0.075	3.661	**<0.001**
Diabetes	0.065	0.050	0.021	1.291	0.197
Ischemic heart disease	0.102	0.066	0.030	1.540	0.124
Congestive heart failure	0.671	0.090	0.128	7.455	**<0.001**
Chronic lung disease	0.056	0.056	0.017	1.003	0.316

Table 3. Continued

	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. Error	Beta		
Thyroid disease	-0.105	0.069	-0.022	-1.528	0.127
Cerebral vascular disease	-0.140	0.082	-0.026	-1.703	0.089
Neoplasm	0.443	0.069	0.103	6.408	**<0.001**
Rheumatic disease	-0.061	0.085	-0.010	-0.719	0.472
Smoking	-0.054	0.046	-0.019	-1.191	0.234
Chronic kidney disease	0.187	0.090	0.032	2.072	**0.038**
Total hospital stay (day)	0.072	0.009	0.173	7.897	**<0.001**
Intensive care unit admission	0.318	0.072	0.093	4.394	**<0.001**
Outcome (discharge-death)	0.210	0.252	0.013	0.832	0.405

Multiple logistic regression analysis; Sig. (*P*) <0.05: statistically significant; BMI, body mass index; ASA, American Society of Anesthesiologists; SIRI, systemic inflammation response index

intergroup differences.

Discussion

This study showed a significant relationship between the SII, SIRI, NLR, and PLR and the increase in a patients' ASA score. In multivariate analysis, some demographic characteristics of the patient, comorbidities, and the postoperative course were independent risk factors predicting increased SII and SIRI. Sex, age, BMI, ASA, hypertension, congestive heart failure, neoplasm, chronic kidney disease, total hospital stay, intensive care unit admission, and the outcome (discharge/death) were independent risk factors predicting the SII; conversely, there was no relationship between the SII and ischemic heart disease, chronic lung disease, thyroid disease, cerebral vascular disease, rheumatic disease, diabetes, or smoking. In addition, whereas sex, age, BMI, ASA, hypertension, congestive heart failure, neoplasm, chronic kidney disease, total hospital stay and intensive care unit admission were independent risk factors predicting the SIRI, there was no relationship between the SIRI score and diabetes, ischemic heart disease, chronic lung disease, thyroid disease, cerebral vascular disease, rheumatic disease, smoking, or outcome (discharge/death). In binary logistic regression analysis, ASA scores were independent risk factors predicting congestive heart failure, neoplasm, chronic kidney disease, and chronic lung disease outcome (discharge/death).

Biomarkers that provide information about inflammatory processes in preoperatively determining the group of high-risk patients may provide additional benefits to the ASA score. Tests that can be useful in preoperatively determining high-risk patients scheduled for surgery may provide significant benefits in the effective perioperative management of patients and better management of hospital resources.[2] Venkatraghavan et al.[3] showed a strong relationship between the NLR and ASA scores in their study. Moreover, Zhang et al.[11] stated that there is a relationship between a high SII and increased ASA score. The current study also showed a relationship between ASA scores and increases in the NLR, PLR, SII, and SIRI. In addition, the ASA score was found to be an independent risk factor predicting increased SII and SIRI.

The relationships between inflammation biomarkers and patients' demographic characteristics and systemic diseases have been investigated in some studies, but conflicting results have been reported. Xia et al.[12] showed that hypertension, diabetes, obesity, smoking, alcohol use, and physical activity status were associated with high SII and SIRI scores. However, they found that, although age was associated with the SIRI, it was not associated with the SII.[12] Furthermore, Venkatraghavan et al.[3] reported that a high NLR was associated with congestive heart failure and malignancy but not with hypertension, diabetes mellitus, chronic kidney disease, ischemic heart disease, or cerebrovascular disease.[3] Zhang et al.[11] showed that a high SII was associated with gender, hypertension, diabetes mellitus, history of ischemic stroke, coronary heart disease, renal dysfunction, and peripheral vascular disease but not with age or BMI. In addition, Imtiaz et al.[13] reported that the NLR had a significant relationship with hypertension and diabetes mellitus but not asthma, arthritis, age, sex, or BMI. However, Furuncuoğlu et al.[14] found that BMI significantly affected SII. Lin et al.[15] reported that SII and SIRI were associated with age but not with gender, hypertension, diabetes, or ischemic stroke. In the present study, sex, age, BMI, ASA, hypertension, congestive heart failure, neoplasm, and chronic kidney disease were independent

risk factors predicting increased SII and SIRI, but there was no relationship between the SII and SIRI on the one hand and ischemic heart disease, chronic lung disease, thyroid disease, cerebral vascular disease, rheumatic disease, or smoking on the other. In addition, in this study, diabetes was an independent risk factor predicting increased the SII, but no relationship was found between the SIRI and diabetes.

Previous research has stated that a high NLR predicts mortality in cardiac and vascular surgeries.[16,17] It has also been reported that a high NLR is associated with increased morbidity and mortality in the context of sepsis.[18] In one study, it was stated that high preoperative NLR is associated with increased postoperative morbidity, prolonged intensive care unit stay, and a longer hospital stay.[17] A high NLR has been shown to be associated with increased tumor necrosis factor alpha and some interleukins [interleukin (IL)-6, IL-7, IL-8, IL-12, IL-17].[19,20] Studies have reported that these inflammatory mediators are associated with recurrent ischemic events and poor outcomes in at-risk patients, such as patients with serious heart disease.[21,22] In a study on the Kailuan community in Tangshan, China, Jin et al.[23] revealed that the SII and SIRI are associated with the risk of cardiovascular diseases and death from any cause. Similarly, in a study conducted in a general population, including many ethnicities, Xia et al.[12] showed that cardiovascular and all-cause mortality risks were associated with high SII and SIRI levels.[12] Lu et al.[1] reported that the SII, NLR, and monocyte to lymphocyte ratio were associated with postoperative cognitive decline, a condition that increases the length of the hospital stay and perioperative mortality, as well as cost.[24,25] In the present study, total hospital stay and intensive care unit admission were independent risk factors predicting increased SII and SIRI scores. However, while the outcome (discharge/death) was an independent risk factor predicting the SII, there was no such relationship between the SIRI and outcome (discharge/death). In binary logistic regression analysis, independent risk factors predicting the outcome (discharge/death) were the ASA score, congestive heart failure, neoplasm, chronic kidney disease, and chronic lung disease.

Study Limitations

The limitation of the present study is that it is retrospective, and all patients were from a single center. Inflammation biomarkers were obtained from laboratory tests performed during preoperative anesthesia preparation in the anesthesia outpatient clinic. The study also raises some questions that need to be answered regarding whether changes in systemic inflammation are an effect or a cause of chronic disease, the study could not itself answer them. A prospective study covering a larger general population and dynamically monitoring inflammation biomarkers at different perioperative times may provide more information on this topic.

Conclusion

In conclusion, the findings of the study showed that there were relationships between the SII, SIRI, NLR, and PLR on the one hand and increases in patients' ASA scores on the other. In addition, some demographic characteristics of the patient, comorbidities, and the postoperative course were independent risk factors predicting increased SII and SIRI levels. These inflammatory values can be calculated simply and easily from the hemogram test, which is frequently studied in pre-anesthetic evaluation. These parameters, which can reflect a patient's current condition and provide important information about the clinical course of the patient perioperatively, can play a helpful role in preoperative risk estimation and the development of a management plan. However, we believe that this should be confirmed prospectively by covering a wider general population and by dynamically monitoring inflammation biomarkers at different times perioperatively.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Tokat Gaziosmanpaşa University Faculty of Medicine (approval no.: 24-KAEK-207, date: 27.06.2024).

Informed Consent: Informed consent was obtained from patients.

Footnotes

Author Contributions: Surgical and Medical Practices - A.G., M.G.B., V.K., A.T.Ş., Y.E.Ş., H.T., T.K., S.K.; Concept - A.G., M.G.B., V.K., A.T.Ş., T.K., S.K.; Design - A.G., M.G.B., V.K., A.T.Ş., H.T., T.K., S.K.; Data Collection and/or/Processing - A.G., M.G.B., V.K., A.T.Ş., Y.E.Ş., T.K., S.K.; Analysis and/or/Interpretation - A.G., M.G.B., V.K., A.T.Ş., H.T., T.K., S.K.; Literature Review - A.G., M.G.B., V.K., A.T.Ş., Y.E.Ş., H.T., T.K., S.K.; Writing - A.G., M.G.B., V.K., A.T.Ş., Y.E.Ş., H.T., T.K., S.K.

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

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Incidence and Risk Factors of Postoperative Complications in Patients Undergoing Robot-assisted Laparoscopic Radical Prostatectomy: A Retrospective Study

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Abstract

Objective: Robot-assisted laparoscopic radical prostatectomy (RALP) is increasingly used in the treatment of prostate cancer due to its minimally invasive nature, reduced perioperative bleeding, and shorter hospital stays. However, the steep Trendelenburg position and CO_2 pneumoperitoneum required for the procedure present unique anaesthetic challenges, particularly in elderly patients with comorbidities. This study aimed to determine the incidence of anaesthetic complications during RALP and identify independent risk factors associated with these events.

Methods: A retrospective observational study was conducted at Ankara Bilkent City Hospital between 2019 and 2024. A total of 1,020 patients who underwent RALP were evaluated. Collected data included demographic characteristics, the American Society of Anesthesiologists (ASA) physical status classification, comorbidities, and intra- and postoperative outcomes. Anaesthetic complications were analyzed, and multivariate logistic regression was performed to identify independent predictors.

Results: The mean patient age was 65.0±6.3 years, with 65.3% classified as ASA II and 61.6% having at least one comorbidity. Anaesthetic complications occurred in 4.4% of patients. Those with complications were significantly older (67.9±6.2 vs. 64.9±6.3 years, P=0.004), had longer hospital stays (8.98±4.45 vs. 6.83±3.18 days, $P < 0.001$), and were more frequently admitted to the post-anaesthesia care unit (PACU) (73.3% vs. 46.8%, $P < 0.001$). Multivariate analysis identified age, hospital stay duration, and PACU admission as independent risk factors.

Conclusion: RALP can be safely performed in experienced centers with individualized anaesthetic management. However, older age, longer hospitalization, and PACU admission significantly increase the risk of anaesthetic complications. These findings emphasize the need for preoperative risk stratification and tailored perioperative care to improve safety outcomes. Prospective, multicenter studies are needed to confirm these results and guide future anaesthetic strategies in robotic urologic surgery.

Keywords: Anaesthetic complications, perioperative care, postoperative care unit, risk factors, robotic prostate surgery

Main Points

- The study analyzed 1,020 patients undergoing robot-assisted laparoscopic radical prostatectomy (RALP) with a mean age of 65 years, most classified as the American Society of Anesthesiologists II, indicating significant comorbidities.
- Anaesthetic complications were observed in 4.4% of cases, emphasizing the need for vigilance in managing these patients.
- Multivariate analysis identified age, prolonged hospital stay, and post-anaesthesia care unit (PACU) admission as independent risk factors for anaesthetic complications.
- Every additional year of age increased complication risk by 1.083 times, while each extra day of hospitalization raised it by 1.128 times. PACU admission led to over a three-fold increase in risk.
- These findings highlight the need for thorough preoperative evaluation and tailored anaesthetic management to improve safety in RALP procedures.

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Introduction

Robot-assisted laparoscopic radical prostatectomy (RALP) has become a widely adopted technique for prostate cancer due to its minimally invasive nature and perioperative benefits, including reduced blood loss, shorter operative times, and decreased length of hospital stay compared to open surgery. However, RALP poses distinct anaesthetic challenges primarily due to the combined effects of steep Trendelenburg positioning and CO_2 pneumoperitoneum, which induce significant physiological changes. The steep Trendelenburg position shifts abdominal contents toward the diaphragm, resulting in reduced lung volumes, impaired pulmonary compliance, and increased airway pressures. These alterations compromise respiratory mechanics and may lead to atelectasis, ventilation-perfusion mismatch, and increased work of breathing. Simultaneously, CO_2 pneumoperitoneum elevates intra-abdominal pressure, which decreases functional residual capacity and promotes hypercapnia and respiratory acidosis.[1] These effects are particularly pronounced in elderly patients and those with underlying pulmonary disease, such as chronic obstructive pulmonary disease (COPD), thereby increasing the risk of perioperative pulmonary complications. Furthermore, elevated intrathoracic and intracranial pressures associated with positioning and pneumoperitoneum may result in hemodynamic instability, airway edema, and neurological sequelae.[2] The cumulative impact of these factors may help explain the observed association between increased age, post-anaesthesia care unit (PACU) admission, and anaesthetic complications in our patient cohort.

Given the physiological challenges associated with RALP, anaesthesiologists should carefully manage ventilation strategies to reduce the risk of hypercapnia, hypoxemia, and other respiratory complications. Pressure-controlled ventilation has been reported to lower peak airway pressures and improve dynamic compliance compared with volume-controlled ventilation, although both methods are commonly used. Additionally, positive end-expiratory pressure (PEEP) can help maintain adequate oxygenation during prolonged pneumoperitoneum.[3]

Patients undergoing RALP are often older and can have several comorbidities, such as hypertension, diabetes mellitus, coronary artery disease (CAD), and renal dysfunction. These factors can complicate anaesthetic management and increase the risk of perioperative complications. The American Society of Anesthesiologists (ASA) physical status classification system is commonly used to evaluate preoperative risk, and higher ASA scores are linked to a greater incidence of postoperative complications.[4]

Advanced age is linked to reduced physiological reserve, especially in the cardiopulmonary and renal systems, increasing the risk of perioperative respiratory complications. Older patients may have impaired responses to hypercapnia, decreased chest wall compliance, and lower pulmonary function. Age-related vascular stiffness and autonomic dysregulation can also worsen hemodynamic instability during procedures like steep Trendelenburg positioning or CO_2 insufflation.[5] A longer hospital stay may indicate preexisting comorbidities, postoperative complications, or delayed recovery, which can elevate anaesthetic risks, including the potential for hospital-acquired infections. PACU admission often signals a need for closer monitoring due to intraoperative instability or high anaesthetic load, particularly in patients who underwent complex procedures or exhibited risk factors like hypothermia or hemodynamic lability.[2]

The increasing prevalence of RALP highlights the necessity for a comprehensive understanding of the anaesthetic challenges associated with this procedure. Identifying risk factors for anaesthetic complications is crucial. Focusing on modifiable perioperative risk factors can optimize anaesthetic care and improve postoperative outcomes.

Despite the physiological challenges of RALP, including steep Trendelenburg positioning and CO_2 pneumoperitoneum, the incidence of anaesthetic complications remains low in a high-volume center. We hypothesize that RALP can be performed safely with individualized perioperative care, as evidenced by the low rate of PACU admissions and anaesthetic complications.

This study aims to assess the safety of RALP by evaluating the incidence of anaesthetic complications and identifying independent risk factors. Additionally, the rates and duration of PACU admission were analyzed to support the assessment of perioperative anaesthetic safety in a high-volume surgical center.

Methods

Study Design and Participants

This study was designed as a retrospective observational analysis conducted at Ankara Bilkent City Hospital from 2019 to 2024. The study group consisted of 1020 patients who underwent RALP during this period. Patients who underwent combined procedures or had incomplete medical records were excluded from the analysis. Ankara Bilkent City Hospital, Medical Research Scientific and Ethical Evaluation Board No. 1 (TABED) approved the study (protocol number: TABED1-24-371, date: 03.07.2024).

Data Collection

Data were retrieved from electronic medical records. The preoperative variables included age, gender, body mass index (BMI), ASA physical status, comorbidities (eg, hypertension, diabetes mellitus, CAD, chronic kidney disease, cerebrovascular accident, and COPD), smoking history, and abnormal laboratory findings. Intraoperative complications were also recorded. Additionally, postoperative outcomes were documented, including the occurrence of pulmonary,

cardiac, or neurological complications, length of hospital stay, rate of admissions to the PACU, and duration of PACU stay.

Statistical Analysis

Descriptive statistics for continuous variables were presented as mean ± standard deviation (SD), median, and interquartile range (IQR, 25th-75th percentiles), while categorical variables were expressed as percentages. The Shapiro-Wilk test was used to assess the normality of data distribution. The Mann-Whitney U test compared continuous variables between two groups. Group comparisons were conducted using the chi-squared or Fisher's exact tests, as appropriate for categorical variables. Independent risk factors associated with the development of anaesthetic complications were analyzed using multivariate logistic regression analysis. All statistical analyses were performed using IBM SPSS version 20 (Chicago, IL, USA), and a *P* value of <0.05 was considered statistically significant.

Results

The study included 1020 patients who underwent RALP. The mean age of the patients was 65.01±6.34 years, with a minimum age of 38 and a maximum age of 83. The mean hospital stay duration was 6.92±3.28 days. Postoperatively, 47.9% (n = 489) of the patients were admitted to the PACU, with an average PACU stay of 9.95±3.95 hours.

Most patients had an ASA score of 2 (65.3%), while 13.8% were ASA I, 20.7% were ASA III, and 0.2% were ASA IV. The prevalence of comorbidities was as follows: diabetes mellitus in 24.2% of patients, hypertension in 41%, CAD in 18.4%, and COPD in 9.9%. Additionally, 61.6% of the patients had at least one comorbidity (Table 1).

Anaesthetic complications occurred in 4.4% (n = 45) of patients. A comparison between patients with and without anaesthetic complications revealed statistically significant differences in the variables. Patients with anaesthetic complications were significantly older (67.93±6.22 vs. 64.88±6.32 years, *P*=0.004). Patients with anaesthetic complications had significantly longer hospital stays (8.98±4.45 days vs. 6.83±3.18 days, *P* < 0.001). Patients who experienced anaesthetic complications had a higher rate of being monitored in the PACU (73.3% vs. 46.8%, *P* < 0.001). No significant differences were observed in PACU stay duration (4.64±4.94 vs. 3.91±3.88 hours, *P*=0.388), ASA scores (*P*=0.379), and comorbidity rates (68.9% vs. 61.2%, *P*=0.302) between patients with and without anaesthetic complications (Table 2).

Multivariate logistic regression analysis identified age, length of hospital stay, and PACU admission as independent risk factors for developing anaesthetic complications. Each 1-year increase in age increased the risk of anaesthetic complications by 1.083 times [odds ratio (OR): 1.083, 95% confidence interval (CI): 1.024-1.142, *P*=0.003]. Each additional day of hospital stay increased the risk by 1.128 times (OR: 1.128, 95% CI: 1.059-1.201, *P < 0.001*). Admission to the PACU was associated with a 3.363-fold increase in the risk of anaesthetic complications (OR: 3.362, 95% CI: 1.694-6.671, p=0.001; Table 3).

