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ERAS in Cardiac Surgery: Wishful Thinking or Reality

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Abstract

Enhanced recovery after cardiac surgery (ERACS) is a multi-disciplinary approach to improve patient outcomes and reduce complications following cardiac surgery. The aim of ERACS protocol is to optimize pre-operative preparation, reduce surgical trauma, and minimize post-operative stress.The protocol has been shown to improve patient outcomes, including shorter hospital stays, lower rates of complications, and faster return to normal activities. It is important to note that ERACS is a multi-disciplinary approach, and requires close collaboration between surgeons, anaesthesiologists, nurses, and other healthcare professionals to ensure successful implementation. Anaesthesiologists play a crucial role in the ERACS protocol, as they are responsible for the management of the patient's anaesthesia and pain management during and after surgery. In this paper provide an overview of the ERACS protocol from the perspective of an anaesthesiologist.

Keywords: Cardiac patient, cardiac surgery, cardiovascular and thoracic anaesthesia, enhanced recovery after surgery, ERAS

Main Point

- In this article, the ERAS adventure in cardiac surgery was evaluated from all aspects.

Introduction

All new initiatives are viewed with skepticism by clinicians. It is always difficult to get out of the ordinary and try to adapt to something new. After all, in addition to ensuring patient satisfaction, we in the medical profession are bound to never compromise on the motto of "premum non nocere". And it is undoubtedly true that the shortage of trained personnel, equipment, and high costs are barriers to undertaking brave new beginnings in the struggling health system. However, all of these realities are in fact the main reasons for undertaking new ventures. Enhanced recovery after surgery (ERAS) protocols (Table 1), an exemplar of novel initiatives and the focus of this paper, are journeying down the same difficult path. Since the day they were defined, the measures have faced a steady barrage of criticism. Detractors have accused the protocols of a variety of shortcomings, including endangering patient safety because of the high costs involved and not having any effect on patient results in general. They have even claimed that the favorable outcomes are the result of psychological reflection of patients' inclusion in a special program (Hawthorn effect).[1] However, studies emphasizing the positive aspects of ERAS applications on patient outcomes along with shortened hospital stays are not to be underestimated.[2-4]

The fact that cardiac patients have more comorbidities as well as cardiorespiratory system problems necessitated a cautious approach to the concepts of early recovery, so ERAS, which was first defined in for colon surgery in 1997, could only actively implemented in cardiac surgery practice in 2016.[5] The implementation of ERAS protocols, which includes many steps starting from the preoperative period and covering the intraoperative and postoperative period, requires the joint and harmonious action of many departments, including the patient, dietitian,

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Table 1. The ERACS Protocol Involves a Number of Interventions, Including
1. Pre-operative counseling and education for patients to reduce anxiety and improve understanding of the surgical process.
2. Optimization of the patient's nutritional status before surgery.
3. Use of minimally invasive surgical techniques to reduce surgical trauma.
4. Multimodal pain management, including nerve blocks and non-opioid pain medications.
5. Early mobilization and rehabilitation, including physical therapy and respiratory therapy.
6. Aggressive management of fluid balance and electrolyte levels to prevent complications.
7. Early removal of invasive monitoring devices such as catheters and drains to reduce infection risk.
8. Early initiation of oral nutrition and medications to reduce the risk of complications.
ERACS, enhanced recovery after cardiac surgery.

physiotherapist, surgeon, anaesthesiologist, intensivist, perfusionist, and nurse. There are many steps in the pre-intra and postoperative periods of the enhanced recovery after cardiac surgery (ERACS) protocols. Which one is the most important step over the entire perioperative process is not clear; carefully preparing the patient for surgery, early extubation, or early removal from the intensive care unit (ICU)? Which is the hardest step to implement? Should ERAS be applied only to patients in good general condition?

With the idea that the answers to many such questions can be determined according to the internal dynamics and resources of each hospital, implementation of institutional ERACS protocols began in Ankara Bilkent City Hospital, Cardiac Surgery and Anaesthesia Clinics in 2020. In the protocol, applied in all surgeries except for emergency surgery, each patient preparing for surgery was informed approximately 1 month before the surgery about the procedures involved, and their smoking/alcohol use, anemia, HbA1c, and their nutritional status were evaluated and comorbidities strictly optimized. However, it is not always possible to examine and evaluate the cardiac surgery patient one month before the surgery, as they may not be able to wait another month. Given that patients with shorter preparation time constitute the majority of all cardiac surgery patients, it is important to note that ERAS protocols are described in the literature as applicable in emergency surgeries and positively impact the results.[6,7]

In emergency surgeries the "preoperative" column of the ERAS steps is bypassed out of necessity. Although this skipped column contains important protocol components, from prehabilitation to smoking cessation, and comorbidity optimization to blood glucose-HbA1c correction, positive surgery outcomes and short hospital stays can still be achieved. The question then comes to mind: is the preoperative ERAS column "expendable"? Would a refined "shorter list", not including all ERAS components, suffice? Conversely, there are publications describing the importance of prehabilitation and protesting that only 5 out of 13 ERAS guidelines mention prehabilitation. Robust randomized controlled trials are required to clarify this issue.

It is one of our surprising findings that 37% of the patients who underwent detailed nutritional examinations in the preoperative period within the scope of our protocol were found to have malnutrition. The chronic inflammatory state, which is the likely etiology of comorbidities such as hypertension, chronic obstructive pulmonary disease, and diabetes mellitus accompanying cardiac disease, also negatively affected nutrition. Following this determination, the nutrition team ensured that these patients were included in a special nutrition program.

The relationship between ERAS and diabetic patients is an ongoing focus of research. Although the relationship between gastroparesis and diabetes in terms of passive regurgitation and pulmonary aspiration was investigated and was not found to be risky,[8-10] it has been observed that different management is required in terms of hyperglycemia. In diabetic (type 1 or type 2) patients, in whom we applied 50 g (12.5%) oral maltodextrin carbohydrate loading in 400 mL liquid in the preoperative 2nd hour, which is included as a weak recommendation in the ERACS protocols,[11] excessive blood sugar elevations were encountered with the start of surgery. Many ERACS protocols do not include diabetic patients in their programs, but we think that a careful protocol can be applied to risky patients as well. As current ERACS protocols do not offer specific recommendations regarding this subgroup of patients, the need for close monitoring of blood glucose levels and management of anti-diabetic medication and case based clinical judgment is evident until more evidence has been available.[12] As such, in our practice, diabetic patients were given carbohydrate rich clear fluids 3 hours instead of 2 hours, preoperatively. By applying a different insulin regimen in the perioperative period, the problem of hyperglycemia was largely resolved. No pulmonary aspiration complication was encountered in patients taking carbohydrate loading, including patients undergoing transesophageal echocardiography.

One of the drugs recommended for premedication in ERACS protocols is 150-300 mg oral pregabalin.[13] Since severe disorientation was found in patients who were given 300 mg of pregabalin in our protocol, this dose was

changed to 150 mg or less. One of bilateral erector spina plan block, serratus anterior plane block, or parasternal block was applied to the patient before anaesthesia, for intraoperative and postoperative analgesia. Anaesthesia is provided by an inhalation agent or propofol infusion, to which short-acting opioid (remifentanil) analgesia is added. The bispectral index (BIS) values are kept between 40-45 throughout the operation in order to prevent anaesthetic-related postoperative delirium and cognitive impairment. Further decrease in BIS is not allowed and midazolam was avoided. At the same time, by monitoring bilateral cerebral oxygenation with near infrared spectroscopy, many vital situations such as prevention of cannula malposition, optimization of pump flow, and detection of critical blood pressure values in severely hypertensive patients are directed. Meticulous glucose monitoring to keep blood glucose <180 gr dL^{-1}, patient blood management and cardiopulmonary bypass (CPB) management with retrograde autologous prime method are routinely performed. Goal directed fluid therapy was managed with hemodynamic monitors, especially from the end of the surgical procedure and the weaning from CPB. In the postoperative period, patients were extubated within 6-8 hours, early mobilization and feeding were started, and strict nausea-vomiting prophylaxis was performed. Within the scope of fast-track and ERACS protocols, extubation is recommended within 6 hours postoperatively.[13-15] On the other hand, it is claimed that there is no significant difference in the duration of ICU and hospital stay between the patients extubated in the first 6 hours and those extubated between 6-12 hours.[15] Although our patients actually met the extubation criteria comfortably from the 3rd-4th hour, unfortunately, conservative teams in the ICU became a barrier to earlier extubation. However, for a relatively newcomer implementation, these are situations where progress can be made over time. In the postoperative period, in addition to regional methods, analgesia management is provided with tramadol and paracetamol. In our clinic, non-steroidal anti-inflammatory drugs are not administered to cardiac patients due to the possibility of prothrombosis, bleeding, and renal damage. In addition, there is no routine steroid administration for anti-inflammation due to insufficient evidence about its effects. In the postoperative period, regular delirium, cognitive function, and Acute Kidney Injury screening are performed (additional data: Ankara City Hospital, ERACS Protocol).

Potential barriers to the implementation of a cardiac surgery ERAS Program are threefold: patient-related factors such as unrealistic expectations, poor health literacy, poor patient engagement, and comorbidities; staff-related factors such as doctor and staff preferences, lack of information, and poor communication and cooperation; and finally system related factors such as lack of medicine, equipment and personnel, lack of leadership, and financial problems.[13]

Our initiative, which is Turkey's first ERACS implementation included 400 patients. It is difficult, however, to say exactly which is the most important step of the ERACS protocol, which steps can be sacrificed, and which are indispensable. In the intraoperative period, in which we, as anaesthesiologists, are most involved, the improvement in patient outcomes - with the use of opioid-reduced methods and regional techniques, the realization of blood management strategies in full harmony, and the intervention of the patient with more monitors - are quite satisfactory. In addition, early extubation may be the intervention which shows that everything is going well with the patient in the early postoperative period. This stage is a critical step that indicates the adequacy of hemodynamic stabilization, cardiorespiratory status and major cerebral functions, and is a sign of early ICU exit. ICU stay or length of hospital stay is often used as a measure of success for ERAS and fast-track protocols, however, length of stay in the healthcare system is more directly related to managerial and organizational issues than to patient recovery. When the ERAS guidelines are examined, the level of evidence and power of anaesthesia management practices are higher.[13,16] The anaesthesiologists plays the most critical role in the management of ERAS pathways by acting as a bridge between the perioperative periods.

Before undertaking the implementation, we considered that the patients would have difficulty following the rules and that the responsible personnel (dietician, physiotherapist, nurses..) would perceive this as an extra routine workload and disrupt the flow (because no one receives payment for implementation applications). However, both the patients and the responsible staff contributed very enthusiastically to the protocol and this prediction turned out to be incorrect. The most difficult obstacle in the initiative was the persuasion of the intensive care team (doctor and nurse) to the idea of early extubation. Although the concept of fast-track extubation has a long history, and although patients already met all the criteria for extubation, staying intubated somehow made the ICU team feel more comfortable and safe. However, over time, the intensive care team realized that many patients were intubated unnecessarily.