Table 1. Patient Characteristics

n = 1020	**Mean ± SD; median (min.-max.); IQR**	
Age (years)	65.01±6.34; 65 (38-83); (61-69)	
Hospital stay (days)	6.92±3.28; 6 (3-32); (5-8)	
PACU stay duration (hours) n = 489	9.95±3.95; 2.5 (0.5-24.0); (1.5-4.5)	
	n	**%**
ASA score		
1	140	13.8
2	665	65.3
3	211	20.7
4	2	0.2
PACU admission		
No	531	52.1
Yes	489	47.9
Diabetes mellitus		
No	773	75.8
Yes	247	24.2
Hypertension		
No	602	59.0
Yes	418	41.0
Coronary artery disease		
No	832	81.6
Yes	188	18.4
Chronic obstructive pulmonary disease		
No	919	90.1
Yes	101	9.9
Comorbidities*		
No	392	38.4
Yes	628	61.6
Anaesthetic complications		
No	975	95.6
Yes	45	4.4

*Including diabetes mellitus, hypertension, coronary artery disease, and chronic obstructive pulmonary disease.

ASA, American Society of Anesthesiologists; IQR, interquartile range; PACU, post-anaesthesia care unit; SD, standard deviation; min.-max., minimum-maximum

Table 2. Comparison of Patients with and without Anaesthetic Complications

	No anaesthetic complications (n = 975)		Anaesthetic complications (n = 45)		*P* value
	Mean ± SD/median (IQR)		Mean ± SD/median (IQR)		
Age (years)	64.88±6.32 65 (61-69)		67.93±6.22 68 (63-73)		**0.004**[b]
Hospital stay (days)	6.83±3.18 6 (5-8)		8.98±4.45 8 (6-11)		**<0.001**[b]
PACU stay duration (hours; n = 489)	3.91±3.88 2.5 (1.5-4.5)		4.64±4.94 3 (1.7-5.5)		0.388[b]
	n	**%**	**n**	**%**	
ASA score					
1	136	14.0	4	8.9	0.379[c]
2	637	65.5	28	62.2	
3	198	20.3	13	28.9	
4	2	0.2	0	0	
PACU admission					
No	519	53.2	12	26.7	**<0.001**[c]
Yes	456	46.8	33	73.3	
Comorbidities					
No	378	38.8	14	31.1	0.302[c]
Yes	579	61.2	31	68.9	

[b], Mann-Whitney U test; [c], chi-squared test/Fisher's exact test.
ASA, American Society of Anesthesiologists; IQR, interquartile range; PACU, post-anaesthesia care unit; SD, standard deviation.

Table 3. Multivariate Logistic Regression Analysis of Risk Factors for Anaesthetic Complications

Variable	B (SE)	Adjusted OR	95% CI	*P* value
Age	0.080 (0.027)	1.083	1.024-1.142	0.003
Hospital stay (days)	0.120 (0.032)	1.128	1.059-1.201	<0.001
PACU admission	1.213 (0.350)	3.362	1.694-6.671	0.001

CI, confidence interval; OR, odds ratio; PACU, post-anaesthesia care unit; SE, standard error.

Discussion

In our study of 1020 RALP patients, the mean age was 65 years with an average hospital stay of 6.9 days, with nearly half (47.9%) requiring postoperative PACU monitoring. Most patients were classified as ASA II and over 60% had at least one comorbidity. Anaesthetic complications occurred in 4.4% of cases; notably, patients with these complications were significantly older (mean age 67.93 vs. 64.88 years), had longer hospital stays (8.98 vs. 6.83 days), and were more frequently admitted to the PACU (73.3% vs.. 46.8%) compared with those without complications. Multivariate analysis identified age, length of hospital stay, and PACU admission as independent risk factors, with each additional year of age and day in the hospital increasing the risk by 1.083 and 1.128 times, respectively, while PACU admission tripled the risk of anaesthetic complications.

A retrospective study by Uğur and Ertuğrul[6] analyzed anaesthesia management in robotic-assisted perineal prostatectomy (RAPP) cases and focused on physiological challenges related to steep trendelenburg positioning and pneumoperitoneum. The study included 131 patients and evaluated intraoperative hemodynamic and respiratory changes and postoperative complications. The findings indicate significant intraoperative decreases in heart rate, systolic and diastolic blood pressure, and mean arterial pressure. Additionally, CO_2 pneumoperitoneum led to increased pCO_2 levels and decreased pH, although no severe acid-base imbalances were observed. The most common postoperative complications were nausea and vomiting, followed by anastomotic leakage. The study highlights the importance of understanding the physiological effects of RAPP on older patients with comorbidities and emphasizes

the need for careful anaesthesia management. The results contribute to optimizing perioperative strategies to mitigate complications associated with robot-assisted surgery.[6]

Porcaro et al.[7] assessed the predictive value of the ASA physical status classification for 90-day postoperative complications after RALP. In their large cohort, higher ASA scores were independently associated with an increased risk of significant complications (as graded by the Clavien-Dindo system). This finding supports the use of ASA classification for preoperative risk stratification and underscores its utility in surgical planning and patient counseling.[7]

The study by Zhang et al.[8] investigated the risk factors associated with hypoxemia during the emergence from anaesthesia in patients undergoing RALP. The study included 316 patients divided into hypoxemia (n = 134) and non-hypoxemia (n = 182) groups based on postoperative oxygen levels. The findings revealed that 38.9% of patients had low preoperative partial pressure O_2. Several clinical parameters, including BMI, preoperative PaO_2 levels, and a history of emphysema and pulmonary alveolar disease, were significantly associated with hypoxemia. The study concluded that these factors are crucial predictors of hypoxemia during the emergence from anaesthesia in patients with RALP. The authors emphasized the importance of preoperative assessment and managing these risk factors to mitigate postoperative hypoxemia and improve patient outcomes.[8]

Aceto et al.[5] provided a narrative review focusing on the challenges of administering anaesthesia during robot-assisted surgery in older people. The authors emphasized that extreme patient positioning (eg, steep or reverse Trendelenburg) combined with pneumoperitoneum can significantly affect cardiovascular stability, lung mechanics, intracranial pressure, and ocular perfusion. The review advocates for tailored anaesthetic techniques and vigilant intraoperative monitoring to mitigate these risks, particularly in older patients with compromised cardiopulmonary reserve.[5]

Høyer et al.[9] examined lung-protective ventilation's hemodynamic, renal, and hormonal effects (eg, low tidal volume with high PEEP) during RALP. Their randomized controlled trial in 24 patients revealed that while lung-protective strategies might transiently reduce renal function (evidenced by decreased creatinine clearance) and increase levels of vasoactive hormones, these effects are reversible. The study underscores the need to balance lung protection with these patients' potential hemodynamic and renal consequences.[9]

Emir et al.[10] compared RAPP with the conventional RALP approach. Their retrospective study found that although RAPP was associated with a more pronounced increase in blood CO_2 levels due to perineal insufflation, respiratory mechanics were less adversely affected than in RALP. The results suggest that differences in surgical approach necessitate distinct anaesthetic considerations, particularly regarding CO_2 management.[10]

Lestar et al.[11] focused on the hemodynamic changes during RALP performed in an extreme (45°) Trendelenburg position. Their investigation in 16 patients with an ASA score of 1-2 showed a marked increase (two-fold to three-fold) in filling pressures (eg, central venous pressure and pulmonary capillary wedge pressure) without compromising cardiac output or gas exchange. However, lung compliance was significantly reduced. These findings highlight the circulatory adaptations required during steep Trendelenburg and the importance of close hemodynamic monitoring.[11]

Danic et al.[12] reviewed anaesthesia considerations in a series of 1,500 cases of RALP. They reported low rates of anaesthesia-related complications overall, with corneal abrasions and airway management challenges being the most common issues. Their extensive experience emphasizes that while robot-assisted prostatectomy is generally safe from an anaesthetic standpoint, careful attention to patient positioning and airway management is crucial.[12]

Our study highlights the incidence of pulmonary complications in patients undergoing RALP and identifies several independent risk factors. The steep trendelenburg position and CO_2 pneumoperitoneum adversely affect respiratory function, leading to complications such as atelectasis and the need for postoperative oxygen support. Our findings are consistent with previous studies that have reported similar complications following RALP.

Compared to other robotic-assisted procedures such as gynecologic or colorectal surgeries, RALP poses unique anaesthetic challenges due to the steep Trendelenburg position maintained for prolonged durations and the proximity of the surgical field to the diaphragm and airway structures. For example, robotic hysterectomy and colorectal resections often require less extreme positioning and shorter pneumoperitoneum duration, potentially resulting in fewer cardiopulmonary perturbations. Moreover, RALP is typically performed in elderly male patients with multiple comorbidities, which further increases anaesthetic risk. These factors highlight that anaesthetic management in RALP must be especially vigilant regarding ventilation strategies, hemodynamic monitoring, and airway protection. Our findings reinforce these concerns, as older age and PACU admission were identified as independent predictors of anaesthetic complications in this specific surgical context.[13-15]

While our study focused on short-term perioperative outcomes, including hospital stay, PACU admission, and

immediate anaesthetic complications, we acknowledge the importance of long-term consequences such as health-related quality of life, postoperative functional status, and long-term morbidity. Prior studies have shown that anaesthetic complications—especially pulmonary and cardiovascular events—can negatively impact rehabilitation, delay return to baseline functional capacity, and increase readmission or long-term dependency on healthcare.[16-18] Future prospective studies with structured follow-up protocols should evaluate the long-term effects of anaesthetic events, including impacts on neurocognitive function, frailty progression, and quality of life in elderly patients undergoing RALP.

Study Limitations

This study has several limitations that must be acknowledged. First, its retrospective design inherently limits the control over confounding variables and depends on the accuracy and completeness of existing medical records. Second, as the study was conducted at a single tertiary center with experienced surgical and anaesthetic teams, the findings may not be generalizable to institutions with different levels of expertise or perioperative protocols. Another significant limitation of our study is the lack of detailed intraoperative data, such as surgical duration, specific anaesthetic techniques, induction and maintenance agents, ventilation strategies, and surgical complexity scores. These variables are known to influence anaesthetic risk and perioperative outcomes. However, as a retrospective analysis relying on electronic medical records, such granular data were not consistently documented and thus could not be included in the statistical models. Variations in anaesthetic techniques, postoperative care models, and institutional practices can influence complication rates and outcomes. Future prospective studies should incorporate standardized intraoperative documentation, including real-time recording of anaesthetic protocols and procedural complexity, to better delineate their role in developing anaesthetic complications.

Conclusion

In this large retrospective cohort of 1,020 patients undergoing RALP, we identified age, prolonged hospital stay, and PACU admission as independent predictors of anaesthetic complications. Despite the physiological demands imposed by steep Trendelenburg positioning and CO_2 pneumoperitoneum, the overall incidence of anaesthetic complications remained low. These findings support our initial hypothesis that RALP can be safely performed in high-volume centers with experienced perioperative teams and individualized anaesthetic planning.

This study adds to the growing evidence on perioperative safety in robotic urologic surgery by providing real-world data on risk stratification and complication rates. Importantly, it underscores the clinical relevance of proactively identifying vulnerable patients and implementing targeted anaesthetic strategies such as optimized ventilation, hemodynamic monitoring, and early PACU triage to reduce adverse events.

Future prospective multicenter trials with standardized intraoperative data collection are warranted to confirm these findings and to evaluate the long-term consequences of anaesthetic complications, including their impact on postoperative recovery, functional capacity, and quality of life.

Ethics

Ethics Committee Approval: Ankara Bilkent City Hospital, Medical Research Scientific and Ethical Evaluation Board No. 1 (TABED) approved the study (protocol number: TABED1-24-371, date: 03.07.2024).

Informed Consent: All participants provided informed consent.

Footnotes

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

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Continuous Low-dose Epidural Morphine and Ketamine Analgesia Improves Quality of Recovery after Major Lumbar Spine Surgery: A Randomised Controlled Trial

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Abstract

Objective: The effect of postoperative analgesia on the quality of recovery (QoR) after major lumbar spine surgery is understudied. We hypothesized that continuous epidural morphine and ketamine administration would provide effective analgesia, thereby improving QoR compared to continuous intravenous morphine and ketamine using the QoR-15 questionnaire.

Methods: A total of 40 patients were randomised to receive either continuous low-dose epidural morphine and ketamine via an intraoperatively placed epidural catheter (Group A) or intravenous morphine and ketamine using a patient-controlled analgesia system (Group B) for 48 hours. All patients were anaesthetized using standard anaesthesia drugs. The primary outcome was QoR at 24 and 48 hours after surgery using the QoR-15 questionnaire. The secondary outcomes were pain score at various time points during the first 48 hours, rescue analgesic requirements, ambulation time, length of hospital stay, and patient satisfaction.

Results: Forty patients were recruited (20 in each group), and all patient data were included in the analysis. The total QoR-15 scores for Group A and Group B at 24 hours were 134.8±6.65 and 128.9±6.12, respectively (P=0.006). The QoR-15 scores at 48 hours for groups A and B were 136.7±6.02 vs 132.10±6.8 (P=0.029), respectively. The pain score was lower in Group A than in Group B at rest and during movement, with P=0.015 and 0.001, respectively, and all the other secondary outcomes were comparable between the groups.

Conclusion: Postoperative analgesia with continuous low-dose epidural morphine and ketamine via an intraoperatively placed epidural catheter provides superior QoR after major lumbar spine surgery as compared to intravenous morphine and ketamine.

Keywords: Epidural analgesia, ketamine, lumbar spine surgery, postoperative pain, quality of recovery

Main Points

- Pain affects recovery; appropriate pain management enhances the quality of recovery (QoR), improving the quality of life.
- Most studies looked at the various modes of analgesia, their effect on acute and chronic pain, and the rescue analgesic requirements following major spine surgery. Literature regarding the impact of analgesia on QoR following major spine surgery is scarce. This study assessed the effect of analgesia on the QoR using the QoR-15 questionnaire following major spine surgery.
- Continuous administration of low-dose epidural morphine and ketamine analgesia via an intraoperatively placed epidural catheter without local anaesthetics provides excellent analgesia and superior QoR following major lumbar spine surgery compared to systemic morphine and ketamine.

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Introduction

The number of patients undergoing major spine surgery for degenerative disease, involving the lumbar spine, is constantly increasing worldwide.[1] Pain after major spine surgery is moderate to severe during the first 48-72 hours.[2-4] Appropriate pain management enhances recovery, reduces chronic pain, and improves the quality of life. Administration of systemic opioids is considered the mainstay for postoperative pain management; controlling pain with a high dose of systemic opioids often leads to excessive sedation, respiratory depression, postoperative nausea and vomiting (PONV), paralytic ileus and prolonged ambulation time, which can affect the quality of recovery (QoR).[5,6] Though postoperative pain is an essential component of the QoR, the assessment of pain outcomes alone does not describe the global dimensions of postoperative recovery.The effect of analgesia on QoR is understudied. This study compared the effects of epidural versus systemic opioids with ketamine on QoR following major spine surgery.

The QoR-40, QoR-15, and QoR-9 questionnaires are routinely used to assess QoR after anaesthesia and surgery.[7] Among all the QoR Questionnaires, the QoR-15 is a simple, validated, equally extensive, yet more efficient evaluation of QoR.[8] It assesses five domains: physical comfort, independence, psychological support, pain, and emotional state. The total score ranges from 0-150, with a high score indicating good QoR. Its use in spine surgery is limited, and most studies have utilized QoR-40 as it was done before the validation of QoR-15.[9,10]

High-dose opioid administration after tissue injury and inflammation can upregulate the N-methyl-D-aspartate receptor (NMDA) in the dorsal horn of the spinal cord. It can lead to central sensitization, opioid-induced hyperalgesia and opioid tolerance.[11,12] Hence, the addition of ketamine (NMDA receptor antagonist) as an anaesthetic adjuvant helps to enhance analgesia while reducing the effects mentioned above.[13,14]

In our institution, intravenous administration of opioids with ketamine (continuous infusion or via the patient control analgesia system), paracetamol (every 6th hour) and non-steroidal anti-inflammatory drugs (every 8th hour) was the standard of practice for pain management after major spine surgery till 2019. Hence, we wanted to compare intravenous morphine and ketamine with epidural morphine and ketamine on QoR using the QoR-15 questionnaire following major spine surgery. We felt that assessment of QoR is better than assessing only the pain to study the analgesic efficacy of a particular analgesic technique. We hypothesized that continuous low-dose epidural morphine and ketamine would provide superior QoR by providing adequate analgesia with minimal side effects compared to intravenous morphine and ketamine administered via a patient-controlled analgesia (PCA) system. The primary outcome was to study the impact of analgesia on QoR using the QoR-15 questionnaire 24 and 48 hours after major lumbar spine surgery. The secondary outcomes were the pain score at various time points, opioid requirement, rescue analgesic requirement, haemodynamics, ambulation time, time taken for solid intake, length of hospital stay, patient satisfaction, and the incidence of side effects of opioids and ketamine during the first 48 hours after surgery.

Methods

This single-centre randomised controlled trial was conducted after obtaining approval from the Institutional Review Board of Christian Medical College, Vellore, India (approval no.: 12320, date: 30/10/2019) and registered with the Clinical Trial Registry of India (CTRI) (CTRI/2019/12/022513). Written informed consent was obtained from all recruited patients, and this study was conducted from January to December 2020 in accordance with the Declaration of Helsinki.

All patients with American Society of Anesthesiologists (ASA) grade 1-2, aged 18-70 years, with normal renal function who underwent transforaminal thoracolumbar/lumbar spine instrumentation, were recruited. Patients with ASA 3-4, body mass index>30 kg m^{-2}, moderate-to-severe chronic obstructive pulmonary disease, impaired renal function (creatinine>1.4 mg dL^{-1}), chronic liver disease, coagulation abnormalities, history of obstructive sleep apnea, allergy to study medications, psychiatric disorders, or chronic opioid use were excluded.

Patients scheduled for thoracolumbar/lumbar interbody fusion were screened, and eligible patients were randomised into group A (epidural morphine and ketamine) or group B (intravenous morphine and ketamine) using a computer-generated randomization sequence. Allocation concealment was performed using sealed, opaque envelopes. Randomization was done immediately before the start of anaesthesia. Patients were informed about the QoR score assessment details at the time of recruitment. QoR was assessed by the principal investigator, who was blinded to the study intervention. Patients were followed up till 48-hours regarding pain, rescue analgesic requirements, ambulation, and incidence of side effects of morphine and ketamine.