Another point of view regarding ERACS was that it would be more appropriate to apply the protocol only to well-being, low-risk, selected patients. However, considering that good results can be obtained without applying a special protocol to patients in good condition, ERACS might be perceived as an unnecessary effort. However, with the widespread effect of an application that has been found to improve patient outcomes and its application to risky patients, it actually may cause more attention to all patients who require care. Similarly, we observed that the application of ERACS in high-risk patients in critical condition had a positive effect on the outcome.[17-19]

ERACS is a procedure that requires multidisciplinary participation. This paper's aim was to discuss the ERACS protocols from the perspective of anaesthesiologist's instead of the whole protocol. One of the facts that emerge in this context is that the anaesthetist is a crucial practitioner who not only provides the ideal anaesthetic approach throughout the procedure, but also helps to improve overall perioperative care. When we summarize the initial unpublished design and implementation of an institutional ERACS protocol for cardiac surgery, the results suggest that compliance with a dynamic preanaesthetic preparation and a range of intraoperative evidence-based practices can translate into more comfortable and shorter hospital stays after cardiac surgery. While no difference was found in terms of complications, a cost reduction of up to 24% stands out as an additional result.[20]

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Narrative Review
Perioperative Care

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Precision Anaesthesia: Advancing Patient-Centered Precision Care Through Repetitive Assessment of PROMs with the Safe Brain Initiative Approach

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Abstract

This article aims to introduce the Safe Brain Initiative (SBI) approach, focusing on collecting and leveraging Patient-Reported Outcome Measures (PROMs) to enhance patient-centred precision anaesthesia and prevent postoperative delirium (POD) and neurocognitive disorders (NCD). The SBI was implemented to systematically address the feedback gap in perioperative care by collecting and analysing real-world data. The initiative focuses on monitoring and preventing POD and NCD, providing effective anaesthesia care, assessing patient and team satisfaction, and evaluating environmental sustainability impact. Based on international guidelines, 18 core recommendations were established to address potential complications and challenges associated with anaesthesia. Preliminary results showed a notable reduction in POD and increased awareness among anaesthesia team members regarding PROMs. The SBI approach demonstrated significant benefits during emergency situations, such as the February 2023 earthquake in Turkey, by providing crucial support and comfort to victims requiring multiple surgical interventions. The SBI presents an innovative, cost-effective, and patient-centred approach to perioperative care. By integrating PROMs and systematic feedback mechanisms, the SBI aims to expedite the advancement of efficient, patient-centered precision perioperative care, improve patient outcomes, and elevate the quality of care. The initiative has shown promising results, and its adoption is growing globally. Collaboration among healthcare providers, researchers, and patients is crucial in shaping the future of anaesthesia practice and further improving patient outcomes. Turkish hospitals are encouraged to join the SBI to benefit from international collaborations and contribute to positive change in perioperative care standards. The SBI project significantly advances precision anaesthesia, emphasising personalised care and patient well-being.

Keywords: Neurocognitive disorders, patient-centered perioperative care, patient-reported outcome measures, postoperative delirium, precision anaesthesia, safe brain initiative

Main Points

- The Safe Brain Initiative (SBI) is an evidence-based project that enhances patient-centred precision anaesthesia by integrating Patient-Reported Outcome Measures to monitor and prevent postoperative delirium and neurocognitive disorders.
- The SBI employs a comprehensive care bundle comprising 18 core recommendations derived from international guidelines, aiming to address potential complications associated with anaesthesia and surgery, such as postoperative pain, nausea, and vomiting.
- Preliminary results from the SBI project have shown a notable reduction in postoperative delirium rates and increased awareness among anaesthesia team members regarding patient-related outcomes, indicating the initiative's effectiveness.
- The SBI project has gained global traction, with multiple hospitals from various countries participating in the initiative, fostering collaboration, knowledge exchange, and shared experiences to elevate the standards of perioperative care.
- By providing healthcare providers anonymous feedback regarding their patients' outcome metrics, they can actively involve patients in their care, leading to better overall health outcomes, increased patient engagement, and reduced costs, contributing to improved patient experiences and continuous quality improvement.

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Introduction

Acquiring systematic feedback on Patient-Reported Outcome Measures (PROMs) remains a significant challenge for healthcare professionals and hospital administrators.[1] PROMs encompass a wide range of patient-reported outcomes related to experiences, symptoms, and functional outcomes following medical interventions, including anaesthesia and surgery.[2,3] Integrating PROMs as a vital component of precision care enables healthcare providers to gather comprehensive patient information directly, leading to personalised treatment decisions and interventions.[4] This patient-centred approach enhances care quality by tailoring interventions, including the targeted application of medical technology, optimising treatment plans (e.g. fine tuning SOPs), and improving health outcomes based on a deeper understanding of individual needs and preferences.[5,6]

Ensuring the integrity of PROMs necessitates direct acquisition from patients without any interpretation by the clinical team or others. This approach is particularly critical in the postoperative setting, where an impartial assessment-uninfluenced by the experiences of individual service providers-is key to advancing precision care. It assists in detaching the influence of personal or departmental traditions and beliefs from the precision of PROMs and Postoperative Delirium (POD) assessments.

Ideally, these measurements should evaluate and classify patients' health and functional status and the consequences associated with perioperative care. By doing so, they furnish a comprehensive assessment of care quality and side effects.[2,3,7] Such a comprehensive and unfiltered view ensures accurate measurement and can contribute to continuous improvements in the quality and personalisation of patient care.

We introduced the Safe Brain Initiative (SBI) project[8] to systematically address this feedback gap by collecting and leveraging real-world health outcome data to monitor, visualise, and enhance patient-centred care and preventive outcomes. The SBI initiative focuses on four key areas:

1. Acquiring PROMs to monitor and prevent POD/neurocognitive dysfunction (SBI-Core).

2. Facilitating strategic guidance for patient-centred anaesthesia management through the SBI-Muda initiative. This project seeks to optimise perioperative efficiency, mitigate POD/neurocognitive dysfunction, and elevate patient-reported outcomes. It provides weekly dashboard updates offering insights into OR and hospital metrics - encompassing e.g. start times or delays, suture-to-incision intervals, time expended in the post-anaesthesia care unit (PACU), and duration of postoperative hospital stays - all of which are contextualised alongside individual core outcomes.