Anaesthesia Protocol

On the day of surgery, after reassessment, patients were taken to the anaesthesia room, and an 18/16G intravenous cannula was placed. After placing an electrocardiogram, non-invasive blood pressure (BP), pulse oximetry, and end-tidal carbon dioxide, anaesthesia induction was carried out with fentanyl (2 μg kg^{-1}), propofol (2 mg kg^{-1}), ketamine (0.5 mg kg^{-1}) and paralyzed using vecuronium (0.1 mg kg^{-1})

and intubated with an appropriate size endotracheal tube. A 20/22G arterial cannula was placed to monitor the invasive arterial pressure after intubation. Anaesthesia was maintained with air, oxygen, and sevoflurane (0.8-1 minimum alveolar concentration) and titrated to maintain a bispectral index between 40-60. The mean arterial pressure was maintained within 15% of the baseline value during surgery. Morphine (0.1 mg kg^{-1}), ketamine (0.05 mg kg^{-1} h^{-1}) and paracetamol (20 mg kg^{-1}) were administered for intraoperative analgesia, and the intraoperative pain response was treated with fentanyl (0.5 µg kg^{-1}). Dexamethasone (4 mg) and Ondansetron (0.1 mg kg^{-1}) were administered for PONV prophylaxis. Lignocaine (preservative-free) 1.5 mg kg^{-1} was administered to facilitate smooth extubation. Residual neuromuscular block (assessed using a train of four ratios) was reversed using neostigmine (0.05 mg kg^{-1}) and glycopyrrolate (0.01 mg kg^{-1}). Extubation was performed once the criteria were met. Postoperative analgesic regimens were followed according to the group allocation. Both groups received paracetamol (1 gm every 6th hour) as part of a multimodal analgesia protocol. At any time point, if the numerical rating scale (NRS) score was >4, intravenous diclofenac (50 mg) was administered as a first rescue analgesic. If pain persists (NRS>4), tramadol (50 mg) and paracetamol (325 mg) combination was administered as a second rescue analgesia drug.

Postoperative Analgesia Protocol for Group A: At the end of instrumentation, after ensuring that there was no cerebrospinal fluid (CSF) leak at the surgical site, the surgeon placed a 20G epidural catheter under direct vision through the cranial end of the laminectomy defect, directed cranially up to 5-6 cm. After ensuring a negative CSF aspiration, 2 mL of 0.9% normal saline was injected. While injecting saline, the anaesthesiologist ensured no undue resistance, and the surgeon ensured that saline did not appear in the surgical field; both measures ruled out catheter malposition. The caudal end of the epidural catheter was taken out through the skin and secured away from the surgical incision site. Morphine (1 mg) and ketamine (10 mg) were administered as bolus through the catheter for over 5 minutes. Seven mg of morphine (0.7 mL) and 50 mg (1 mL) of ketamine were diluted in 0.9% normal saline (48.3 mL) and loaded in a 50 ml continuous analgesia drug delivery (CADD) pump, which was set at the rate of 1 mL hr^{-1} for 48 hours (morphine-0.14 mg, ketamine-1 mg hr^{-1}). Infusion was initiated soon after extubation.

Postoperative Analgesia Protocol for Group B: Patients in Group B received intravenous morphine and ketamine through PCA using a CADD pump. Morphine (50 mg) and ketamine (50 mg) were diluted in 44 mL 0.9% normal saline at a concentration ratio 1:1 and loaded into a 50 mL CADD pump. Patients received a 0.015 mL kg^{-1} $bolus^{-1}$ of the study drug with a lockout period of 10 mins (six boluses $hour^{-1}$), which was delivered intravenously for 48 hours.

Data Analysis

Preoperatively, demographics, ASA status, presenting symptoms, duration of back pain and its severity, radicular pain, neurological deficits, and associated comorbidities were recorded. Intraoperatively, the levels of instrumentation, blood loss, crystalloid administration, fentanyl, propofol requirement, duration of surgery, and anaesthesia were documented. Postoperatively, the heart rate, BP, respiration, and sedation scores were noted regularly. Pain scores were measured using the NRS (0=No pain, 10=Worst pain) at rest and during movement at arrival and 2, 6, 12, 24, 36, and 48 hours after arrival to the ward (7-time points). The total dose of morphine consumed at 24 and 48 hours in the intravenous group was noted (Group B). The time taken to receive the first dose of rescue analgesia after arrival to the postoperative ward was noted, and the total doses of rescue analgesic and antiemetic administered to control pain and PONV, respectively, were recorded during the first 24 and 48 hours. The time to start moving in and around the bed without support was taken as the ambulation time, and the time of solid diet intake and the duration of hospital stay were noted. Patient satisfaction was assessed using a NRS (1-10) and graded as excellent (9-10), very good (7-8), good (5-6), fair (3-4), poor (1-2) and compared between the groups.

QoR was assessed using the QoR-15 questionnaire. The questionnaire consisted of 15 questions that examined five domains of patient recovery, such as physical comfort (questions 1-4,13), physical independence (questions 5,8), psychological support (questions-6,7), emotional state (questions-9,10,14,15) and pain (questions-11,12). Each question uses a Likert scale (0-10), with a total score ranging from 0-150. A higher score indicates good QoR. In the original questionnaire, we modified the 8th question as "Able to move, turn around or sit up in the bed without support". This study examined the total score and the score for the individual domains (five domains) at 24 and 48 hours after surgery and compared them between groups A and B.

Literature on QoR using QoR-15 following major spine surgery was unavailable while designing this study. Hence, the statistical input was taken from the article by Mariappan et al.[9] The authors compared QoR using the QoR-40 score following anterior cervical discectomy and fusion in patients who received a superficial cervical plexus block versus those who received no block for perioperative analgesia. In this study, we used the QoR-15 instead of the QoR-40 questionnaire; hence, we had taken a six-point difference in the total QoR-15 score to show a clinically meaningful difference of 15%, with an alpha error of 5% and a 95% confidence interval. The required sample size was 15 in each group. With 15% dropouts, we decided to study approximately 20 subjects in each arm for 40 subjects.

Statistical Analysis

Descriptive statistics are reported as mean and standard deviation for continuous variables (normally distributed) and as median and interquartile range (IQR) for skewed data. All categorical variables were reported as frequencies and percentages. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used for normality. To compare the mean difference between groups, the Student's and Independent Samples t-tests was used for normally distributed data, and the Mann-Whitney U test was used for data with skewed distribution. Chi-square and Fisher's exact tests were used to determine the association between groups and categorical variables. A generalized estimating equation was used to compare the two groups over time for postoperative haemodynamics and sedation scores during the first 48 hours at specified intervals. All tests were two-sided at a significance level of α=0.05. All analyses were performed using SPSS software (version 21.0; IBM Corp, Armonk, NY, IBM Corp).

Results

A total of 46 patients were screened, of whom 40 were recruited. Twenty patients received epidural morphine and ketamine (Group A), and another 20 received intravenous morphine with ketamine (Group B) for postoperative analgesia. All patients underwent lumbar instrumentations except four in Group A (epidural) and two in Group B (intravenous), who underwent thoracolumbar instrumentation involving T11 and below. The results were analysed using the intention-to-treat method; none were lost to follow-up. Figure 1 depicts a consort diagram. The demographics and baseline characteristics were comparable between the groups (Table 1). The intraoperative propofol and fentanyl requirements, blood loss, total intravenous fluid administration, duration of anaesthesia, surgery, and instrumentation levels were comparable between the groups (Table 2).

The total QoR-15 score at 24 hours for Group-A (epidural morphine and ketamine) and Group-B (intravenous morphine and ketamine) were 134.8±6.65 versus 128.9±6.12, respectively (*P*=0.006). The QoR scores at 48 hours for groups A and B were 136.7±6.02 versus

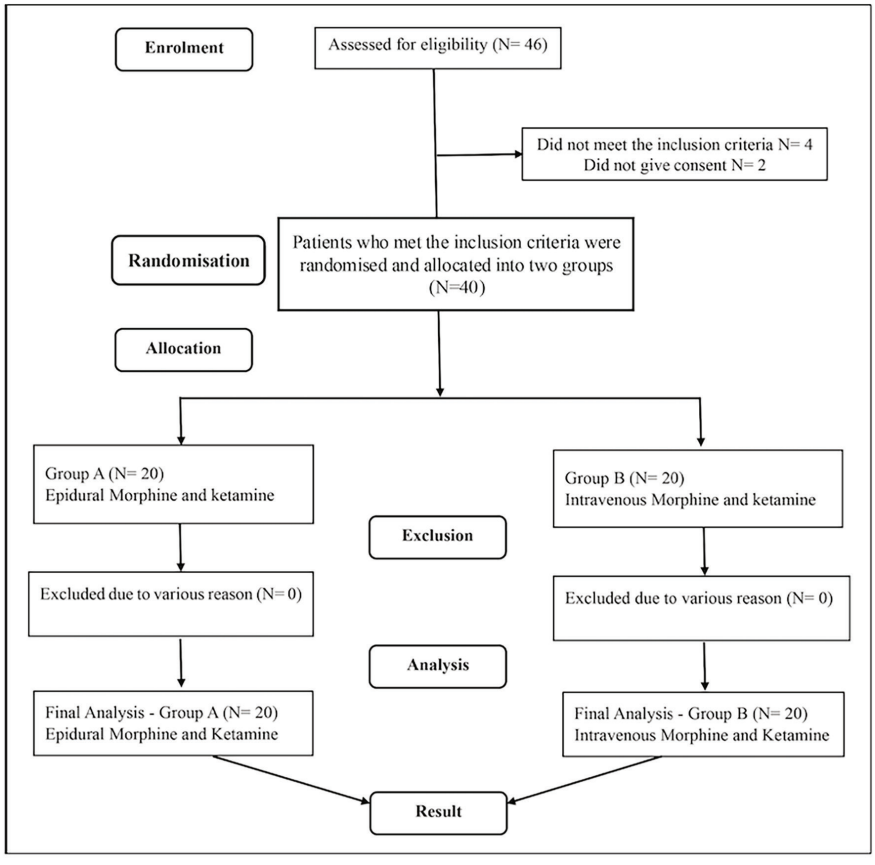

Figure 1. Consort diagram.

132.10±6.8 (*P*=0.029), respectively. The QoR-15 scores for the five subdomains were compared between groups. The subdomain scores of physical independence and emotional support were significantly higher in Group A at 24 hours. The pain and emotional support scores were significantly better in Group A at 48 hours. The other subdomain scores were comparable between the groups. The total QoR-15 scores and the scores for each domain are shown in Table 3.

The mean NRS ranged between 1-4 at most time points, both at rest and during movement, for both groups. A pain score of <4 at most time points, even during movement, signifies that both techniques provided good-quality analgesia following thoracolumbar/lumbar spine instrumentation and fusion. The pain score was significantly lower in group A (epidural) than in group B (intravenous), both at rest and during movement, at each time point (*P*=0.015 and 0.001, respectively) (Figure 2). The mean dose of morphine consumed during the first 24 hours in group B was 18.25±11.36 mg, and for 48 hours was 27.4±13.3 mg. Patients in group A received a fixed dose of 4.5 mg of epidural morphine at 24 hours and 8 mg at the end of 48 hours. The time taken to receive the first dose and the number of patients who received rescue analgesia during the first 24, 24-48 hours were comparable between the groups (Table 2). None of the patients in either group needed a second rescue analgesic drug.

Table 1. Demographics, Comorbidities, and Presenting Symptoms Between the Groups

Parameters/Groups	Group A Epidural morphine and ketamine (n = 20)	Group B Intravenous morphine and ketamine (n = 20)	*P* value
Age (yr); mean ± SD	47.05±11.93	48.10±11.61	0.779
Gender; n (%)			
Male	5 (45.5)	2 (16.7)	0.1930
Female	6 (54.5)	10 (83.3)	
Weight (kg); mean ± SD	64.90±9.21	64.05±9.24	0.772
Height (cm); mean ± SD	158.3±11.8	156.4±11	0.591
BMI (kg/m^2); mean ± SD	26.3±3.26	25.9±2.58	0.685
Comorbidities; n (%)			
Type II DM	5 (25)	6 (30)	1.000
Hypertension	4 (20)	9 (45)	0.091
Presenting symptoms; n (%)			
Back pain	20 (100)	20 (100)	
Radiating pain	17 (85)	19 (95)	0.605
Bladder/bowel involvement	2 (10)	1 (5)	1.000
Lower limb weakness	2 (10)	0 (0)	0.487

BMI, body mass index; DM, diabetes mellitus; N, number; SD, standard deviation.

Table 2. Intraoperative, Postoperative Parameters and Side Effects Between the Groups

Parameters/Groups	Group A Epidural morphine and ketamine (n = 20)	Group B Intravenous morphine and ketamine (n = 20)	*P* value
Intraoperative parameters			
Levels of instrumentation; n (%)			
Two levels	13 (65)	16 (80)	0.606
Three to four levels	4 (20)	3 (15)	
Five levels	3 (15)	1 (5)	
Requirement of fentanyl (μg); mean ± SD	218±58.5	213±78	0.811
Requirement of propofol (mg); mean ± SD	195.0±46.85	241.05±107	0.086
Blood loss (mL); median (IQR: 25,75)	550 (425,900)	500 (400,625)	0.329

Table 2. Continued			
Parameters/Groups	**Group A Epidural morphine and ketamine (n = 20)**	**Group B Intravenous morphine and ketamine (n = 20)**	***P* value**
Crystalloid (mL); mean ± SD	2482.50±1205	2022.50±599.26	0.135
Duration of anaesthesia (mins); mean ± SD	318.00±74.9	295.60±52.4	0.280
Duration of surgery (mins); mean ± SD	244.75±79.40	231.7±63.67	0.568
Postoperative parameters			
Time taken to receive the first dose of rescue analgesia (hours); median (IQR: 25,75)	0 (0, 1.75)	0 (0, 1.75)	0.984
Number of patients who received rescue analgesia - 0-24 hours post-surgery; n (%)	5/20 (25)	4/20 (20)	1.000
Number of patients who received rescue analgesia - 24-48 hours post-surgery; n (%)	4/20 (20)	3/20 (15)	1.000
Time for ambulation (hours); mean ± SD	15.41±4.11	12.56±5.14	0.061
Time for solid food intake (hours); median (IQR: 25,75)	19.25 (6.88, 21.83)	14.78 (4.18, 20.38)	0.791
Duration of hospital stay (days); mean ± SD	5.00±2.44	5.15±1.81	0.827
Postoperative side effects			
PONV; n (%)	3/20 (15)	9/20 (45)	0.082
Abdominal distension; n (%)	1/20 (5)	5/20 (25)	0.182
IQR, interquartile range; N, number; PONV, postoperative nausea and vomiting; SD, standard deviation.			

Table 3. Quality of Recovery-15 Score: Total Score and Scores for Each Domain at 24 and 48 Hours after Surgery			
Parameters/Groups	**Group A Epidural morphine and ketamine (n = 20)**	**Group B Intravenous morphine and ketamine (n = 20)**	***P* value**
QoR-15 - total score			
Score at 24 hours	134.8±6.7	128.9±6.1	0.006*
Score at 48 hours	136.7±6.0	132.1±6.8	0.029*
Subdomain score at 24 hours			
Pain	17.9±1.3	17.25±1.2	0.115
Physical comfort	46.1±2.9	44.55±3.4	0.127
Physical independence	14.8±1.9	13.5±1.4	0.017*
Physical support	19.3±1.2	19.4±0.9	0.649
Emotional support	36.6±2.5	24.6±2.9	0.027*
Subdomain score at 48 hours			
Pain	18.1±1.3	17.2±1.5	0.036*
Physical comfort	46.7±3.0	45.2±4.0	0.186
Physical independence	15.7±1.3	15.4±1.3	0.550
Physical support	19.3±0.9	19.8±3.7	0.523
Emotional support	36.9±2.0	35.5±2.3	0.027*
QoR, quality of recovery; *Statistically significant.			

Postoperative haemodynamics (heart rate and BP) were comparable between the groups at all time points during the postoperative period. Figure 3 depicts the haemodynamics between the groups at various time points during the first 48 hours after surgery. The ambulation time was 15.41±4.11 hours for group A, while this was 12.56±5.14 hours for group B (*P*=0.061). The median time taken to resume their solid diet was 19.25 hours (IQR 25,75- 6.88, 21.83) for group A, while it was 14.78 (IQR 25,75- 4.18, 20.38) hours for group B (*P*=0.791). Both parameters were comparable between the groups. The duration of hospital stay was similar between the groups (Group A vs. B-5.00±2.44 vs. 5.15±1.81 days *P*=0.827).

There were 11/20 (55%) patients who had very good-to-excellent satisfaction in group A compared to 7/20 (35%) in group B (*P*=0.204). The proportions of patients who had fair satisfaction in groups A and B were 1/20 (5%) and 5/20 (25%), respectively (*P*=0.182). However, these differences were not statistically significant.

There were 3/20 (15%) patients in group A who had PONV, compared to 9/20 (45%) in group B (*P*=0.082). The proportion of patients with abdominal distention and constipation in groups A and B was 1/20 (5%) and 5/20 (25%), respectively (*P*=0.182). None of the patients in either group experienced excessive sedation, respiratory

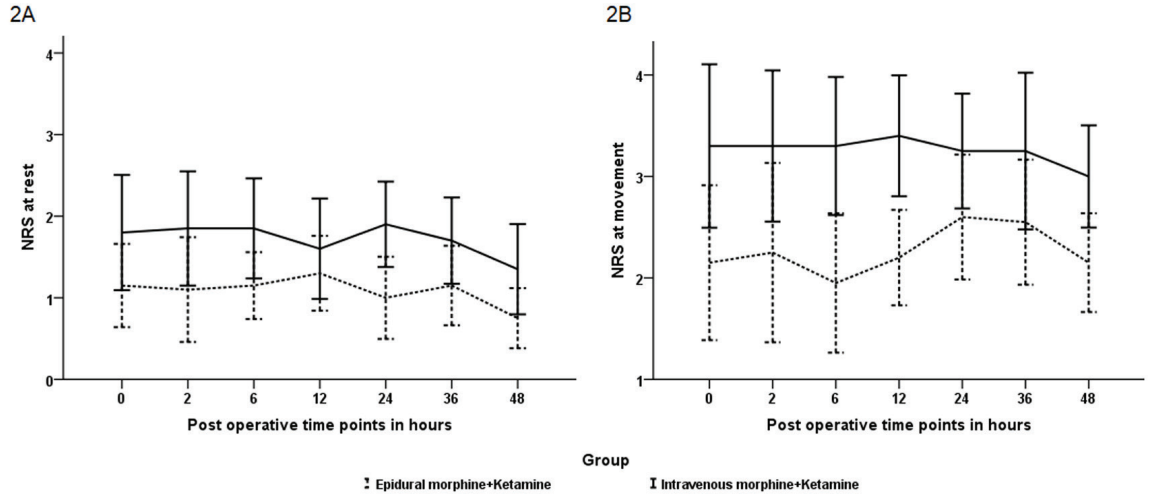

Figure 2. Numerical rating scale at rest (2A) and movement (2B) at various time points during the first 48 hours postoperative period.

NRS, numerical rating scale.