3. Assessing patient and team satisfaction with perceived care quality (SBI-Us).

4. Evaluating and reducing environmental sustainability impact (SBI-Green).

By focusing on these areas, the SBI aims to strengthen the perioperative healthcare system, improve patient outcomes, and advance the understanding and practice of precision anaesthesia (Figure 1).

PROMs in Perioperative Care

Within the sphere of anaesthesia, PROMs have an amplified importance compared to other specialties.[3,7] This distinction arises from anaesthesia's direct impact on patients' immediate experiences and subsequent outcomes during and post-surgery.[9] Critical PROMs to consider in a postoperative environment encompass postoperative pain, postoperative nausea and vomiting (PONV), thirst, stress and anxiety, overall well-being, and odynophagia (resulting from airway manipulation). In a broader context, outcomes like POD and perioperative neurocognitive disorders (PND) warrant close attention.

However, these outcomes are often monitored sporadically or superficially, neglecting the crucial need for continuous quality enhancement and precision in anaesthesia care.[10] When the assimilation of individual and local patient outcome data is omitted, healthcare professionals forfeit a realistic appraisal of their individual or departmental methodologies' efficacy. Moreover, the lack of structured, anonymous individual feedback deviates from the primary goal of anaesthesia: prioritising patient well-being. Developing comprehensive evaluation and feedback systems to address these issues is imperative, paving the way for effective learning trajectories and promoting sustained quality improvement.[11]

Figure 1. Four Focus areas of the Safe Brain Initiative.

The consistent assessment of PROMs during the early postoperative period is paramount for several reasons.[7] The fluctuating nature of recovery demands regular evaluations to document evolving symptoms, pain thresholds, functional status, and overall health. By closely monitoring PROMs, healthcare providers can swiftly identify escalating symptoms or complications, thus enabling timely interventions and optimising patient care.[12] Furthermore, continual assessments enable the evaluation of treatment effectiveness over a given period, guaranteeing the achievement of desired outcomes and offering the chance for necessary modifications. By adapting care planning based on symptom changes and recovery progression, this personalised approach augments precision and individualisation in patient care.[13] The assessment process also encourages patients to be more involved, fostering a sense of engagement and facilitating active participation in their recovery process.[14] Regular evaluations provide patients with a platform to voice their worries, pose questions, and participate in shared decision-making, enhancing the overall patient experience in the long run.

What is the SBI?

The SBI provides an evidence-based bundle of care to monitor and improve PROMs in Anaesthesiology and to prevent and reduce POD and PND in the perioperative period.[8] It is a 360° concept for implementing and operationalising real-world evidence, with a data-driven dashboard solution for systematic feedback to healthcare personnel. With its comprehensive approach across the four-level domain, the SBI aims to leverage real-world healthcare outcomes data to monitor, visualise, and enhance preventive patient-centred routine care and outcomes.

The SBI incorporates an extensive care bundle comprising 18 core recommendations (Figure 2). These recommendations primarily focus on non-invasive interventions to detect, prevent, and reduce adverse outcomes, including POD, PND, PONV, perioperative stress, perioperative anxiety, inadequate pain/nociception management, and patient discomfort. By implementing these recommendations, the SBI aims to address and mitigate potential complications and challenges associated with anaesthesia and surgery, ultimately improving patient outcomes and enhancing the overall surgical and perioperative experience.

1. Delirium monitoring: Implement measures to monitor and detect delirium in the perioperative period.

2. Preoperative pain: Address and treat pain before surgery to improve patient experience.

3. Stress: Employ strategies to lessen perioperative stress, fostering a more tranquil patient environment.

4. Anxiety: Recognize, address and reduce perioperative anxiety in patients through appropriate interventions and support.

5. Oral fluid fasting duration: Curtail unnecessary pre and post-surgery fasting periods.

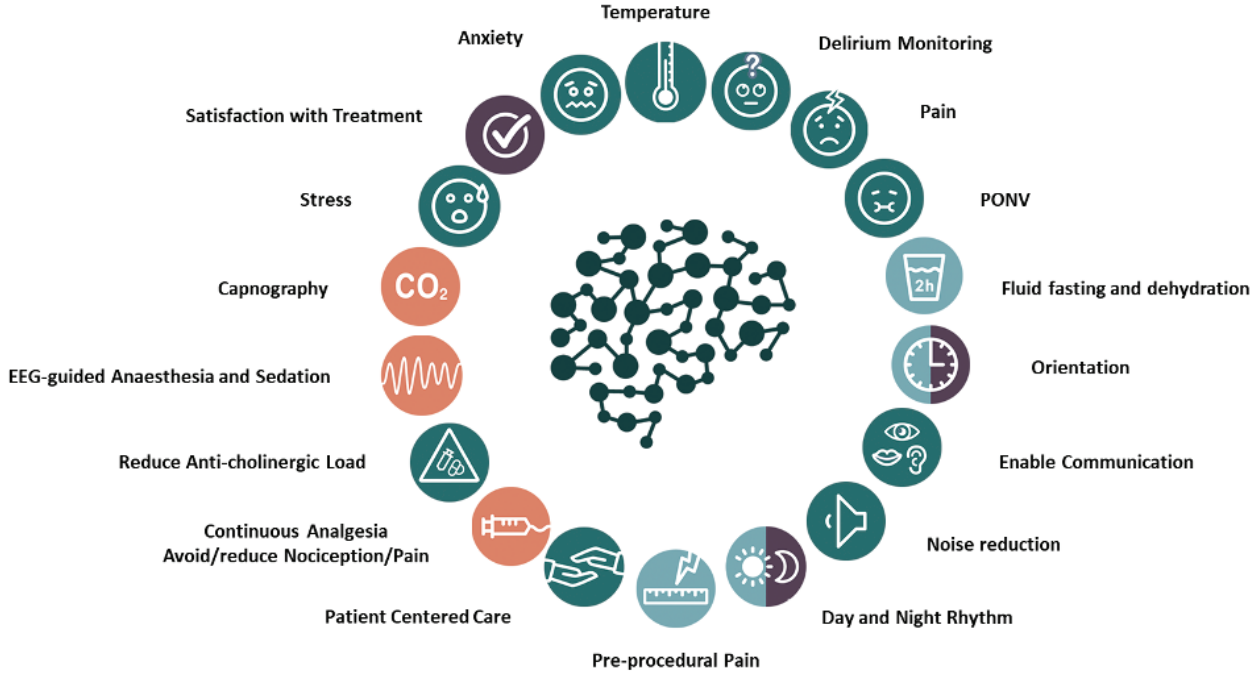

Figure 2. A multicomponent evidence-based approach: The 18 SBI core recommendations.