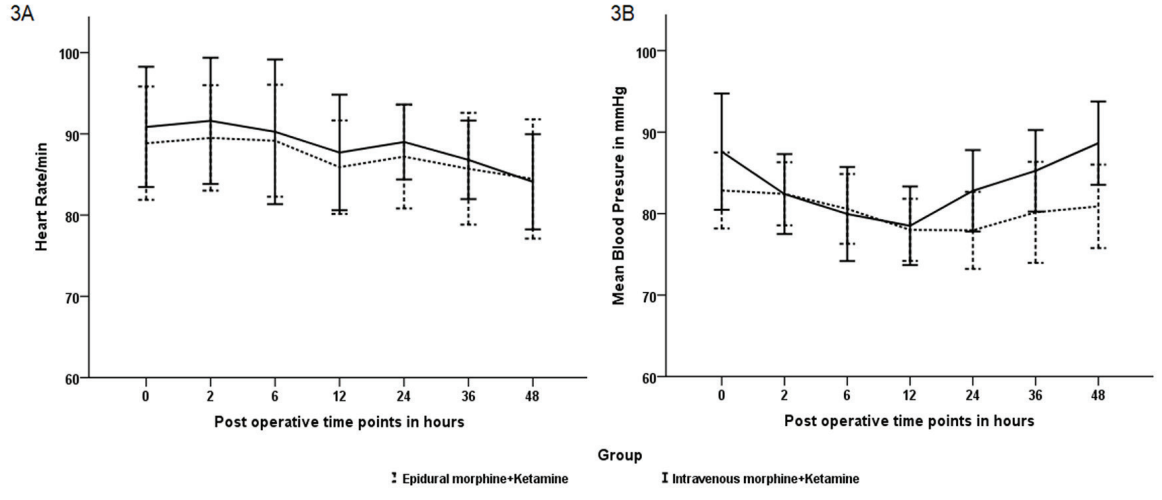

Figure 3. Heart rate (3A) and mean blood pressure (3B) at various time points during the first 48 hours postoperative period.

depression, constipation, nystagmus, hallucinations, or pruritus that required treatment. The urinary catheter was removed on the second postoperative day, after which none of them had urinary retention.

Discussion

This single centre randomised controlled trial compared QoR between patients who received epidural versus intravenous morphine and ketamine for postoperative analgesia following thoracolumbar/lumbar spine instrumentation showed that epidural morphine and ketamine analgesia provided superior QoR as compared to intravenous morphine and ketamine at 24 hours. The pain scores at rest and movement were lower at all time points in the epidural group than in the intravenous group, indicating that epidural analgesia provided better pain relief than the intravenous group.

A study by Leslie et al.[10] has shown that postoperative pain affects the QoR in neurosurgical patients. There are studies comparing the different modes of analgesia on pain outcomes following spine surgery.[1,2,4,15,16] Studying the pain outcome alone does not describe the global dimensions of postoperative recovery. Hence, we decided to study the impact of different modes of analgesia on QoR following spine surgery. There are only a few studies available in this regard[9,17], and Kleif and Gögenur[18] classified QoR into four categories: excellent (136-150), good (122-135), moderate (90-121), and poor (0-89), based on the total QoR-15 score. Our study showed that both analgesic techniques provided good QoR at 24 h and good-to-excellent QoR at 48 h after major spine surgery. None of the patients in this study had a moderate or poor QoR (score<120).

Myles et al.[19] recommended that a difference of 6 points in the QoR-15 score is considered significant to show the clinically meaningful difference between the two interventions. Similarly, our study also showed a statistically significant difference of 6 points between the groups at 24 hours, confirming that epidural analgesia using continuous low-dose epidural morphine and ketamine improves QoR. The study results by Myles and Myles[19] were published after the commencement of our research. Hence, we could not utilize this study results for the sample size calculation.

Continuous/patient-controlled administration of intravenous opioids with or without adjuvants or epidural analgesia using local anaesthetics with opioids is commonly utilised for postoperative analgesia following major lumbar spine surgery. A recent meta-analysis of randomised controlled trials[20] compared the analgesic efficacy of epidural and intravenous analgesia in major spine surgeries. Our study results showed that epidural analgesia provided superior analgesia and better patient satisfaction than intravenous analgesia. This study results were similar to the meta-analysis.[20] The NRS at different time points during the first 48 hours was significantly lower in the epidural group than in the intravenous group.

The epidural dose used in the current study was selected based on our pilot study and our previous study by Prabhakar et al.[21] in that study, single-shot epidural morphine (4 mg) and ketamine (30 mg) were administered for postoperative analgesia following lumbar laminectomy±discectomy, which provided 23±3 hours of analgesia. Since the current study was a major spine instrumentation surgery, we administered 8 mg morphine and 60 mg ketamine epidurally as a continuous infusion for 48 hours.

In this study, morphine was administered as a low-dose infusion for 48 hours rather than an intermittent bolus to prevent infection and reduce the side effects. Studies have shown that continuous infusion of low-dose epidural morphine was associated with fewer side effects than intermittent epidural morphine bolus in cardiac and thoracic surgeries.[22,23] To the best of our knowledge, this study is the first to administer a continuous infusion of epidural morphine and ketamine without local anaesthetics for postoperative analgesia following major lumbar spine surgery, which makes it unique. A combination of local anaesthetics and opioids is widely used for epidural analgesia following spine surgery.[4,24] Although the addition of local anaesthetics to opioids has an additive effect, we did not add local anaesthetics because they can interfere with neurological assessment following spine surgery. Even a dilute concentration of local anaesthetics can cause hypotension due to sympathetic blockade, which can be detrimental following spine surgery.

We chose to add ketamine as an anaesthetic adjunct to both intravenous and epidural morphine because of its multimodal effects. The use of opioids after the tissue injury can cause upregulation and activation of NMDA receptors, which can lead to central sensitization, opioid-induced hyperalgesia, and opioid tolerance.[11,12,25,26]

The addition of ketamine has been shown to reduce the above mechanisms, hence decreasing the opioid requirement and its related complications.[25,26]

Study Limitations

Although epidural analgesia improves QoR following lumbar spine surgery, this technique cannot be utilized for analgesia in patients who have undergone previous lumbar spine surgery. Inserting an epidural catheter through scar tissue is technically challenging and can create an occult CSF leak, which increases morbidity. In addition, this technique cannot be used in patients who develop intraoperative CSF leaks. This study compared continuous infusion of low-dose epidural morphine and ketamine with patient-controlled intermittent intravenous administration of morphine and

ketamine, which resulted in an inequivalent dose that could have influenced the study results.

Conclusion

Continuous administration of low-dose epidural morphine and ketamine via an intraoperatively placed epidural catheter provides superior QoR following major lumbar spine surgery as compared to systemic morphine and ketamine analgesia.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Institutional Review Board of Christian Medical College, Vellore, India (approval no.: 12320, date: 30/10/2019).

Informed Consent: Written informed consent was obtained from all recruited patients.

Footnotes

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

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Original Article

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The Effect of Using Smart Glasses Integrated Ultrasonography in Radial Artery Catheterization: A Prospective Randomized Trial

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Abstract

Objective: The use of ultrasonography (USG) in arterial catheterization, in which the comfort of the practitioners and hand-eye coordination are very important, is frequently needed by anesthesiologists in daily practice. We aimed to investigate whether radial artery catheterization with smart glasses-integrated USG would increase success and satisfaction.

Methods: One hundred twenty patients who were >18 years old and would have undergone elective surgery with an indication for radial artery catheterization between August and December 2022 were included in this prospective randomized study. Patients who underwent catheterization in the last month and had contraindications were excluded. In the Standard USG Group, catheterizations were performed with standard USG, and in the Smart Glass Group, with smart glasses-integrated USG. Two anesthetists, a junior practitioner with experience with 20-50 catheterizations and a senior practitioner with experience with over 50 catheterizations, performed the catheterizations. The subcutaneous distance, radial artery depth, and diameter in short axis, catheterization time, and ergonomic satisfaction were recorded.

Results: Sixty patients in standard USG group and 59 patients in Smart Glass Group, with similar demographics, were included in statistical analysis. The mean first catheterization time by junior practitioners, with smart glasses integrated USG, was shorter than standard USG (49.07±29.91 sec vs. 99.73±75.18 sec, P <0.001). The junior practitioner was more satisfied with smart glasses-integrated USG. There was no significant difference between groups in terms of interventions made by the senior practitioner.

Conclusion: Radial artery catheterization with smart glasses integrated USG shortens catheterization time, and increases satisfaction by increasing the comfort of USG use for junior practitioners.

Keywords: Catheterization, radial artery, smart glasses, ultrasonography

Main Points

- The use of ultrasonography (USG) in radial artery catheterization significantly increases successful catheterization and minimizes complications.
- Smart glasses allow the practitioner to simultaneously view the screen and the procedure area.
- The radial artery catheterization with smart glasses integrated USG increases the satisfaction of the junior practitioner by shortening the catheterization time.

Introduction

In daily practice, anesthesiologists commonly perform arterial catheterization for continuous blood pressure monitoring, cardiac output assessment, and blood gas sampling. Because of its proximity to the skin, the radial artery is preferred. Nonetheless, in the presence of obesity, hypotension, or tachycardia, palpation of the radial artery may be difficult.[1] Thus, complications such as hematoma, thrombosis, or mechanical injury may arise during the

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procedure.[2] Compared to the traditional landmark technique, ultrasonography (USG) guidance significantly increases successful catheterization and minimizes complications.[3] In addition to USG and anatomical knowledge, coordination skills between hand, eye, procedure area, and screen are necessary for USG-guided vascular access.[4] Extra head and eye movements lengthen the procedure, destabilize the probe position, and result in the loss of the target image and an improper change in needle direction.[5] Prolonged procedure time and repetitive movements aggravate the practitioner's musculoskeletal fatigue and affect success.[6] Smart glasses project the USG image in real-time directly in front of the practitioner's eyes, allowing the practitioner to simultaneously view the screen and the procedure area.[5] This innovative technology is attractive for invasive procedures because it allows the practitioner to access various data without touching the device.[7]

The primary aim of this study was to evaluate the success rate and anesthesiologist's satisfaction of two practitioners with different levels of experience in radial artery catheterization with smart glasses-integrated USG. The secondary aim was to evaluate the cannulation time and complications between groups.

Methods

This prospective randomized study was conducted between August and December 2022 in Ankara University Hospital after the approval of the Ankara University Medical Faculty Ethics Committee (approval no: I08-498-22, date: 15.09.2022). The study was registered at ClinicalTrials.gov (NCT06271499) and conducted following the principles of the Helsinki Declaration. Patients over 18 years of age who underwent elective surgery with an indication for radial artery catheterization were included. Patients who underwent radial artery catheterization in the last month, and with any contraindication, negative Allen test, and peripheral vascular disease were excluded. Written informed consent was obtained during the preoperative examination.

Patients were randomly divided into two groups utilizing the sealed envelope method. In the Standard USG Group, patients underwent radial artery catheterization with a wireless USG probe (C10RL 7.5/10 MHz linear probe, Konted, China) connected to a tablet. In Smart Glass Group, the ultrasound image, obtained with the same wireless USG probe, was first transferred to a tablet via Wi-Fi, and then the image was transferred to the smart glasses (Moverio BT-40 model smart glasses, Epson, Korea) via a cable. Thus, with smart glasses, the practitioner was able to visualize both the catheterization site and the ultrasound image simultaneously while performing the catheterization. In Figure 1, the practitioner is using smart glasses during radial artery catheterization. Although the ultrasound image projected on the smart glasses display is not visible in the photo, it was clearly viewable in real-time by the operator during the procedure. The catheterizations were performed by two anesthetists with different experiences: a junior practitioner with experience in 20-50 radial artery catheterizations, and a senior practitioner with experience in over 50 radial artery catheterizations. Since practitioners had no experience with smart glasses before the study, they performed five catheterizations on a model with smart glasses integrated USG.

After general anesthesia induction, the modified Allen test was performed on the non-dominant hand to determine the catheterization side. The wrist was positioned at a 45° angle with support. After skin asepsis, the radial artery was visualized 2-3 centimeters proximal to the wrist in the short axis, and the subcutaneous distance, radial artery depth, and diameter were recorded. The radial artery puncture was performed with step-by-step monitoring of the needle tip in the short axis. Following the puncture, the radial artery was catheterized with a 3 French, 8 cm catheter (VYGON, Arterial Leadercath, France). When the artery waveform was being monitored, the catheterization was considered successful. The time between the puncture and the appearance of the artery waveform was recorded as catheterization time. If the puncture could not be performed, the catheterization was considered unsuccessful. The radial artery was re-imaged after catheterization to assess for any complications, and measurements were recorded in the short axis. In Standard USG Group, catheterizations were performed

Figure 1. Radial artery catheterization with smart glasses integrated USG.

USG, ultrasonography.

with the wireless USG probe, and in Smart Glass Group, all catheterizations were performed with the smart glasses-integrated USG probe. The ergonomic satisfaction of the practitioner was evaluated with a 5-point Likert scale (1: Very dissatisfied, 2: Dissatisfied, 3: Undecided, 4: Satisfied, 5: Very satisfied).

Statistical Analysis

A prior power analysis was conducted using G*Power software (version 3.1.9.2) to estimate the minimum required sample size. The analysis was based on a medium effect size (Cohen's d=0.5), a significance level (α) of 0.05, a desired statistical power of 80%, and a two-tailed independent samples t-test. The calculation indicated that at least 54 participants per group would be required to detect a statistically significant difference between the groups. The assumed effect size reflects a clinically meaningful difference and corresponds to the standardized difference between group means relative to the pooled standard deviation. Since group means and standard deviations are reported in the results section, the effect size can be inferred. A two-tailed test was used as it is standard practice unless a specific directional hypothesis is being tested.

Quantitative variables were described by mean and standard deviation, and qualitative variables were described by the number of patients (percentage). To determine whether there was a difference between the categories of the qualitative variable and two categories of the quantitative variable, the Student's t-test was used if the normal distribution assumptions were met, and the Mann-Whitney U test was used otherwise. The relationship between two qualitative variables was analyzed with Chi-square and Fisher's exact tests. Since the assumptions of normal distribution were not met, Spearman's correlation test was used to examine the relationship between two quantitative variables. The program SPSS 11.5 was used to analyze the data. P <0.05 was defined as the statistical significance level.

Results

One hundred twenty patients were included to account for the possibility of data loss. The statistical analysis included 60 patients in the Standard USG Group, and 59 patients in the Smart Glass Group (Figure 2). Between the groups studied,

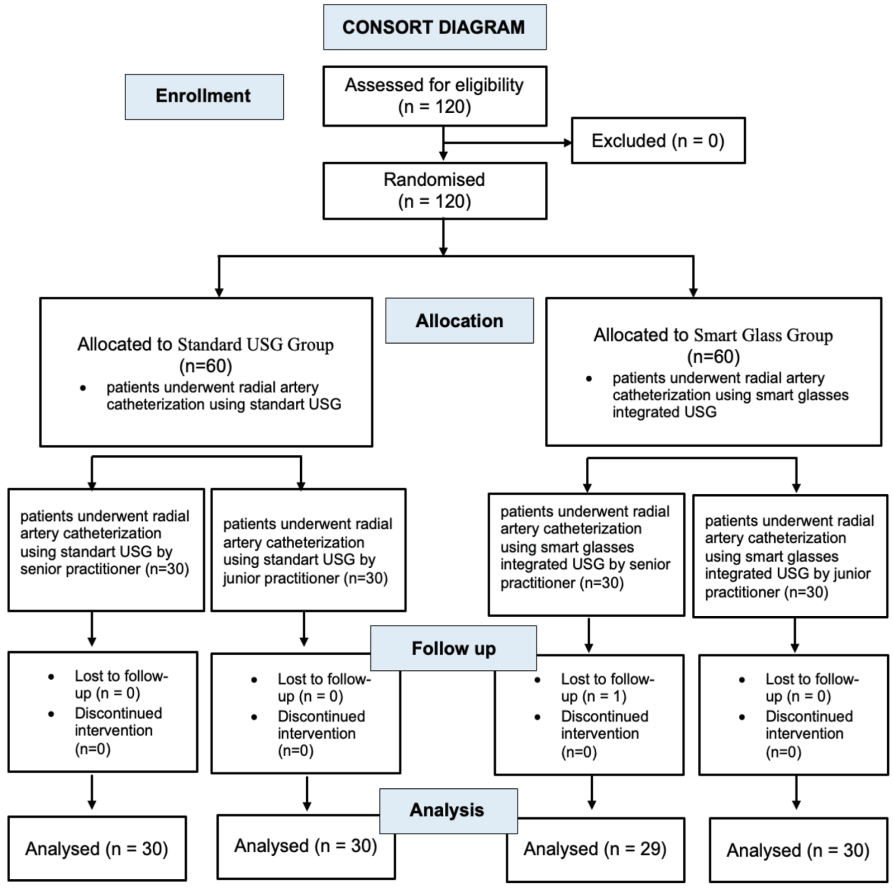

Figure 2. CONSORT flow diagram for the study.

Table 1. Patients' Demographics and Measured Parameters

		Group		*P* value
		Standard USG group (n:60)	Smart Glass Group (n:59)	
Gender, n (%)	Female	20 (33.3)	22 (37.3)	0.652
	Male	40 (66.7)	37 (62.7)	
Age (year)	Mean ± SD	60.97±11.30	65.85±12.29	0.026*
BMI	Mean ± SD	27.93±5.19	26.63±5.03	0.169
Hypertension, n (%)	Yes	35 (58.3)	36 (61.0)	0.765
	No	25 (41.7)	23 (39.0)	
Diabetes, n (%)	Yes	21 (35.0)	23 (39.0)	0.653
	No	39 (65.0)	36 (61.0)	
Hyperlipidemia, n (%)	Yes	25 (41.7)	25 (42.4)	0.938
	No	35 (58.3)	34 (57.6)	
Subcutaneous distance (mm)	Mean ± SD	2.9±1.0	2.8±0.8	0.549
Pre-catheterization depth (cm)	Mean ± SD	2.4±0.6	2.4±0.5	0.814
Pre-catheterization diameter (cm)	Mean ± SD	2.6±0.7	2.8±0.7	0.637
Post-catheterization depth (cm)	Mean ± SD	2.4±0.6	2.4±0.6	0.858
Post-catheterization diameter (cm)	Mean ± SD	2.6±0.7	2.5±0.7	0.485
First catheterization, n (%)	Successful	53 (88.3)	57 (96.6)	0.163
	Unsuccessful	7 (11.7)	2 (3.4)	
First catheterization time (sec)	Mean ± SD	79.43±63.74	46.90±30.89	<0.001*
Second catheterization time (sec)	Mean ± SD	74.50±44.20	74.50±38.89	1.000

BMI, body mass index; cm, centimeter; sec, seconds SD, standard deviation; **P* <0.05 is taken as statistically significant.

demographics were comparable-except for age. In the standard USG group, 7 first catheterizations were unsuccessful, and in the Smart Glass Group, 2 first catheterizations were unsuccessful, and a second catheterization was needed (Table 1). One patient in standard USG group, and one in Smart Glass Group, had a hematoma. During the surgery, the catheter was dysfunctional in one patient of the Standard USG Group and in one patient of the Smart Glass Group.

The junior practitioner was successful on 26 of the first 30 catheterizations with standard USG and 29 of the first 30 catheterizations with smart-glasses-integrated USG. The first catheterization time by a junior practitioner was significantly longer in the Standard USG Group than in the Smart Glass Group. The senior practitioner was successful in 27 of 30 catheterizations with standard USG and 28 of 29 with smart-glasses-integrated USG. The first catheterization time by a senior practitioner was not significantly different between groups. The junior practitioner's satisfaction levels varied significantly between groups. However, the senior practitioner's satisfaction level revealed no significant difference between groups (Table 2).

In standard USG group, the junior practitioner's first catheterization time was longer than the senior practitioner's (99.73±75.18 sec and 59.13±41.98 sec, respectively, *P*=0.006); however, in Smart Glass Group, there was no significant difference (49.07±29.91 sec and 44.66±32.24 sec, respectively, *P*=0.426). The satisfaction levels of the senior practitioner were significantly higher than that of the junior practitioner in Standard USG Group(3.40±1.04 and 2.60±1.07, respectively, *P*=0.008); however, in Smart Glass Group, there was no significant difference (3.76±0.95 and 3.67±0.96, respectively, *P*=0,665).

In the Standard USG Group, the mean catheterization time with a satisfaction level of 1-2-3 was 100.21±69.21 seconds, and with a satisfaction level of 4-5 was 40.86±21.96 seconds (*P* <0.001). In Smart Glass Group, the mean catheterization time with a satisfaction level of 1-2-3 was 69.64±37.99 seconds, and with a satisfaction level of 4-5 was 33.38±13.83 seconds (*P* <0.001). There was a moderate negative correlation between the catheterization time and anesthesiologist satisfaction in the Standard USG Group (r =-0.698 and *P* <0.001; r =-0.742 and *P* <0.001), and a strong negative correlation in the Smart Glass Group (r =-0.632 and *P* <0.001; r =-0.867 and *P* <0.001).

Table 2. Comparison of Veriables Between Groups

Experience	Variables		Group		*P* value
			Standard USG group	Smart Glass Group	
The junior practitioner	First catheterization, n (%)	Successful	26 (86.7)	29 (96.7)	0.353
		Unsuccessful	4 (13.3)	1 (3.3)	
	First catheterization time (sec)	Mean ± SD	99.7±75.9	49.1±29.9	<0.001*
	Second catheterization time (sec)	Mean ± SD	99.3±23.2	102.00±-	1.000
	Satisfaction Level, n (%)	1	7 (23.3)	0 (0.0)	0.001*
		2	4 (13.3)	4 (13.3)	
		3	13 (43.4)	8 (26.7)	
		4	6 (20.0)	12 (40.0)	
		5	0 (0.0)	6 (20.0)	
	Satisfaction level	Mean ± SD	2.6±1.05	3.67±0.94	<0.001*
The senior practitioner	First catheterization. n (%)	Successful	27 (90.0)	28 (96.6)	0.612
		Unsuccessful	3 (10.0)	1 (3.4)	
	First catheterization time (sec)	Mean ± SD	59.1±42.0	44.7±32.2	0.106
	Second catheterization time (sec)	Mean ± SD	25.0±28.3	47.00±-	0.667
	Satisfaction level, n (%)	1	1 (3.3)	1 (3.4)	0.527
		2	5 (16.7)	1 (3.4)	
		3	9 (30.0)	8 (27.6)	
		4	11 (36.7)	13 (44.9)	
		5	4 (13.3)	6 (20.7)	
	Satisfaction level	Mean ± SD	3.40±1.02	3.76±0.93	0.172

SD, standard deviation; sec, seconds; **P* <0.05 is taken as statistically significant.

Discussion

This study shows that radial artery catheterization by the junior practitioner with smart glasses integrated USG does not affect the success of catheterization; however, it shortens the catheterization time. The decreased catheterization time as a result of improved hand-eye coordination with smart glasses integrated USG boosts the satisfaction rate in comparison to standard USG.

Currently, USG is utilized in daily anesthesia practice. The real-time image obtained by USG during vascular interventions improves the success rate by allowing the anatomy to be understood and the needle tip to be tracked.[7] Catheter insertion in small vessels can be tricky for even experienced practitioners. USG-guided radial artery catheterization had a higher success rate than the palpation technique in pediatric patients.[8] A study by Ganesh et al.[9] comparing USG-guided radial artery catheterization to palpation technique in pediatric patients showed that USG-guided catheterization did not improve the success rate. The success rate was 13.8% in palpation technique and 13.9% in USG-guided catheterization. These low success rates may be attributed to inexperienced clinicians working with the pediatric population. However, in this study, in cases where the practitioner failed with the palpation technique, the more experienced practitioner performed catheterization with USG guidance.[9]

Numerous factors influence the success rates of USG-guided procedures. In the study by Jang et al.[10] evaluating radial artery catheterization in pediatric patients, the first catheterization success rate was greater in the smart glasses-integrated USG group, than in the USG-guided group. Our population consists of adults with greater radial artery diameters than the paediatric population, which may explain why there was no difference in the first catheterization success rate between the groups. In a study by Kim et al.,[11] radial artery catheterization in the long-axis was compared between smart glasses integrated USG with laser guidance and smart glasses integrated USG alone. The results showed that first catheterization success, first-pass success, and successful artery catheterization without redirecting the needle were greater with laser guidance.[11] The practitioner's experience can be the most significant factor influencing the success rates of USG-

guided procedures. A study by Stolz et al.[12] showed that the success rate of USG-guided peripheral vascular access by learners increases as the number of attempts rises. Since it enhances hand-eye coordination, catheterization using smart glasses integrated USG is more effective for junior practitioners than it is for senior practitioners.[13] In our study, there was no significant difference in the first catheterization success rate; this outcome can be explained by practitioners completing the learning curves. The relatively high first catheterization success rate observed in our study, especially for the junior practitioner, may be attributed to several factors. A standardized protocol and training were provided prior to the study, which likely enhanced the junior practitioner's performance. Moreover, patient selection and preparation might have contributed to favorable conditions for catheterization. These factors may have collectively contributed to higher success rates compared to those reported in the literature.

One of the most significant drawbacks of USG-guided catheterizations is that the screen and intervention area are in different locations. This problem impairs hand-eye coordination by causing unwarranted head-neck movements. In a simulation study comparing USG-guided peripheral venous access with and without smart glasses, smart glasses were found to reduce the catheterization time.[14] With smart glasses integrated ultrasound guidance, the real-time image is kept in line of sight.[15] Thus, unwanted movements, which can lead to changes in the depth or direction of the needle, diminish. In our study, the junior practitioner completed catheterization faster with smart glasses-integrated USG.

A potential technical limitation of using smart glasses is the risk of connection latency between the ultrasound device and the display. In our study, however, the wireless transmission was stable throughout the procedures, and no noticeable delay was observed that interfered with real-time visualization or catheterization performance. Nevertheless, it is important to note that latency may vary depending on the specific device used and network conditions in other clinical settings, which could potentially affect the generalizability of these results.

Radial artery catheterization with smart glasses integrated USG increases the practitioner's satisfaction due to the physical comfort, increased success rate, and a reduced catheterization time. Reducing repetitive movements provides practitioners with ergonomic benefits.[10] In our study, the junior practitioner's satisfaction was higher with smart glasses integrated USG-guidance. This outcome may be due to the fact that the junior practitioners frequently switch their attention between the USG screen and the intervention area. The use of smart glasses integrated with USG can boost practitioners' satisfaction by removing distractions. In addition to smart glasses, laser guidance could allow visualization of the needle tip in the sagittal plane in the long-axis view.[11] The simple and understandable inclusion of swiftly evolving technology in our daily practice can make our lives easier, increasing the technology's applicability.

Vascular procedures have risks. Even with standard USG guidance, high complication rates might be observed as small-diameter blood vessels are susceptible to injury. In a study by Jang et al.[10] evaluating radial artery catheterization in pediatric patients, the complication rate was 5.2% in the smart glasses integrated USG group and 29.3% in the standard USG group. Subcutaneous nitroglycerin injection in pediatric patients has been shown to reduce the complication rate from 32.1% to 3.5% in USG-guided catheterization.[16] A hematoma was observed in one patient in the Standard USG Group, and one patient in the Smart Glass Group, during our study. This may be attributed to our small sample group and the fact that pediatric procedures are more intricate making complications more prevalent.

Study Limitations

Our study has some limitations. One important limitation of this study is the involvement of only two anaesthesiologists-one junior and one senior practitioner. The limited number of participants may not adequately represent the broader population of anaesthesiologists, potentially introducing practitioner selection bias. The outcomes observed could be influenced by individual skill differences rather than reflecting generalizable trends. Future studies should aim to include a larger and more diverse group of practitioners to minimize potential bias and enhance the external validity of the results. Second, a potential limitation is the influence of the learning curve effect, particularly for the junior practitioner. As the study progressed, the junior practitioner might have gained experience and improved performance, which could have impacted the outcomes. Although procedural standardization was used to minimize variability, the learning effect could not be entirely avoided and should be considered when interpreting the results. Third, this study was conducted in a single center with a specific population. As such, findings may not be completely generalizable; multicenter studies are needed to validate these results across wider populations. Another limitation is that the head and neck movements of practitioners were not evaluated. It may be beneficial to analyze the practitioner's physical comfort objectively. Lastly, there was no documented imaging time for the radial artery. Using smart-glasses-integrated USG may affect the time between the beginning of a procedure and when it is acquiring the correct image.

Conclusion

Technical and ergonomic improvements enhance our daily clinical practice. The radial artery catheterization with smart

glasses integrated USG keeps the real-time image within the practitioner's line of sight, and increases the satisfaction of the junior user by shortening the catheterization time. Consequently, in a continuously changing world, new studies are required so that technology can play an active role in clinical practice.

Ethics

Ethics Committee Approval: This prospective randomized study was conducted between August and December 2022 in Ankara University Hospital after the approval of the Ankara University Medical Faculty Ethics Committee (approval no: I08-498-22, date: 15.09.2022).

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

Footnotes

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

Declaration of Interests: One author of this article, Onat Bermede, 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.

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Automatic Gas Control Mode Versus Manual Minimal-flow and Medium-flow Anaesthesia in Breast Surgery: A Comparative Study

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Abstract

Objective: This study compared automatic gas control (AGC) mode with manual minimal-flow and manual medium-flow techniques in elective breast surgery, evaluating sevoflurane consumption, cost, hemodynamics, and recovery.

Methods: Following ethics approval, 90 American Society of Anaesthesiologists I-II patients (age 18-65 years) undergoing elective breast surgery were randomized to AGC mode (Group AGC, n = 30), manual minimal-flow control (Group ManCo, n = 30), or manual medium-flow control (Group ModFA, n = 30). All received standard induction after preoxygenation, with maintenance via sevoflurane and remifentanil infusion in a mixture of oxygen and medical air. After reaching a minimum alveolar concentration of 1.0, sevoflurane was adjusted to maintain a bispectral index of 40-60. Mean arterial pressure (MAP), heart rate, peripheral capillary oxygen saturation, bispectral index, inspired sevoflurane fractions and expired sevoflurane fraction, end-tidal carbon dioxide, temperature, and instantaneous sevoflurane consumption were recorded pre-induction and every 15 minutes. Extubation time, recovery time, surgery duration, and total anaesthesia time were documented. Total sevoflurane consumption and cost were calculated postoperatively.

Results: Sevoflurane consumption and related costs were significantly lower in Group AGC versus Groups ManCo and ModFA (both $P < 0.001$) and lower in Group ManCo than in Group ModFA ($P < 0.001$). MAP and recovery times did not differ significantly among groups ($P > 0.05$). Pre-extubation temperature was higher in Group AGC compared to Group ManCo ($P = 0.014$) and Group ModFA ($P = 0.002$). Extubation time was longer in Group ManCo versus Groups AGC and ModFA ($P < 0.001$).

Conclusion: AGC mode significantly reduces sevoflurane consumption and cost compared to both manual minimal-flow and manual medium-flow techniques, without adversely affecting hemodynamics or recovery.

Keywords: Consumption, cost analyses, sevoflurane, minimal flow anaesthesia

Main Points

- Automatic gas control (AGC) mode significantly decreases sevoflurane use, as well as reduces the expense.
- Hemodynamic parameters and recovery times were similar during AGC, manual minimal-flow anaesthesia, and manual moderate-flow anaesthesia.
- AGC mode provides quicker anaesthetic washout and earlier extubation, whereas manual minimal-flow anaesthesia delays extubation.

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Introduction

General anaesthesia is characterised by the reversible loss of consciousness, amnesia, analgesia, and muscle relaxation.[1] Intravenously administered drugs are used during the induction of general anaesthesia, whereas inhalational agents are delivered using carrier gases, typically oxygen (O_2) and medical air, for maintenance. The flow rate (L min^{-1}) of the carrier gas directly influences the speed and depth of anaesthesia as well as the consumption of the inhalational agent.[2] Recent technological advances have transformed anaesthesia workstations and monitoring techniques, leading to the development and introduction of low-flow anaesthesia. This method uses rebreathing systems that, after carbon dioxide (CO_2) absorption, return at least 50% of the exhaled gas mixture to the patient's lungs. Baker-Simionescu classified fresh gas-flows ≤1 L min^{-1} as low-flow anaesthesia and flows of 250-500 mL min^{-1} as minimal-flow anaesthesia.[2,3]

Low-flow anaesthesia has substantial economic, environmental, and clinical advantages. The primary advantage of this method is the reduced consumption of carrier medical gases and inhalational anaesthetic agents due to the increased rebreathing fraction. This reduction not only lowers costs but also limits the emission of anaesthetic agents with greenhouse gas properties into the atmosphere, thereby promoting environmental sustainability. Furthermore, this technique enables the maintenance of inspired gas temperature and humidity within physiological ranges, thereby minimizing disruption to airway physiology.[3]

Low-flow anaesthesia can be delivered via manual or automatic gas control (AGC) systems. With manual control, the anaesthetist must continuously monitor the anaesthetic and O_2 concentrations, and make frequent adjustments to maintain safe and effective anaesthesia. In contrast, AGC systems autonomously regulate fresh gas flow to achieve targeted end-tidal anaesthetic agent (EtAA) and O_2 concentrations. The AGC mode is an advanced feature that enables fully automated, gas-controlled, minimal-flow anaesthesia.[4,5]

Although low-flow anaesthesia and AGC have each been investigated previously, few randomized controlled trials have directly compared AGC with manual minimal-flow anaesthesia in terms of both clinical and economic outcomes. To our knowledge, this is the first study to include a three-arm comparison (AGC, manual minimal-flow, and manual medium-flow) in breast surgery, thereby providing not only a direct evaluation of anaesthetic consumption and recovery but also a clinically relevant benchmark for interpreting the advantages of AGC.

The primary outcomes of this study were the effects of AGC and manual minimal-flow techniques on inhalational anaesthetic agent consumption and the cost of breast surgery. Secondary outcomes included assessment and comparison of the effects of these techniques on haemodynamic parameters and postoperative recovery.

Methods

Study Design

This prospective, randomized controlled trial was conducted at Zonguldak Bülent Ecevit University Hospital between March 15, 2021, and March 10, 2022, after approval from the Zonguldak Bülent Ecevit University Ethics Committee (approval no.: 2021/05, date: 10.03.2021) and registration at ClinicalTrials.gov (NCT05404269). Written informed consent was obtained from all participants.

Eligibility Criteria

Women 18-65 years of age with an American Society of Anesthesiologists (ASA) physical status I-II who were scheduled for elective breast surgery under general anaesthesia for ≥1 h were enrolled. Exclusion criteria included coronary artery disease, congestive heart failure, decompensated diabetes mellitus, renal or hepatic insufficiency, chronic obstructive pulmonary disease, opioid sensitivity, malignant hyperthermia, history of tobacco, alcohol, or drug abuse, significant anaemia, sepsis, body mass index >35 kg m^{-2}, pregnancy, or lactation, and known allergies to the study medications.

Randomization

Patients who fulfilled the inclusion criteria were randomly assigned using the sealed envelope method into three groups: AGC [receiving anaesthesia via AGC mode (n = 30)]; ManCo [receiving manual minimal-flow anaesthesia (n = 30)]; and ModFA, the control group receiving manual medium-flow anaesthesia (n = 30).

Anaesthesia Management

Demographic variables, including age, height, weight, and ASA physical status, were recorded for all patients. All data were monitored and documented by the same investigator (G.Ç.). The same anaesthesia workstation (Maquet Flow-i C20, Getinge AB, Gothenburg, Sweden) was used for every patient. Before each procedure, the anaesthesia circuit was tested for leaks, and the gas monitor was calibrated. Standard safety limits were preset for all alarms, setting the lower threshold for fraction of inspired oxygen (F_iO_2) to 30%. A disposable anaesthesia circuit and bacterial filter were used for each patient. Soda lime (KNG-Lime, KNGMED, İzmir, Türkiye) served as the CO_2 absorbent and was replaced after every use.

Heart rate (HR), non-invasive mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), bispectral index (BIS), and train-of-four (ToF) response (IntelliVue MX 550, Philips,

Amsterdam, Netherlands) were continuously monitored, and core temperature was measured via a nasopharyngeal probe. The operating room temperature was maintained at 22-24˚C. Intravenous (IV) access was obtained using an 18-20 gauge cannula in the antecubital vein or dorsum of the hand. 0.9% saline was infused at a rate of 10 mL kg^{-1} h^{-1}.

All patients were preoxygenated via face mask with 100% F_iO_2 at a rate of 6 L min^{-1} for 3 min using a tidal-volume technique. Anaesthesia was induced with IV lidocaine 1 mg kg^{-1} (Jetmonal 2%, Osel İlaç, İstanbul, Türkiye), propofol 2.5 mg kg^{-1} (propofol 1%, Fresenius Kabi AG, Hamburg, Germany), and fentanyl citrate 1 µg kg^{-1} (Talinat, Vem İlaç, Ankara, Türkiye), followed by rocuronium bromide 0.6 mg kg^{-1} IV (Esmeron, MSD, Hameln, Germany). Endotracheal intubation was performed when the ToF count reached zero. Post-intubation, remifentanil hydrochloride infusion was initiated at 0.05 µg kg^{-1} min^{-1} (Ultiva, GSK Manufacturing S.p.A., Verona, İtaly).

During maintenance, ventilation was set to a tidal volume of 6-8 mL kg^{-1}, a respiratory rate of 12-14 breaths min^{-1}, an I:E ratio of 1:2, positive end-expiratory pressure 5 cmH_2O, and end-tidal CO_2 of 30-40 mmHg. Sevoflurane (Sevorane 100%, AbbVie, Campoverde di Aprilia, Italy) was used in medical air for inhalational maintenance, combined with the remifentanil infusion. Sevoflurane concentration was titrated individually to maintain BIS values between 40 and 60, while neuromuscular management was guided by TOF monitoring (reversal at TOF ≥2; extubation at TOF ratio ≥0.9).

In group AGC, the anaesthesia workstation was preset to AGC mode before intubation (fresh gas flow ≥0.5 L min^{-1}; speed of "4"; target EtAA, 1.0 minimum alveolar concentration (MAC); target F_iO_2, 40%), and the mode was activated immediately post-intubation.