SBI, Safe Brain Initiative, EEG: electroencephalography.

6. PONV: Implement and fine-tune preventative measures and treatments for nausea and vomiting post-surgery.

7. Postoperative pain: Evaluate and effectively finetune preventive and postoperative pain treatment.

8. Facilitate communication: Ascertain that patients bring their dentures, hearing aids, and glasses to the Operating Room, PACU, and throughout the perioperative pathway, where applicable. This strategy aids in maintaining orientation and fostering and enhancing patient-centred communication between healthcare professionals and patients, thereby ensuring a transparent and effective exchange of information.

9. Patient-centered clinical practice: Emphasize a patient-centred approach where the patient's preferences, needs, and values are considered and respected.

10. Anticholinergic influence: reduce the use and influence of anticholinergic medications on cognitive function where possible.

11. Electroencephalography (EEG) monitoring: Utilise the patient's brain activity using EEG to individualise and finetune sedation application and to detect and prevent adverse neurological events.

12. Continuous analgesics and nociceptive monitoring: Use continuous analgesia techniques (e.g. remifentanil), and validated nociceptive monitoring to finetune and manage nociception/pain during and after surgery.

13. Use of Capnography in sedated patients: Implement capnography under sedation to ensure adequate ventilation and detect possible complications immediately.

14. Circadian rhythm: Support the patient's circadian rhythm and incorporate strategies to support the natural sleep-wake cycle during the perioperative period.

15. Patient satisfaction: Measure and address patient satisfaction to improve the quality of care provided for all relevant perioperative care periods.

16. Noise: Minimize noise levels in the perioperative environment to promote a calmer and more comfortable patient and staff atmosphere and interaction.

17. Orientation: Minimize any potential impacts on patient orientation resulting from the side effects of perioperative care. Strive to maintain or enhance a patient's baseline orientation concerning spatial awareness, temporal comprehension, and personal data throughout the perioperative period, except during anaesthesia.

18. Temperature: Maintain proper perioperative temperature management to prevent hypothermia or hyperthermia and promote patient comfort.

The interventions recommended by the SBI are designed to minimise or alleviate the iatrogenic burden on patients' postoperative outcomes. These recommendations are derived from international guidelines or expert consensus and aim to enhance the patient's perioperative experience, minimise complications, and promote positive outcomes. By implementing these non-invasive measures, healthcare providers can contribute to safer, more patient-centred perioperative care. The SBI recognises the importance of aligning interventions with evidence-based guidelines to ensure optimal outcomes and improve the overall quality of care for patients undergoing anaesthesia and surgery.

The SBI has the following objectives:

• To offer an innovative, non-profit solution that enables anaesthesiologists, anaesthesia nurses, and anaesthesia departments to access and review their patients' actual results and complications. The primary focus of the SBI is on the systematic monitoring and prevention of POD and PND, as well as PROMs, particularly in elderly and frail adults.

• To provide educational support for the routine assessment of the effects of implemented, modified, or newly introduced prevention and/or treatment strategies. These effects will be compared and analysed using high-quality, real-world data, allowing healthcare professionals to evaluate the impact of their interventions.

• To establish a solid foundation that enables healthcare professionals at the individual and departmental levels to embrace a continuous quality improvement process. The SBI aims to create an environment where healthcare providers can learn from real-world outcomes, identify areas for improvement, and implement changes that enhance the overall quality of care provided.

By achieving these objectives, the SBI strives to advance anaesthesia care, promote patient safety, and facilitate ongoing improvements in patient outcomes and experiences.

Patient-centred models of care, such as the SBI, are cost-effective and improve outcomes by actively involving patients in health decisions and ensuring their preferences are heard and acted upon.[6,13,15] This approach leads to better overall health outcomes, increased patient engagement in their own care, and reduced costs.[16-18]

The Impact of the SBI on Perioperative Care and Patient Support during Emergency Situations

Instituted in 2020 at Ankara University's Faculty of Medicine, the SBI overcame initial implementation hurdles to evolve into a crucial instrument in enhancing the calibre of patient-centric perioperative care. To date, the SBI has enrolled over 5,000 surgical patients in Ankara University alone, showcasing a significant decline in the rates of

postoperative delirium and augmenting the consciousness of anaesthesia team members about patient-related outcomes.

Beyond its routine benefits in perioperative practice, the SBI approach has demonstrated transformative impacts on improving the quality of perioperative care, particularly during the devastating earthquake that struck Turkey in February 2023. In the chaotic aftermath of the earthquake, the SBI strategy offered pivotal support and solace to victims necessitating multiple surgical procedures. In the context of perioperative care, from all SBI parameters, thirst emerged as a significant concern for these crush victims. The preoperative assessment of thirst was fundamental in addressing this issue effectively. By repetitively evaluating and quantifying the level of thirst preoperatively and postoperatively, the healthcare providers were equipped with valuable insights to tailor appropriate interventions and hydration strategies; and enhance patient comfort along with optimizing surgical outcomes and overall perioperative care.

Another significant concern arose from preoperative high levels of pain, which adversely affected patient comfort and surgical positioning. Efficient management of preoperative pain was crucial before the induction of anaesthesia, and the SBI approach played a central role in addressing this challenge.

Also, the systematic assessment of stress and anxiety levels and the well-being of patients emerged as a valuable non-pharmacological tool for premedication. Non-pharmacological management of high-stress levels was successfully attained through the implementation of interventions such as warm blankets, a hand-holding approach, and comforting talks. These strategies proved effective in mitigating psychological distress and enhancing patient well-being. This empathetic atmosphere nurtured by the SBI received high praise from patients, who affectionately referred to the anaesthesia team as "hand-holding doctors" due to their compassionate demeanor. This approach demonstrated instrumental in optimizing patient comfort and readiness for surgery, ultimately contributing to improved surgical outcomes and perioperative care. This strategy paved the way for fostering trust and mutual understanding between patients and the anaesthesia team, playing a critical role in safeguarding patients' welfare and ensuring their safety during such crises.

The Global Scope of the SBI Project

The SBI project is an encompassing platform dedicated to facilitating scientific and practical benchmarking, promoting collaborative best practices, and inspiring a positive competitive environment for collective growth on various levels. It introduces a data-driven dashboard solution that furnishes systematic feedback for healthcare professionals (as depicted in Figure 3). Currently, the SBI network extends to multiple hospitals throughout Denmark, Germany, Switzerland, Saudi Arabia, and Turkey, fostering a diverse and cooperative landscape. The community of centres subscribing to the SBI is consistently expanding each month. Moreover, the European Society of Anaesthesiology

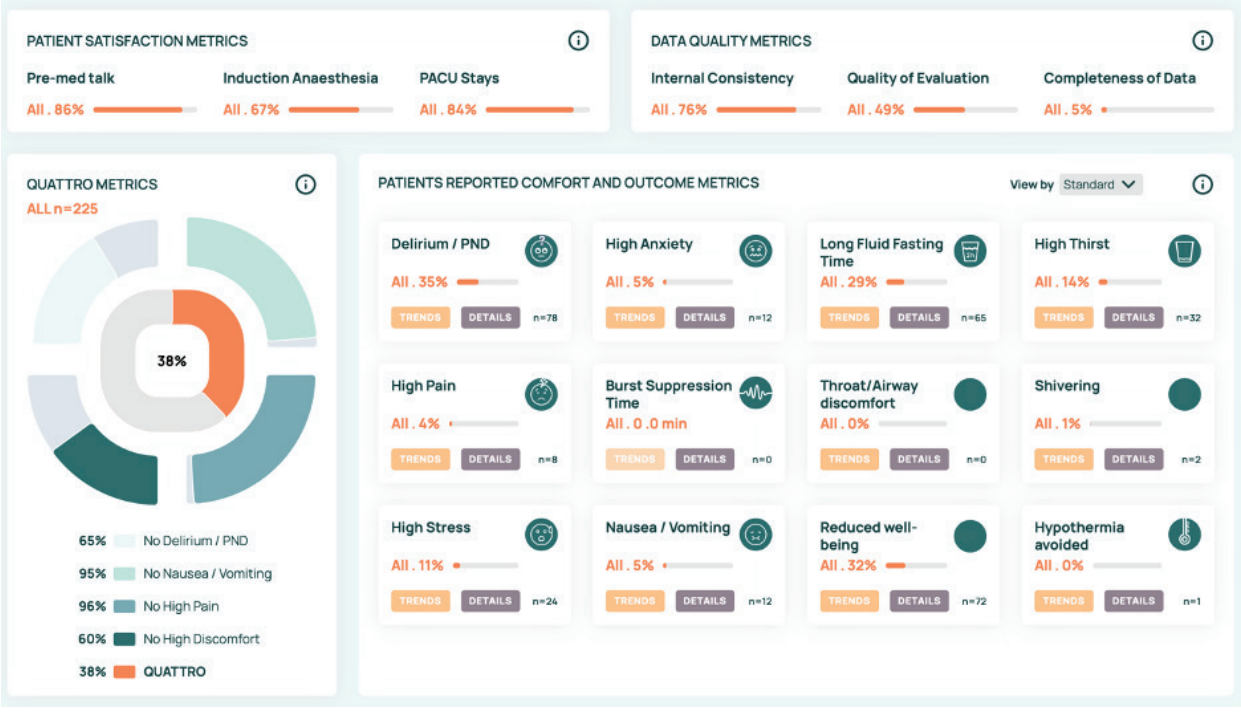

Figure 3. SBI dashboard example.

SBI, Safe Brain Initiative.

and Intensive Care has recently endorsed the SBI by acknowledging it as a Research Group within the Society in recognition of its substantial value and prospective impact. Additional details and insights about the project can be retrieved from the SBI's official website: safebraininitiative.com. This online platform is invaluable for those seeking comprehensive insights and updates regarding the initiative, its objectives, and ongoing developments.

Joining the SBI provides many benefits. These include access to resources and tools that help put best practices into action, ongoing monitoring of perioperative outcomes, and chances to participate in implementation projects with other hospitals. By combining PROM assessments from various hospitals during the early postoperative phase, we're jointly working towards developing systematic strategies and components for precision anaesthesia. It's important to recognize that this field is still nascent, and incorporating PROM assessments is a major step forward in enhancing our knowledge and application of precision anaesthesia.

We strongly encourage Turkish hospitals to take part in this initiative to reap the benefits of international cross boarder collaborations, the exchange of expertise, scientific contributions, and collective experiences with affiliate institutions. Membership in the SBI can bolster a hospital's standing as a centre devoted to clinical excellence and patient-centred welfare.

The SBI is devoted to continuously enhancing and refining our methodologies and elements in providing bespoke and precise anaesthesia care. Collaborations among healthcare providers, researchers, and patients from diverse countries are pivotal in sculpting the future of anaesthesia practice and bolstering patient outcomes. We cordially invite all Turkish hospitals to participate in this meaningful international effort to foster beneficial changes and expansion in perioperative care.