In the ManCo and ModFA groups, fresh gas flow was manually set to 4 L min^{-1} (approximately 50% O_2/50% air) with the vaporiser at 2.5% sevoflurane immediately after intubation, and these parameters were maintained for 10-15 min to achieve an end-tidal anaesthetic agent of 1.0 MAC. When the target EtAA concentration was achieved, the flow of fresh gas was adjusted from 0.5 L min^{-1} to 2 L min^{-1}.

During maintenance in all groups, fresh gas flow remained constant, sevoflurane vaporiser settings were adjusted to maintain BIS at 40-60, and O_2 concentration was modified to maintain an F_iO_2 of 40%.

During intraoperative monitoring, a MAP <65 mmHg prompted the administration of 5-10 mg IV ephedrine, and an HR <50 beats min^{-1} prompted 0.5 mg IV atropine. If F_iO_2 fell to <30%, $EtCO_2$ exceeded 45 mmHg, or SpO_2 dropped to <93%, fresh gas flow was increased to 4 L min^{-1}, and the patient was withdrawn from the study.

A multimodal analgesic regimen was administered to control postoperative pain. Approximately 20 min before the conclusion of surgery, patients received IV tramadol 1 mg kg^{-1} (Madol, Koçak Farma, İstanbul, Türkiye), paracetamol 10 mg kg^{-1} (Paracerol, 10 mg mL^{-1} IV vial; Polifarma, Türkiye), and metoclopramide 10 mg (Metpamid, Sifar İlaç, İstanbul, Türkiye) for nausea-and-vomiting prophylaxis.

Approximately 15 minutes before the anticipated end of surgery, anaesthetic discontinuation was initiated. In the AGC group, this was achieved by setting the target EtAA concentration to 0 within the AGC system (speed setting 2), which effectively shut-off agent delivery and triggered automated fresh-gas adjustments for washout. In the ManCo and ModFA groups, the vaporizers were manually turned off at the same time point while the assigned fresh-gas flows were kept constant.

After final skin closure, fresh-gas flow was increased to 4 L min^{-1} and manual ventilation with 100% O_2 was applied until spontaneous breathing resumed. Neuromuscular blockade was then reversed using IV atropine (0.02 mg kg^{-1}; Atropin Sülfat Ampul, Galen, Türkiye) followed by IV neostigmine (0.05 mg kg^{-1}; Neostigmin Ampul, Adeka, Türkiye). Patients were extubated once they achieved a ToF ratio ≥0.9, BIS >80, and adequate spontaneous ventilation. In the post-anaesthesia care unit, all patients received 4 L min^{-1} O_2 via a face mask, and those with a VAS score >3 received rescue analgesia with IV tenoxicam (20 mg; Tilcotil, Deva Holding, Türkiye).

Baseline measurements of MAP, HR, and SpO_2 were recorded before induction. After intubation, the MAP, HR, SpO_2, BIS, fraction of inspired and expired sevoflurane (F_iSEVO and F_eSEVO, respectively), end-tidal carbon dioxide ($EtCO_2$), nasopharyngeal core temperature, and instantaneous sevoflurane consumption were recorded at 5, 10, 15, 20, 30, 60, and 90 min.

Extubation time was defined as the interval from vaporiser shut-off, to tracheal extubation, and recovery time as the interval from extubation to achieving a modified Aldrete score ≥9. Surgical duration was measured from the skin incision to the final suture, and the duration of anaesthesia was measured from induction to extubation.

Statistical Analysis

Sample size was calculated using one-way analysis of variance (ANOVA) of data from a pilot study. After enrolling 10 per group patients, preliminary analysis of sevoflurane consumption indicated an α of 0.05, a β of 0.20 (80% power), and an effect size of 0.33. These parameters indicated that at least 30 patients were required per group.

Statistical analyses were performed using Jamovi version 2.2.5 (Jamovi Project, 2021; https://www.jamovi.org). Continuous variables were evaluated for normality using

histograms and the Shapiro-Wilk test. Data conforming to the normal distribution are expressed as mean ± standard deviation, whereas non-normal data are expressed as median (interquartile range, IQR, i.e., 25^{th}-75^{th} percentile). For comparisons among ≥3 independent groups, outliers were first identified using boxplots, and variance homogeneity was assessed using Levene's test. If normality and equal variances were confirmed, one-way ANOVA was performed using Fisher's F test, when variances were equal, or with Welch's correction when they were not, followed by Tukey's or Games-Howell post-hoc tests, each of which includes adjustment for multiple comparisons to control type I error. Non-parametric data or data violating ANOVA assumptions were analyzed using the Kruskal-Wallis test with Dwass-Steel-Critchlow-Fligner post-hoc comparisons, which also incorporate multiplicity adjustment. Categorical variables are expressed as number (n), and percentage, and are compared using Pearson's chi-squared or Fisher's exact tests. All statistical tests were two-sided, and differences with P <0.05 were considered to be statistically significant

Results

A CONSORT flow-diagram illustrating patient enrolment is presented in Figure 1. Ninety patients were included. There were no significant differences among the groups in terms of demographic characteristics or ASA physical status (P >0.05) (Table 1).

There were no significant differences in surgical, anaesthetic, or recovery times between the groups (P >0.05). However, extubation time differed significantly among the groups (P <0.001) (Table 2). Pairwise comparisons demonstrated that extubation times in the ManCo group were significantly longer than those in the AGC and ModFA groups (both P <0.001). No significant differences were observed between the AGC and ModFA groups (P >0.05).

Sevoflurane consumption differed significantly among the groups (P <0.001) (Table 3). Hourly consumption was lower in the AGC group than in both the ManCo and ModFA groups (P <0.001 for each comparison) and was also lower in the ManCo group than in the ModFA group (P <0.001).

Sevoflurane-associated costs also differed significantly among the groups (P <0.001) (Table 3). The costs in the AGC group were lower than those in both the ManCo and ModFA groups (P <0.001 each), and the costs in the ManCo group were also significantly lower than those in the ModFA group (P <0.001).

Statistically significant differences were observed among the groups in both instantaneous and total sevoflurane consumption (P <0.001) (Figure 2, Table 4). In the post-hoc analyses, no significant difference was observed between the ManCo and ModFA groups in instantaneous sevoflurane consumption at 5, 10, or 20 minutes (P >0.05).

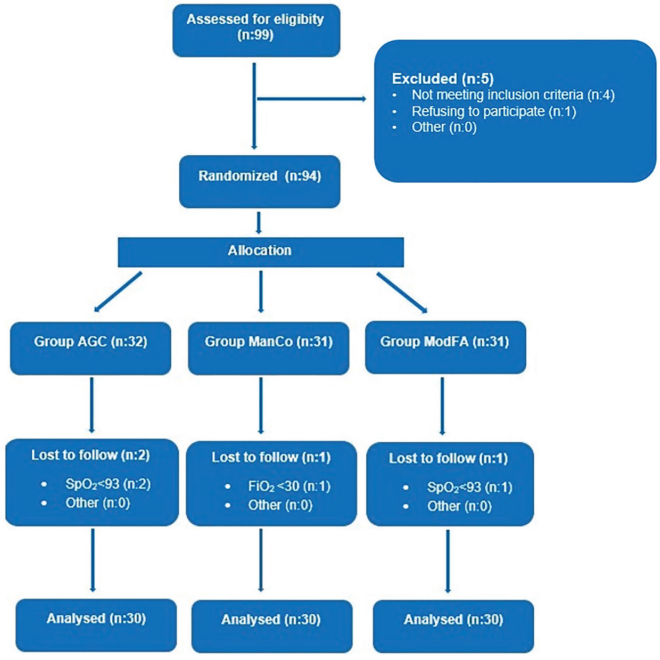

Figure 1. CONSORT flow diagram of the study.

AGC, automatic gas control; ManCo, manual minimal-flow control; ModFA, manual medium-flow control; F_iO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation.

In contrast, all other pairwise comparisons indicated that consumption in the AGC group was significantly lower than that of both the ManCo and ModFA groups (P <0.05), and that consumption in the ManCo group was significantly lower than that of the ModFA group (P <0.05).

There were no significant differences among the groups in MAP, SpO_2, or $EtCO_2$ at any time point (P >0.05). At the 5th minute after intubation, the mean HR values were 83 beats/min in the AGC group, 86 beats/min in the ManCo group, and 81 beats/min in the ModFA group. Although the overall analysis revealed a statistically significant difference (P=0.042), post-hoc comparisons showed no clinically relevant intergroup differences. No other time points demonstrated statistically significant differences (P >0.05).

Pairwise comparisons of F_iSEVO values showed that at 5 and 10 minutes, the AGC group had significantly lower values than both the ManCo and ModFA groups (P <0.05). At 15 and 20 minutes, F_iSEVO values were significantly lower in the AGC group compared with both the ManCo and ModFA groups, and the ManCo group also had significantly lower values than the ModFA group (all P <0.05). For F_eSEVO, values at 5 and 10 minutes were significantly lower in the AGC group compared with both ManCo and ModFA groups (P <0.05). At 60 minutes, F_eSEVO values in the AGC group were significantly lower than in the ModFA group (P <0.05), while no significant differences were observed between AGC and ManCo, or between ManCo and ModFA.

Table 1. Comparison of Demographic Characteristics and ASA Scores Between Groups

	Group AGC (n = 30)	Group ManCo (n=30)	Group ModFA (n=30)	*P*
Age (years), median (IQR)	49.5 (41.5-58.0)	52.5 (41.2-59.7)	53.0 (44.2-62.0)	0.517[a]
Height (cm), mean ± SD	161.9±5.9	160.7±5.1	162.2±5.2	0.519[b]
Weight (kg), median (IQR)	72.0 (62.0-80.0)	69.0 (65.0-73.8)	68.0 (56.8-79.5)	0.621[a]
ASA I/II (n)	6/24	14/16	7/23	0.050[c]

Data are presented as median (IQR) for non-normally distributed variables and mean ± SD for normally distributed variables.

ASA, American Society of Anesthesiologists; AGC, automatic gas control; ManCo, manual minimal-flow control; ModFA, manual medium-flow control; IQR, interquartile range; SD, standard deviation

[a]: Kruskal-Wallis test, [b]: One-way ANOVA, [c]: chi-square test.

Table 2. Surgery-related Clinical Data

	Group AGC (n = 30)	Group ManCo (n = 30)	Group ModFA (n = 30)	*P* value
Surgical time (min), median (IQR)	117.5 (97.5-135.0)	107.5 (95.0-130.0)	110.0 (96.3-125.0)	0.586[a]
Anaesthesia time (min), median (IQR)	132.5 (112.5-150.0)	125.0 (115.0-150.0)	125.0 (111.3-140.0)	0.651[a]
Extubation time (min), mean ± SD	14.0±1.2	19.4±3.1	14.1±1.4	**<0.001**[b]
Recovery time (min), median (IQR)	2.5 (2.0-3.0)	3.0 (2.5-3.0)	2.5 (2.0-3.0)	0.097[a]

Data are expressed as median (IQR) or mean ± SD, as appropriate.

ASA, American Society of Anesthesiologists; AGC, automatic gas control; ManCo, manual minimal-flow control; ModFA, manual medium-flow control; IQR, interquartile range; SD, standard deviation; min, minimum

[a]: Kruskal-Wallis test, [b]: One-way ANOVA.

Table 3. Comparison of Sevoflurane Consumption and Cost Between Groups

	Group AGC (n = 30)	Group ManCo (n = 30)	Group ModFA (n = 30)	*P* value
Sevoflurane consumption (mL hour^{-1}), mean ± SD	7.01±1.10	9.80±1.54	15.05±1.28	**< 0.001**[a]
Sevoflurane cost (TL hour^{-1}), median (IQR)	24.6 (23.7-29.1)	35.6 (31.9-40.1)	55.7 (51.7-59.6)	**< 0.001**[b]

Data are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate.

AGC, automatic gas control; ManCo, manual minimal-flow control; ModFA, manual medium-flow control; IQR, interquartile range; SD, standard deviation; TL, Turkish Lira

[a]: One-way ANOVA, [b]: Kruskal-Wallis test.

There were no statistically significant differences in BIS values among the groups at any recorded time point (*P* >0.05, Table 5).

There were no significant differences in body temperature among the groups at any time point, except immediately before extubation (*P*=0.002). Immediately before extubation, a significant difference in core temperature was observed among the groups (*P*=0.002). Pairwise comparisons showed that the AGC group had significantly higher values compared to both the ManCo and ModFA groups (*P*=0.014 and *P*=0.002, respectively), while no significant difference was found between the ManCo and ModFA groups (*P* >0.05).

During the study, four patients were excluded due to hypoxemia. One patient in the ManCo group was excluded because F_iO_2 decreased below 30%. In the AGC group, two patients were excluded due to SpO_2 dropping below 93%, and in the ModFA group, one patient was excluded for the same reason.

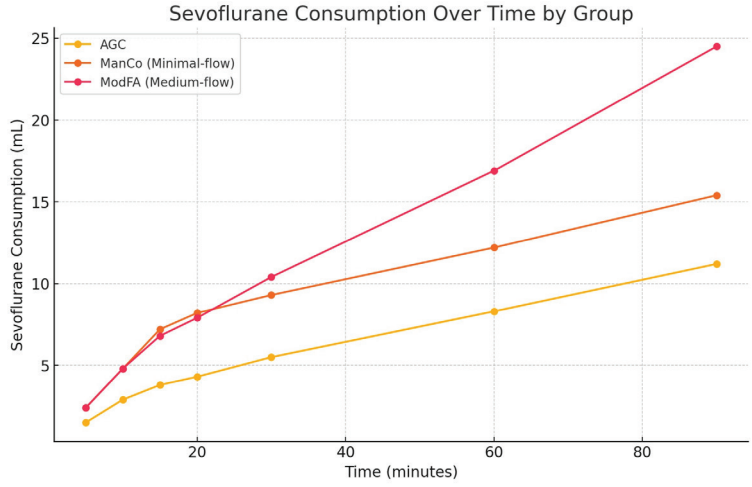

Figure 2. Comparison of time-point sevoflurane consumption values between groups.

AGC, automatic gas control; ManCo, manual minimal-flow control; ModFA, manual medium-flow control.

Table 4. Comparison of Time-point Sevoflurane Consumption Values Between Groups

	Group AGC (n = 30)	Group ManCo (n = 30)	Group ModFA (n = 30)	*P* value
Sevoflurane consumption at 5 min (mL), median (IQR)	1.5 (1.4-1.6)	2.4 (2.3-2.4)	2.4 (2.2-2.4)	< 0.001[a]
Sevoflurane consumption at 10 min (mL), median (IQR)	2.9 (2.7-3.2)	4.8 (4.7-4.8)	4.8 (4.6-5.0)	< 0.001[a]
Sevoflurane consumption at 15 min (mL), median (IQR)	3.8 (3.3-4.0)	7.2 (7.1-7.4)	6.8 (6.3-6.9)	< 0.001[a]
Sevoflurane consumption at 20 min (mL), median (IQR)	4.3 (4.0-4.9)	8.2 (7.9-9.1)	7.9 (7.5-8.4)	< 0.001[a]
Sevoflurane consumption at 30 min (mL), median (IQR)	5.5 (5.0-6.2)	9.3 (8.9-10.8)	10.4 (9.6-10.9)	< 0.001[a]
Sevoflurane consumption at 60 min (mL), median (IQR)	8.3 (7.8-9.5)	12.2 (11.8-14.1)	16.9 (15.6-18.3)	< 0.001[a]
Sevoflurane consumption at 90 min (mL), median (IQR)	11.2 (10.9-12.8)	15.4 (14.6-18.9)	24.5 (22.8-25.8)	< 0.001[a]
Total sevoflurane consumption (mL), mean ± SD	14.1±3.5	18.1±4.3	28.8±6.6	< 0.001[b]

Data are presented as median (IQR) or mean ± SD, as appropriate.
AGC, automatic gas control; ManCo, manual minimal-flow control; ModFA, manual medium-flow control; IQR, interquartile range; SD, standard deviation
[a]: Kruskal–Wallis test, [b]: One-way ANOVA.

Table 5. Comparison of Time-point BIS Values Between Groups

	Group AGC (n = 30)	Group ManCo (n = 30)	Group ModFA (n = 30)	*P* value
At the 5th minute after intubation (%), median (IQR)	52.0 (49.0-60.0)	51.5 (48.2-55.5)	50.5 (48.0-54.0)	0.110
At the 10th minute after intubation (%), median (IQR)	45.5 (42.0-51.5)	47.0 (41.0-50.8)	45.0 (40.0-48.8)	0.081
At the 15th minute after intubation (%), median (IQR)	42.5 (40.2-49.5)	42.0 (40.2-46.8)	41.0 (39.0-44.0)	0.312
At the 20th minute after intubation (%), median (IQR)	42.0 (40.0-48.0)	42.0 (40.2-46.0)	41.0 (39.0-45.0)	0.386
At the 30th minute after intubation (%), median (IQR)	43.0 (41.2-46.0)	42.0 (40.0-45.5)	42.0 (40.0-44.8)	0.396
At the 60th minute after intubation (%), median (IQR)	45.0 (41.2-48.0)	44.0 (41.2-46.0)	44.0 (41.2-49.0)	0.845
At the 90th minute after intubation (%), median (IQR)	44.0 (41.0-47.0)	44.0 (41.0-50.0)	42.0 (40.0-48.0)	0.489
Before extubation (%),median (IQR)	88.0 (86.2-89.0)	88.0 (86.0-89.8)	88.0 (85.0-88.8)	0.336

Data are presented as median (IQR) as appropriate.
AGC, automatic gas control; ManCo, manual minimal-flow control; ModFA, manual medium-flow control; IQR, interquartile range

Discussion

In this randomized controlled study, AGC significantly reduced sevoflurane consumption and costs compared with manual minimal-flow and medium-flow anaesthesia, without compromising hemodynamic stability or recovery profiles. These findings indicate that AGC provides both economic and clinical advantages over conventional techniques. Although the primary objective of our study was to compare AGC with manual minimal-flow anaesthesia, we also included a manual medium-flow group to reflect routine clinical practice and to provide a broader context for interpreting the differences across three distinct flow strategies.

Low-flow anaesthesia is generally not recommended for short procedures, with the literature indicating that procedures lasting <30 min are not suitable for this method. [6] In our study, the mean duration of anaesthesia was 132 minutes, confirming that the patient cohort was appropriate for low-flow anaesthesia.

The primary disadvantages of inhalational agents in general anaesthesia are their high cost and the environmental damage caused by their greenhouse-gas emissions.[3,7] Modern anaesthesia workstations designed to handle these problems use integrated software to produce accurate gas mixtures and constantly regulate fresh gas flow to maintain the optimal agent concentration.[8] In our study, we used the Maquet Flow-i Anaesthesia Workstation, which meets all of these monitoring requirements, electronically controls fresh gas supply, and maintains system leaks to 150 mL min^{-1}.

Although several volatile agents can be employed in low-flow anaesthesia, sevoflurane is one of the most frequently chosen due to its low blood-gas solubility and its ability to be administered at large concentrations.[9] Compounds A and B have been found to accumulate during sevoflurane-based low-flow anaesthesia that continues for greater than 5 h; however, this does not appear to have a clinically significant effect on renal or hepatic function.[10] Considering these risks, we excluded cases exceeding 4 hours from the study and used sevoflurane as the inhalation agent.

Reducing fresh gas flow during low-flow anaesthesia can decrease the delivered O_2 concentration and increase the risk of hypoxia. To reduce this risk, an inspired O_2 concentration ≥30% is recommended.[9] Although hypoxemia was uncommon, four patients had to be excluded for safety reasons (one in ManCo, two in AGC, and one in ModFA). This highlights the importance of continuous oxygenation monitoring, particularly under low- and minimal-flow anaesthesia, where transient fluctuations may pose clinical risks.

Intraoperative awareness during general anaesthesia has been found to occur in approximately 0.1-0.2% of cases.[11] Because low-flow procedures may increase the risk of awareness, we used BIS monitoring in all patients to determine anaesthetic depth and reduce the potential of intraoperative awareness. During the study, eight patients reported BIS values >60; in this group, the inhaled sevoflurane concentration increased until the BIS decreased to <60. A comparison of BIS values among the groups indicated no statistically significant differences.

Maintaining haemodynamic stability during anaesthesia is crucial for patient safety. Ceylan et al.[12] found that maintaining a fresh gas flow rate of 1 L min^{-1} under low-flow anaesthesia did not impair haemodynamic parameters. Similarly, Skalec et al.[13] compared AGC and manual gas control under low-flow anaesthesia and found no significant hemodynamic differences. In our study, no significant intergroup differences in haemodynamic parameters were observed, except for MAP 5 minutes after intubation. At 5 min post-intubation, the HRs were 83, 86, and 81 beats/min in the AGC, ManCo, and ModFA groups, respectively, with no clinically significant intraoperative effects.

The addition of remifentanil infusion to anaesthesia maintenance contributes haemodynamic stability. Remifentanil alone is not associated with hypnosis or loss of consciousness; however, when combined with anaesthetics, it enhances their effects.[14] In a study comparing minimal-flow anaesthetic efficacy and sevoflurane versus desflurane consumption, using a remifentanil infusion during maintenance was found to significantly improve hemodynamic stability.[15] In another study comparing AGC mode with manually regulated minimal-flow anaesthesia, remifentanil infusion significantly improved intraoperative analgesia management.[5] In our study, to support hemodynamic stability, we administered a remifentanil infusion at 0.05 μg kg^{-1} min^{-1} during anaesthesia maintenance.

Several variables affect recovery following general anaesthesia, including the pharmacokinetic characteristics of the inhalational medication and patient ventilatory capacity.[16] The most commonly used method for assessing recovery is the modified Aldrete score, with a score ≥9 considered to be acceptable.[17] Our study demonstrated no significant difference in time for achieving a modified Aldrete score ≥9 among the three groups. In a study using sevoflurane for anaesthesia maintenance, the end-tidal and manual control techniques were compared, and the interval from sevoflurane discontinuation to extubation was reported to be similar in both groups.[18] Similarly, Lortat et al.[19] compared the AGC and manual control methods in low-flow desflurane anaesthesia and found no significant difference in extubation time. In this study, the interval from vaporiser shut-off to tracheal extubation was defined as "extubation time." Our results demonstrated that the extubation time was significantly longer in the ManCo group than in both the AGC and ModFA groups, with no significant difference between the AGC and ModFA groups. Although the extubation times varied among the groups, the similarity in recovery duration was likely due to our study design. We believe that the primary cause of the prolonged extubation time in the ManCo group was that, although the vaporiser was turned off approximately 10-15 minutes before the conclusion of surgery, the fresh gas flow was not increased during this interval under the minimal-flow technique. It should also be considered that the longer extubation time in the ManCo group may partly reflect the standardized timing of vaporizer shut-off across groups, in addition to the slower anaesthetic washout under minimal-flow conditions. After vaporizer discontinuation, F_iSEVO decreases toward zero; however, under minimal-flow conditions (0.5 L min^{-1}), the long circuit time constant leads to a slower fall in FeSEVO, thereby prolonging anaesthetic washout. These findings demonstrate the potential advantages of AGC in reducing extubation time.

Hypothermia is a common and serious complication of general anaesthesia. Preservation of heat and humidity is essential not only for maintaining thermoregulatory mechanisms but also for ensuring normal airway physiology.[9] Bilgi et al.[20] demonstrated that low-flow desflurane anaesthesia more effectively preserved respiratory function and mucociliary clearance than high-flow administration. All patients in our study were fitted with heat-and-moisture-exchange filters, and core temperature was monitored via a nasopharyngeal probe, with values ranging from 35.7 ˚C to 36.8 ˚C. Pre-extubation measurements revealed that patients in the AGC group maintained higher temperatures than those in the ManCo and Group 3 cohorts, suggesting that AGC may be more effective in preserving thermal homeostasis.

Low-flow anaesthesia reduces greenhouse gas emissions and consumption of inhalational agents, leading to economic advantages.[21-23] In one study, anaesthesia accounted for 1% of total hospital costs. Anaesthetic medications accounted for 5.7% of total pharmaceutical spending, with inhalational agents accounting for 20% of that.[16] The primary factors affecting the cost of volatile anaesthetic agents include the selling price, potency, administered concentration, and fresh gas flow rate. Among these parameters, only the fresh gas flow rate was clinically variable. Reducing the fresh gas flow rate improves rebreathing, which reduces consumption of the inhalational agent and waste gas emissions. As a result, fresh gas flow becomes the most important predictor of agent cost; more specifically, as flow decreases, so do consumption and cost.[16,24,25] There are several techniques used in low-flow anaesthesia, two of which are AGC and manual control. With AGC, the device automatically adjusts both the vaporiser and fresh gas flow to reach and maintain the target inhalational agent concentration. In manual control, these adjustments are made by the operator.[26] Tay et al.[3] compared end-tidal gas concentration monitoring by AGC versus manual control in approximately 3600 general anaesthesia cases. In the AGC group, hourly inhalational agent consumption was, on average, USD 5 lower, total anaesthesia costs decreased by 27%, and the greenhouse-gas footprint was reduced by 44%. The manual control group demonstrated increased agent consumption,

although this difference was not statistically significant. The investigators in that group frequently adjusted the vaporiser and O_2 settings.[18] Carette et al.[26] reported that on the FLOW-i workstation, the AGC mode not only reduces costs, but also reduces the workload of low-flow anaesthesia by substantially decreasing the frequency of vaporiser and oxygen adjustments. Lortat et al.[19] reported that the use of AGC in desflurane anaesthesia significantly reduced agent consumption. Similarly, in our study, mean sevoflurane consumption was 7.01±1.10 mL h^{-1} in AGC mode, 9.80±1.54 mL h^{-1} in manually controlled minimal-flow, and 15.05±1.28 mL h^{-1} in manually controlled moderate-flow. Similarly, sevoflurane costs were calculated for each mode. They averaged 24.6 Turkish Lira (TL) per hour in the AGC mode, 35.6 TL per hour in manually controlled minimal flow, and 55.7 TL per hour in manually controlled moderate flow. These findings strongly indicate that the AGC mode has a significant advantage in terms of reducing agent usage and associated costs. This significant reduction associated with AGC supported its economic efficacy. The study's main methodological advantages for an effective cost analysis included comparable demographic characteristics between groups and standardised surgery and anaesthetic durations. Furthermore, by using the same breast surgery process in all cases and a single anaesthesia workstation, the design was improved.

In our study, the number of patients analyzed declined progressively after 70 minutes. However, the advantages of low-flow anaesthesia in terms of inhalational agent use and cost have become apparent with longer procedures. One of the main limitations of this study is that, although our findings support the low-flow technique, understanding its environmental and economic implications requires additional research with longer procedures and larger patient cohorts.

Another limitation was the exclusion of participants with ASA scores ≥III. Additionally, smokers were excluded to maintain group homogeneity. The design of this study improved the internal validity; however, it limited the generalizability of our findings to larger patient groups.

Conclusion

In this study of patients undergoing breast surgery, we compared minimal-flow anaesthesia procedures using AGC versus manual gas control in terms of inhalational agent use, cost, haemodynamic parameters, and recovery time. Sevoflurane consumption was significantly lower in the AGC group than in the manually controlled minimal-flow and moderate-flow groups. This decrease was also observed in cost analysis, confirming the economic benefits of AGC. Furthermore, there were no statistically significant differences among the groups in haemodynamic parameters or recovery time; this demonstrates that the AGC mode reduces inhalational agent use without compromising haemodynamic stability or recovery time, making it superior to manual control. Furthermore, as emphasised in the literature, its safety and usage advantages encourage low-flow anaesthesia, with emphasis on its cost-effectiveness.

Ethics

Ethics Committee Approval: This prospective, randomized controlled trial was conducted at Zonguldak Bülent Ecevit University Hospital between March 15, 2021, and March 10, 2022, after approval from the Zonguldak Bülent Ecevit University Ethics Committee (approval no.: 2021/05, date: 10.03.2021) and registration at ClinicalTrials.gov (NCT05404269).

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

Footnotes

Author Contributions: Surgical and Medical Practices - G.Ç., Ö.P.; Concept - G.Ç., Ö.P.; Design - G.Ç., Ö.P., Ç.B., K.B., B.G.A., H.A.; Data Collection and/or/Processing - G.Ç., Ö.P., M.A.C., B.G.A., G.K., H.A.; Analysis and/or/Interpretation - G.Ç., Ö.P., Ç.B.; Literature Review - G.Ç., Ö.P., R.D.O.; Writing - G.Ç., Ö.P.

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Case Report
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Central Line Guidewire Knot in a Paediatric Patient with Bronchial Leiomyosarcoma Undergoing Left Pneumonectomy: A Case Report

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Abstract

We report the unanticipated intraoperative complication of a guidewire knot during central venous line insertion in the left internal jugular vein (IJV), in a child scheduled for a left pneumonectomy for leiomyosarcoma of the left lung under general anaesthesia. After an uneventful guidewire placement in the left IJV under ultrasound guidance, difficulty was encountered in advancing the central venous catheter over the guidewire. Resistance was felt when initiating the removal of the guidewire. The guidewire knot was identified with intraoperative fluoroscopic imaging. After consultation with the surgical team, the knot in the guidewire was removed by immediate venotomy. Intraoperative lung isolation and tracheal extubation after the surgery were uneventful. This report emphasises the importance of vigilance during central venous catheterisation in paediatric patients whose anatomical variations and smaller vessels exacerbate the risk of such complications. Ultrasound-based preprocedural Rapid Central Venous Assessment, and intra-procedural guidewire-tip navigation may help prevent coiling/knotting. Furthermore, it highlights the need for rapid recognition and surgical readiness to resolve unexpected issues during routine procedures.

Keywords: Guidewire knotting, internal jugular vein catheterisation, one-lung ventilation, paediatric anaesthesia, ultrasound-guided central venous catheterisation

Main Points

- A knot in a central line guidewire can occur in the distal internal jugular vein in paediatric patients with distorted anatomy despite ultrasound guidance with an out-of-plane approach.
- Pre-procedural ultrasound-guided Rapid Central Venous Assessment and intraprocedural tip navigation may help to avoid guidewire coiling and knotting.
- Resistance during guidewire removal may indicate knotting, especially if the guidewire coils around vessel walls.
- Blind, forceful removal must be avoided as it may lead to tissue entrapment and damage.
- The key to a successful outcome is prompt recognition of this complication and individualised management according to the scenario and available resources.

Introduction

We share the challenges faced in the anaesthetic management of a child scheduled for left pneumonectomy for leiomyosarcoma of the lung, and the complications encountered with subsequent management. This case underscores the need for vigilance during central venous catheterisation in paediatric patients.

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Case Report

A 10-year-old child weighing 20 kg, with a body mass index of 11.3 kg m^2, presented to the paediatric outpatient department of our institute with cough and expectoration for 6 months, and shortness of breath for 2 weeks. The child was accompanied by his father. Pre-operative contrast-enhanced computed tomography (CT) suggested a large, ill-defined, heterogeneously enhancing lesion in the posteroinferior aspect of the left side of the thoracic cavity. The lesion infiltrated the left main bronchus, completely occluding the lower lobe and partially occluding the upper lobe. Furthermore, the lesion caused a mediastinal shift to the left and was associated with abdominal metastasis, which was confirmed as a spindle cell neoplasm/leiomyoma on CT-guided biopsy (Figure 1). Pulmonary function tests showed borderline airway obstruction, which improved on bronchodilator therapy. During the pre-operative assessment, the child complained of pain on deep inspiration, and decreased air entry was observed in the left lung. The rest of the general and systemic examinations were unremarkable. The pulmonologist advised peri-operative bronchodilator nebulisation. The parents provided written informed consent for surgery and general anaesthesia, epidural catheterisation, invasive central and arterial line insertion, one-lung ventilation, post-operative mechanical ventilation, and intensive care.

The right-sided double-lumen tube (DLT) size was estimated pre-operatively on a CT scan based on the size of the trachea and the right and left bronchi.

On the day of the surgery, after the uneventful induction of anaesthesia, a 28 Fr right-sided DLT was placed under direct laryngoscopic vision and confirmed with a paediatric fibreoptic bronchoscope. Sevoflurane with an air-oxygen mixture was used for anaesthesia maintenance, with a 0.5 mg kg^{-1} h^{-1} infusion of atracurium for muscle relaxation. Analgesia was maintained with an epidural infusion of 0.125% levobupivacaine with 1 µg mL^{-1} fentanyl through an 18G epidural catheter inserted at the T6-T7 level. The surgery was performed in the right lateral position. The plan was to insert an ultrasound-guided, left internal jugular vein (IJV) 5.0 French triple-lumen central venous catheter of 8 cm length. The needle was placed in the left IJV in a single attempt using an out-of-plane approach, and the guidewire was passed without resistance through the needle up to a sufficient length of 15 cm. After dilating the subcutaneous tract with a dilator, the triple-lumen catheter was railroaded over the guidewire; however, it failed to pass beyond 4 cm. Resistance was felt when attempting to remove the guidewire. Ultrasonography confirmed that the guidewire was present in the IJV lumen. Fluoroscopy performed in the operating theatre with the C-arm showed a knot in the guidewire (Figure 2).

As the patient was under general anaesthesia in the operating theatre, exploration of the IJV to remove the guidewire knot was planned in discussion with the surgical team. Venotomy was performed under aseptic conditions, and the guidewire knot was observed to be in the wall of the vein. The knot was removed after dilating the venotomy, and the site was sutured. A 5 French femoral central line was placed in the right femoral vein.

After thoracotomy, the child tolerated one-lung ventilation well, with no episodes of desaturation. During the separation of the adhesions between the lung and precordium, norepinephrine infusion was titrated to correct hypotension.

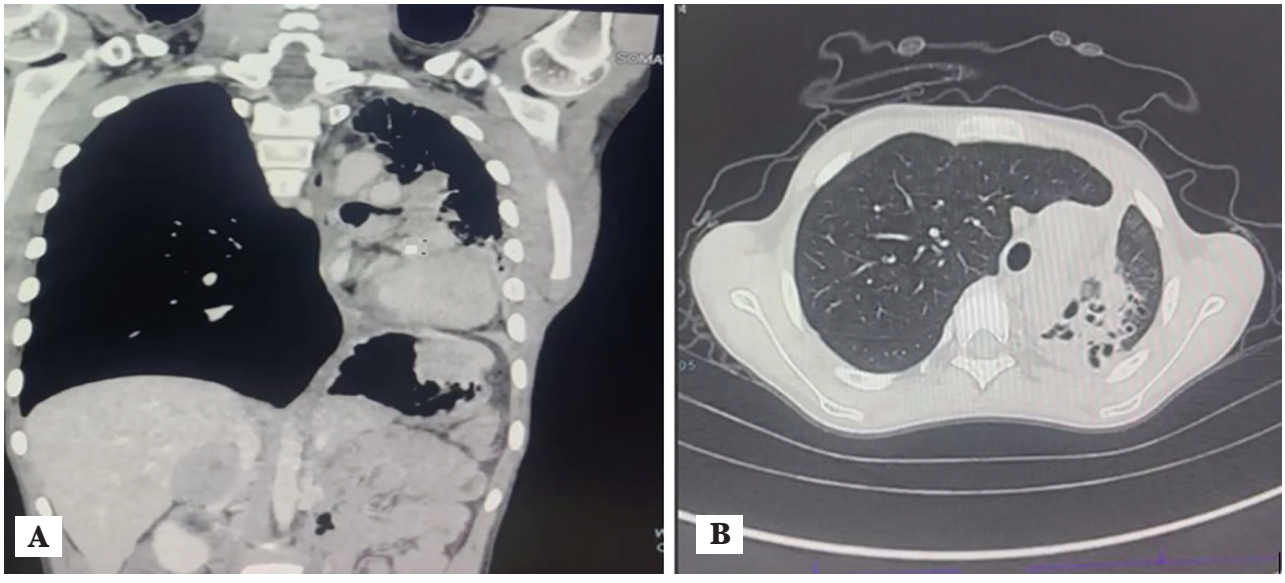

Figure 1. Contrast enhanced computed tomography (CECT) showing mediastinal shift to the left side. A) Sagittal view; B) Coronal view.

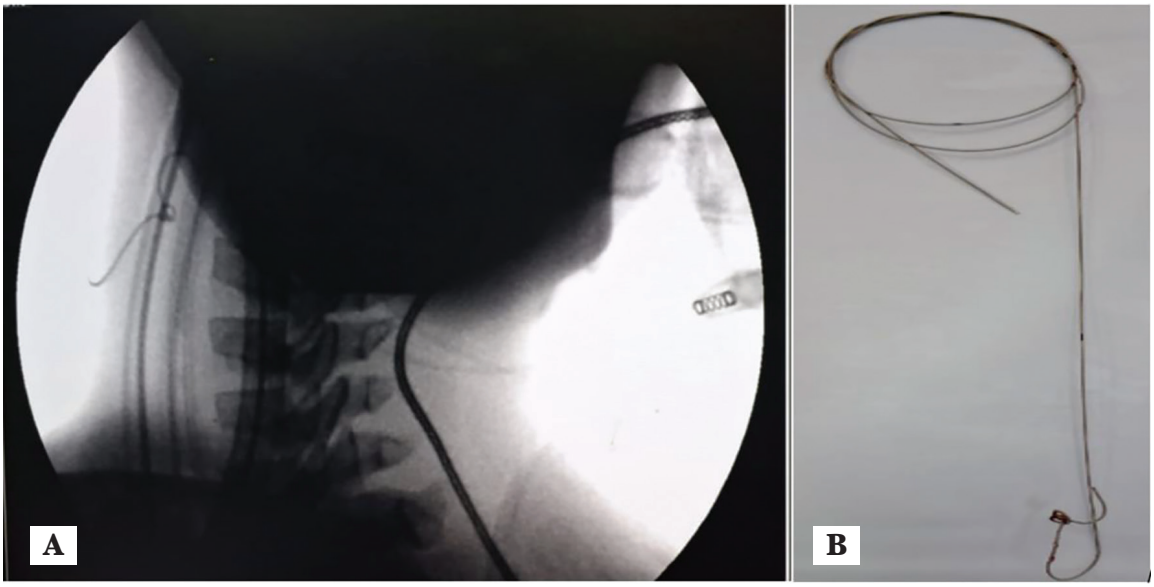

Figure 2. The central line guidewire knot: A) Fluoroscopic view of central line guidewire knot in left internal jugular vein; B) The knotted central line guidewire after surgical extraction.