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Effects of Different Crystalloid Fluids on Renal Tissue in an Experimental Model of Hemorrhagic Shock

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Abstract

Objective: The type of fluid that should be used in uncontrollable hemorrhages remains an area of research. This study was designed to compare the effects of resuscitation with Ringer's lactate (RL) solution versus a normal saline (NS) solution on hemodynamics, renal tissue histopathology, coagulation, and apoptosis in a rat model of hemorrhagic shock.

Methods: The study employed groups designated as the control, hemorrhage, NS, and RL groups. Heart rate, mean arterial pressure, and respiratory rate were monitored. Annexin A5 values were assayed, rotational thromboelastometry analysis was performed, and excised kidney tissue samples were histopathologically analyzed.

Results: Blood pressure levels were found to be significantly higher in the control group than those measured in the other groups. While the clotting time (CT) and clot formation time (CFT) in the hemorrhage group were significantly longer than those in the control and RL groups, the CT and CFT measured in the control group were significantly shorter compared to the RL group. The mean Annexin A5 level was in the hemorrhage group, which was significantly higher compared to the other groups. In the renal histopathological evaluation, the scores of proximal tubular injury, distal renal tubular injury, and interstitial renal tubular injury were found to be significantly lower in the control group compared to the other groups.

Conclusion: This study demonstrated that NS or RL can be used safely to improve the hemodynamic symptoms resulting from hemorrhagic shock as a means to reduce apoptosis, and to decrease findings in favor of coagulopathy in bedside coagulation tests during the early stages of hemorrhagic shock until the time of starting a blood transfusion.

Keywords: Annexin A5, hemorrhagic shock, normal saline, Ringer's lactate, ROTEM

Main Points

- Significant hypotension and tachycardia occur following hemorrhagic shock and clot formation is delayed as trauma-induced coagulopathy intensifies and hypotension deepens.
- Traumatic hemorrhage causes microcirculatory alterations resulting in histopathological injury and apoptosis in renal tissue.
- Normal saline and Ringer's lactate can be safely used in the early phase of traumatic hemorrhagic shock during the time till blood is available to start transfusion.

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Introduction

The most common cause of hypovolemic shock includes traumatic hemorrhagic shock triggered by soft tissue damage, as well as an immune response in addition to acute hemorrhage.[1] Trauma, which is the leading cause of preventable deaths, still results in high mortality rates due to life-threatening and uncontrollable hemorrhaging.[2] The aim of damage control resuscitation, an aspect of damage control surgery introduced to prevent such deaths, is to maximize tissue oxygenation by achieving the targets of hemostasis, homeostasis, and hemodynamics, and to control bleeding.[3] According to a recently published systematic review, no comparative study has to date investigated the effects of these fluid types on microcirculation.[4]

This study was designed to compare the effects of resuscitation using a Ringer's lactate (RL) solution versus normal saline (NS) on hemodynamics, renal tissue histopathology, coagulation, and apoptosis in a rat model of hemorrhagic shock.

Methods

This experimental trial was approved by the Animal Experimentation Ethics Committee at University of Health Sciences Turkey (protocol number: 46418926-605.02; date: 27.06.2019; chairperson: Prof. Dr. Sadrettin Pençe). Twenty 6-month-old Wistar rats were used in this trial. No preliminary study was performed leading to the death of animals. Rats were randomized into 4 groups and each group included 5 experimental animals.

Allocation to Groups

Group C (control group): The group to which hemorrhage was not applied (n = 5).

Group H (hemorrhage group): The group to which hemorrhage was applied but in which rats did not receive any therapy (n = 5).

Group NS (normal saline group): The group to which hemorrhage was applied and in which rats were given intravenous (IV) NS (n = 5).

Group RL (Ringer's lactate group): The group to which hemorrhage was applied and in which rats were given an infusion of RL (n = 5).

Following a 1-hour period, blood samples were collected to observe the effects of hemorrhagic shock at the tissue level. Then, crystalloid fluid was infused into the rats.

Selection and Preparation of Animals

Male Sprague-Dawley rats weighing 214-268 g were used after 5-7 days of acclimatization. Rats were maintained in separate cages for 12 h during the day and 12 h at night. The ambient temperature was controlled.

Anaesthesia Protocol

To avoid expected or unexpected side effects related to anaesthesia, the determined anaesthesia method was carefully applied to the animals by an experienced anaesthesiologist. The depth of anaesthesia was controlled by the pinch reflex. To correct the hypothermic state of the animals under anaesthesia, a homoeothermic blanket maintaining a constant body temperature at 37 °C was used. Rats received an intraperitoneal injection of ketamine hydrochloride at a dose of 90 mg kg^{-1} and xylazine hydrochloride at a dose of 10 mg kg^{-1} for anaesthesia.

Monitoring

Hemoglobin oxygen saturation, respiratory rate per minute, heart rate, and core temperature were measured noninvasively and recorded. Blood pressure, respiratory rate, and heart rate were monitored using an electrophysiological data acquisition system (PowerLab 16/35, AD Instruments, Castle Hill, Australia). Blood pressure was measured at the carotid artery with a 24-catheter employing a reusable BP transducer (MLT0380/D, AD Instruments, Castle Hill, Australia). The carotid artery was also used to collect blood samples and to generate hemorrhage. The tail vein of rats was cannulated for IV fluid infusion. Respiratory rate and heart rate were measured non-invasively and recorded. The respiration rate was measured using PowerLab-connected pulse transducers (TN1012/ST, AD Instruments, Castle Hill, Australia). Heart rate was measured using PowerLab-connected biological amplifiers (Bio Amp FE231, AD Instruments, Castle Hill, Australia).