Electrolytes and blood gas parameters were monitored and corrected with serial arterial blood gas analysis. The urine output was 0.5-1 mL kg^{-1} h^{-1} throughout the surgery. After ensuring an adequate margin from the carina, the paediatric surgical team performed a left pneumonectomy. The tracheal and bronchial lumen of the DLT was thoroughly suctioned, and the bronchial cuff was deflated. The DLT was removed after ensuring that no bleeding or tissue debris was present in the carina, using a check bronchoscopy. A cuffed polyvinyl chloride endotracheal tube of size 5.5 was inserted into the tracheal lumen under video laryngoscopic guidance.

The neuromuscular blockade was reversed after adequate, pain-free respiratory efforts, and the trachea was extubated. Analgesia was sufficiently maintained via patient-controlled epidural infusion of 0.1% bupivacaine with 1 µg mL^{-1} fentanyl at a background infusion rate of 3 mL h^{-1}, with a demand dose of 3 mL, a maximum of 3 doses per hour, and a lockout interval of 10 minutes. The patient's post-operative recovery was good.

Discussion

When performing left pneumonectomy in a 10-year-old child, the primary anaesthetic concern is achieving good lung isolation to facilitate surgery and manage intraoperative oxygenation and haemodynamics. Leiomyosarcoma is a specific type of malignant spindle cell neoplasm arising from the lower respiratory tract. This tumour originates from the smooth muscle and is rare in paediatric populations, with only a few cases reported in the literature.[1,2] There are certain unique considerations specific to anaesthesia management in a paediatric patient, with left bronchial leiomyosarcoma, scheduled for left pneumonectomy. These concerns are related to the multidisciplinary pre-operative assessment to select the optimal technique for one-lung ventilation, hemodynamic monitoring, peri-operative analgesia, and fast-tracking of anaesthesia. We have discussed the complications of the guidewire knot encountered in the placement of the central venous catheter in the left IJV and its related preventive and management strategies.

A systematic, standardised approach like Rapid Central Venous Assessment before central venous catheterisation may help identify anatomical alterations or thrombus in previously catheterised veins. Rapid evaluation of the six central veins in the supra/infraclavicular area can help to rule out abnormalities like thrombosis, stenosis, external compression, anatomical variation, and to choose an appropriate catheter vein size (1:3 or less).[3] This is important, as guidewire coiling and knotting are often reported when re-catheterising a previously catheterised vein or during thrombosis. These complications can be both extravascular and intravascular.[4,5] Though we inserted the guide wire using the out-of-plane approach, it may have been prudent to navigate the tip's direction using the in-plane approach as part of the "SIC" protocol (Safe Insertion of Central Catheters).[6] Immediately after ultrasound-guided venipuncture, ultrasound should be used to assess the correct direction of the guidewire (ultrasound-based tip navigation) by scanning the veins of the supraclavicular region with the same linear probe used for needle insertion.[6] In a paediatric patient, using a hockey stick probe may facilitate this. However, a micro-introducer kit with a 21G echogenic needle and a 0.018" nitinol guidewire with a

straight soft tip, to allow tip navigation, is recommended, especially in infraclavicular venipunctures. An intracavitary electroencephalogram is the most cost-effective and accurate intraprocedural method for determining the tip location.[7]

The tensile strength of guidewires is limited, and excessive force during insertion can easily cause coiling. Upon removal, this coiling can tighten into a knot. These issues are often faced in subclavian vein cannulation owing to its non-linear course, predisposing the guidewire to coil or loop over the first rib. Complications such as guidewire breakage, impaction and paradoxical embolisation of fractured wire segments have also been recorded.[5,8] Guidewire kinking has been noted more frequently in the paediatric population, especially younger children.[9]

While knotting is more commonly associated with subclavian vein cannulations, reports of knots in the femoral vein exist.[10] Applying force to remove a knotted guidewire should be avoided, as it can lead to shearing of the inner and outer coils, resulting in severe vascular injury if the coil and knot are intravascular.[11] A knotted guidewire should be removed under fluoroscopic guidance when available or via open surgical exploration.

Knotting during left IJV cannulation has also been reported, especially in cases where anatomical structures are altered, as was observed in our patient.[12] Potential complications should be anticipated at any stage of central line insertion.

Conclusion

Besides ultrasound-guided guidewire insertion, real-time or post-advancement navigation of the guidewire through the needle throughout the vein (up until the superior vena cava for the neck veins) is a crucial step which may help avoid coiling and subsequent knotting of the guidewire at the time of insertion. Prompt recognition, prevention of unnecessary force on removal, and surgical intervention can rectify the complication, enabling the pneumonectomy to progress smoothly. This case offers valuable insights for emerging anaesthesiologists, highlighting the significance of awareness and preparedness for unexpected complications.

Ethics

Informed Consent: The parents provided written informed consent for surgery and general anaesthesia, epidural catheterisation, invasive central and arterial line insertion, one-lung ventilation, post-operative mechanical ventilation, and intensive care.

Footnotes

Author Contributions: Surgical and Medical Practices - S.R., S.T.K., P.K.S., R.C.; Concept - S.R., S.T.K., P.K.S., R.C.; Design - S.R., S.T.K., P.K.S., R.C.; Data Collection and/or/Processing - S.R., S.T.K.; Literature Search - S.R., S.T.K.; Writing - S.R., S.T.K., P.K.S., R.C.

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Lung Isolation in a Child with Kinsbourne Syndrome for Paraspinal Neuroblastoma Excision in the Prone Position

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Abstract

Kinsbourne syndrome, also known asor opsoclonus-myoclonus-ataxia syndrome, is a rare paediatric neurological disorder characterised by abnormal eye movements, myoclonus, and ataxia. Its anaesthetic management presents significant challenges, especially when one-lung ventilation (OLV) is required in the prone position. This case report describes the anaesthetic management of a two year-old child with Kinsbourne syndrome undergoing T9-T11 paravertebral neuroblastoma excision. Because of the patient's size and the need for lung isolation, a Fogarty embolectomy catheter was used for OLV. Anaesthesia was induced with intravenous fentanyl, propofol, and atracurium, followed by the insertion of a 4.0 mm cuffed endotracheal tube to facilitate Fogarty catheter insertion. The catheter was positioned in the right bronchus under fibre-optic guidance; after which, a 4.5 mm cuffed tube was inserted, and the patient was placed in the prone position. Continuous fibre-optic monitoring ensured proper catheter placement. Anaesthesia was maintained with oxygen, air, and isoflurane. The patient remained haemodynamically stable, was extubated postoperatively, was observed in the paediatric intensive care unit for 24 hours, and was subsequently transferred to the ward. This case highlights the challenges of OLV in paediatric patients and demonstrates the effectiveness of a Fogarty catheter for lung isolation when traditional devices are unsuitable, emphasising the importance of multidisciplinary collaboration and continuous monitoring.

Keywords: Airway management, cardiovascular and thoracic anaesthesia, paediatric anaesthesia, perioperative care

Main Points

- Complexity of Anaesthesia in Opsoclonus-myoclonus-ataxia (OMA) with Neuroblastoma: OMA (Kinsbourne) syndrome associated with paraspinal neuroblastoma presents unique perioperative challenges, particularly regarding airway and respiratory management.
- Lung Isolation in Small Children: Standard double-lumen tubes are unsuitable in infants/toddlers; a Fogarty embolectomy catheter proved an effective alternative for one-lung ventilation (OLV), allowing safe tumour resection in the prone position.
- Challenges of OLV in Paediatrics: Risks of hypoxia, hypercapnia, airway trauma, and catheter migration necessitate fibre-optic-guided placement and continuous intraoperative monitoring.
- Fogarty catheters can be a practical and safe solution for paediatric lung isolation, provided multidisciplinary coordination, fibre-optic confirmation, and vigilant monitoring are maintained.

Introduction

Neuroblastoma is a common extracranial solid tumour in paediatric patients, typically originating in the adrenal medulla or paraspinal ganglia. Surgical resection often requires specific anaesthetic considerations, mainly when the lesion involves the thoracic region. The presence of opsoclonus-myoclonus-ataxia syndrome (OMA), also

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known as Kinsbourne syndrome, a paraneoplastic condition associated with neuroblastoma, further complicates the perioperative management. This case report presents the anaesthetic approach for a two-year-old male child with neuroblastoma at the T9-T11 level, highlighting lung isolation using a Fogarty embolectomy catheter in the prone position, an uncommon yet necessary technique for the resection of paraspinal tumours.

Case Report

A two-year-old male patient (height/weight: 86 cm/11.5 kg), diagnosed with a T9-T11 paravertebral neuroblastoma associated with OMA, was scheduled for tumour resection. The pre-operative assessment revealed a normal cardiorespiratory status and mild ataxia, with no other systemic involvement. Due to the tumours location, a thoracic approach with lung isolation was deemed necessary to provide adequate surgical exposure and prevent contamination of the contralateral lung. Informed written parental consent for anaesthesia was obtained.

Anaesthesia Plan

Induction: Anaesthesia was induced with intravenous fentanyl (2 µg kg^{-1}), propofol (2 mg kg^{-1}), and atracurium (0.5 mg kg^{-1}) to achieve muscle relaxation. Subsequently, the patient was intubated with an appropriately sized #4.0 cuffed endotracheal tube.

Lung Isolation: Initially, a 4 French Fogarty embolectomy catheter was passed through the #4.0 endotracheal tube until resistance was encountered that prevented further advancement of the catheter. The cuffed endotracheal tube was then deflated and removed. Another #4.5 cuffed tube was subsequently introduced under fibre-optic guidance, until it reached the vocal cords. The fiber-optic was further introduced to visualise the carina and right bronchus, facilitating precise positioning of the Fogarty catheter. The catheter was placed in the right bronchus, and the cuff was inflated with 1 mL of air, confirming the isolation of the right lung. This technique was selected due to the patient's small size, which made the use of double-lumen endotracheal tubes unfeasible, and the need for selective lung isolation while the patient was in the prone position.

Positioning: The patient was placed in the prone position, with careful padding of pressure points and maintenance of neutral alignment of the head and neck. Continuous monitoring of airway pressures and oxygenation was crucial, given the potential difficulties associated with one-lung ventilation (OLV) in this age group (Figure 1).

Maintenance: Anaesthesia was maintained using a mixture of oxygen (50%), nitrous oxide (50%), and isoflurane (1%). Muscle relaxation was achieved through intermittent doses of atracurium. Monitoring included end-tidal carbon dioxide (CO_2), pulse oximetry, and arterial blood gas analysis to ensure adequate ventilation and oxygenation during OLV.

Intraoperative Course

The patient remained haemodynamically stable throughout the procedure. The use of the Fogarty catheter allowed successful isolation of the right lung, ensuring adequate visualisation of the tumour without compromising ventilation. Blood gas levels remained within acceptable limits, with only a minimal increase in partial pressure of CO_2 in arterial blood. No complications were observed related to positioning, and the surgery proceeded as planned, culminating in the complete resection of the tumour.

Postoperative Management

Postoperatively, the patient was extubated in the operating room following the return of adequate spontaneous ventilation and neuromuscular function. He was closely monitored in the paediatric intensive care unit (PICU) for 24 hours due to concerns regarding respiratory compromise

Figure 1. Positioning with Forgarty catheter in prone position.

and the potential effects of OMA. No postoperative complications were noted, and the patient was discharged from the PICU on postoperative day 2.

Discussion

The anaesthetic management of neuroblastoma resection, particularly in the presence of OMA, poses multiple challenges, notably in airway management, patient positioning, and the risk of respiratory complications. Lung isolation techniques in paediatric patients differ significantly from those used in adults due to anatomical limitations, including narrower airways and greater susceptibility to airway trauma. Traditional methods, such as double-lumen tubes, are unsuitable for infants and young children. As demonstrated in this case, the Fogarty embolectomy catheter serves as an effective alternative for achieving lung isolation in paediatric patients, offering controlled ventilation to one lung while providing an unobstructed surgical field.[1]

OLV in paediatric patients, particularly in infants and toddlers, presents several challenges, including hypoxia and hypercapnia. Achieving effective lung isolation with minimal airway trauma is critical, particularly when prone positioning is utilised. Various techniques for lung isolation include the use of bronchial blockers, such as the Arndt, Cohen, or Fogarty embolectomy catheters, as employed in this case. The appropriate device selection is contingent upon the child's age, size, and surgical requirements.[2]

The most commonly used techniques for lung isolation in children include:

1. Endobronchial intubation involves using a single-lumen endotracheal tube pushed into one of the mainstem bronchi. This technique is simple and widely used in younger children; however, it lacks precision. It may result in unintentional movement, particularly during patient repositioning, as was observed in the present case.[3]

2. Bronchial blockers, such as the Arndt or Cohen blockers, are frequently employed in paediatric patients, allowing for selective occlusion of one lung while ventilating the other. However, their placement can be technically demanding in younger children and may necessitate additional equipment such as fibre-optic bronchoscopes for accurate positioning. Additionally, in infants, these blockers can increase airway resistance, complicating the maintenance of adequate ventilation during OLV.[3,4]

3. Fogarty embolectomy catheters, as used in this case, offer a viable alternative for small paediatric patients. Their small size and ease of insertion make them suitable when bronchial blockers or double-lumen tubes are impractical. Nevertheless, the primary concern with this technique is the potential for catheter migration or airway obstruction, requiring continuous monitoring and fibre-optic confirmation of placement throughout the surgery.[5,6]

Concerns Regarding Prone Positioning and OLV

Prone positioning introduces additional challenges in managing OLV, as it significantly changes ventilation mechanics due to altered chest wall compliance and intra-abdominal pressure.[7]

These changes may lead to:

1. Increased airway pressures: The prone position can elevate airway pressures under OLV, primarily due to decreased compliance of the dependent lung and mechanical compression of the chest wall by the operating table.

2. Ventilation-perfusion mismatch: In the prone position, ventilation is directed towards the non-dependent lung, which, during OLV, becomes the sole ventilated lung. This shift can cause significant ventilation-perfusion mismatch, potentially leading to hypoxia, especially in younger patients with a smaller functional residual capacity.[7,8]

3. Haemodynamic changes: The combination of the prone position and OLV can reduce venous return due to the compression of abdominal organs and large vessels. This reduction may lead to hypotension, further impairing oxygen delivery. Therefore, maintaining adequate intravascular volume and frequent monitoring of haemodynamics are crucial.

4. Limited access to airway management: A major concern with prone positioning during OLV is restricted access to the airway. If the lung isolation device becomes dislodged or airway obstruction occurs, repositioning and reintubation can be challenging. This risk necessitates continuous vigilance and the availability of fibre-optic bronchoscopy equipment to ensure proper placement of the catheter or bronchial blocker.

5. Postoperative complications: Prone positioning with OLV increases the risk of atelectasis in the non-ventilated lung, particularly if recruitment manoeuvers or adequate postoperative physiotherapy are not performed. In paediatric patients, these postoperative respiratory complications may be more pronounced, necessitating meticulous postoperative care, including respiratory support.[9]

In this case, careful consideration of the patient's size and the need for prone positioning led to the selection of the Fogarty catheter for lung isolation. The catheter placement was confirmed via fibre-optic bronchoscopy, while close monitoring of ventilator parameters ensured that the patient tolerated OLV effectively despite the challenges linked to prone positioning.

Conclusion

This case highlights the complexities of managing paediatric patients requiring lung isolation for neuroblastoma resection, particularly in the prone position. Effective lung isolation techniques, such as Fogarty embolectomy catheters, can be successfully implemented in young children. However, careful attention must be paid to the complications associated with prone positioning and OLV, including increased airway pressures, ventilation-perfusion mismatch, and haemodynamic instability. Continuous monitoring, alongside the availability of fibre-optic equipment, is vital to ensure safe and effective anaesthetic management during these challenging procedures.

Ethics

Informed Consent: Informed written parental consent for anaesthesia was obtained.

Footnotes

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Medical Jousting in Research Publications: A Call for Ethical Discourse

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Dear Editor,

The "Letter to the Editor" (LOE) section in academic journals has a rich history dating back to the 15th century when van Leeuwenhoek[1] wrote regularly to the Royal Society of London, sharing his landmark scientific observations. Over time, this practice evolved into a formalised forum for intellectual discourse. It became a platform to critique published articles, offer fresh insights, and draw attention to overlooked aspects of studies.[2,3] This section has played a pivotal role in advancing scientific dialogue, fostering transparency, encouraging collaboration, and driving the refinement of knowledge. Functioning as a form of post-publication peer review, it ensured authors were held accountable for their work. However, despite its intent to promote constructive debate, this platform has at times been misused, with instances of what can be described as "medical jousting."

Medical jousting, traditionally observed in clinical practice as verbal criticism or disputes among healthcare professionals, is increasingly evident in research publications. In this context, it manifests as authors leveraging letters to the editor or commentary within articles to discredit or undermine previous research. This practice deviates from the original purpose of scholarly critique, which is to enhance understanding, not to disparage.

In academic journals, medical jousting can take several forms. Critiques may lack balance, omit opposing research, or use dismissive language. Authors sometimes misrepresent studies or employ hostile, unprofessional responses, including personal attacks, instead of constructive discourse, undermining scholarly communication and the advancement of knowledge in the field.

Such practices have far-reaching implications. They not only erode trust in academic publishing but also discourage researchers—especially early-career scientists—from participating in scientific discourse for fear of undue criticism. Furthermore, they create a toxic environment that stifles collaboration, which is the cornerstone of medical progress.[4]

The style of writing in these letters is often informal, with highly subjective language that appears judgmental. Magnet and Carnet[5] observed that the lexicon used frequently leaned towards the disparaging, occasionally even crossing into the derogatory. They noted the presence of emotionally charged verbs, adjectives, and negative prefixes such as *mis-* and *dis-*. Some authors even employed sarcasm and banter in their tone. At least 56% of the original authors chose not to respond to these letters, possibly due to their personal and critical nature. Interestingly, a survey conducted by the researchers revealed that readers often found LOE concise and manageable for regular reading. However, many admitted they did not always follow up by reading the original article. This raises a significant concern: a harshly worded letter could potentially create a bias among readers toward the original author, influencing perceptions unfairly.[5]

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Addressing medical jousting in research publications requires a concerted effort from authors, reviewers, and journal editors. The original purpose of letters to the editor—to act as a bridge between published research and further inquiry—remains as important as ever. However, for it to fulfil this role, it must be used responsibly.

Footnotes

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Sibel Temür
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