Protocol for Hemorrhagic Shock

The hemorrhagic shock protocol[5] was initiated 60 min after all rats had been anaesthetized. The target blood volume loss was determined as 40%. Hemorrhage was performed in three stages. In the first stage, a 25% loss was achieved and the hemorrhage rate was 0.5 mL min^{-1}. In the second stage, 10% blood loss was achieved at a rate of 0.2 mL min^{-1}. In the third and final stage, 5% blood loss was achieved at a rate of 0.1 mL min^{-1}. Hemorrhage was achieved in rats using a double-lumen femoral vein catheter. While blood was drawn from one lumen with a syringe, a sterile sodium citrate solution was administered through the other lumen. The procedure was interrupted in a case when the mean arterial pressure fell below 40 mmHg. Later, hemorrhage was continued when a pressure of 45 mmHg was maintained for more than 15 s. The hemorrhagic shock protocol was applied for a total period of 60 min, then IV crystalloid infusions were started in the study groups.

Rotational thromboelastometry (ROTEM), Annexin A5, and lactate levels were recorded at T0 and T1 as follows:

T0: The time when the blood sample was taken before the initiation of hemorrhage (baseline measurement).

T1: The time when the blood sample was taken after resuscitation.

At the end of the procedures, the vascular catheters were removed, the incisions were closed and the rats were sacrificed. Finally, tissue samples were collected and examined.

Resuscitation Fluids

Animals were randomized to receive RL or NS three times the volume of blood lost. Resuscitation fluids were heated to 37 °C and infused within 30 min. Plasma obtained from blood samples and collected in citrated tubes was stored at -80 °C and used for immunoassay methods. Samples collected for blood gas analysis were kept in a heparinized tube until analysis.

Rotational Thromboelastometry

Ninety cartridges were used for the ROTEM[6,7] procedure. Of the parameters evaluated for ROTEM, clot formation time (CFT) represents the time (min) from a clot amplitude of 2 mm until a clot amplitude of 20 mm is achieved. Maximum clot firmness (MCF) represents the point where the clot reaches its highest strength and firmness. A10 represents the clot amplitude at 10 min of clotting.

Renal Histopathological Evaluation

Kidney tissue samples were collected and fixed with a 10% neutral buffered formalin solution and embedded in paraffin. Serial sections of 4-5 µm thick paraffin blocks were obtained with Thermo microtome, and the sections were hematoxylin and eosin-stained. The sections were photographed using a Leica DM2000 light microscope and with the camera of the iPhone X mobile phone. Sections were evaluated for proximal and distal tubular injury, glomerular injury, and interstitial and vascular injury.

	0	1 (minimum)	2 (mild)	3 (moderate)	4 (severe)
A. Proximal tubular injury	<10%	10-25%	25-40%	40-50%	>50%
B. Distal tubular injury	<10%	10-25%	25-40%	40-50%	>50%
C. Glomerular injury	<10%	10-25%	25-40%	40-50%	>50%
D. Interstitial injury	<10%	10-25%	25-40%	40-50%	>50%
E. Vascular injury	<10%	10-25%	25-40%	40-50%	>50%

Scoring Used for Assessment of Kidney Injury

Monitoring Endothelial Injury, Apoptosis, and Coagulation Using the Enzyme-Linked Immunosorbent Assay Method

Annexin 5 measurements were performed using enzyme-linked immunosorbent assay (ELISA) kits. To obtain serum, blood samples (5 mL) were collected into a tube containing vacutainer serum separator gel, and the tubes were kept at room temperature and centrifuged at 100x g for 10 min within the first hour of blood collection. After separation, the serums were frozen at -20 °C, and Annexin A5 measurements were performed using ELISA kits.

Statistical Analysis

The SPSS Statistics 22.0 software was used for the analyses. We employed the descriptive statistics of mean, standard deviation, median, minimum, maximum, frequency, and ratio. The Kolmogorov-Smirnov test was used to measure the distribution of the variables. Quantitative independent data were analyzed using the Mann-Whitney U test. Dependent quantitative data was analyzed using the Wilcoxon test. For the analysis of repeated parameters, repeated measure analysis of variance (ANOVA) was used. Quantitative independent data were analyzed using a chi-square test, but if the conditions for this test were not met, we used the Fisher test. A one-way ANOVA test and the post-hoc Tukey test were used for normally distributed numerical data.

Results

Vital Parameters

The "respiratory rate at min 60" was statistically significantly lower in the control group than in the NS group (P=0.049, Table 1). The respiratory rates of rats during hemorrhage were similar between the groups (Figure 1).

The "heart rate measured at min 60 after hemorrhage" was found to be statistically significantly higher in the control group compared to the hemorrhage and NS groups (P=0.014). The heart rates measured at the "0

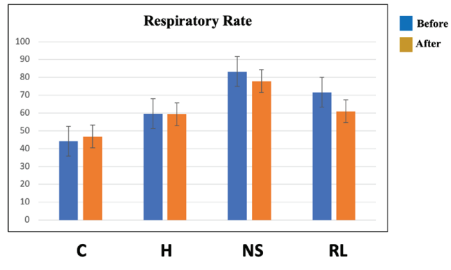

Figure 1. Comparison of respiratory rates recorded while inducing hemorrhage in the experiment animals.

C, control group; H, hemorrhage group; NS, normal saline group; RL, Ringer's lactate group.

and 30 min of crystalloid infusion" were statistically significantly higher in the control group than in group H ($P < 0.05$, Table 2).

"Blood pressure levels measured at the "10 and 15 min of hemorrhage" and at "0 min of infusion" were found to be statistically significantly higher in the control group than those measured in the other groups (P=0.001, Table 3). The blood pressure values measured at "30 and 60 min of the crystalloid infusion" in the hemorrhage group were found to be statistically significantly lower than the measurements in the C, NS, and RL groups (P=0.001). The blood pressure values measured at "10 min of the crystalloid infusion" in the control group were found to be statistically significantly higher compared to the same values in the H and RL groups, while it was statistically significantly higher in the NS compared to the H group ($P < 0.05$). The blood pressure value measured at "15 min of infusion" was statistically significantly lower in the hemorrhage group than the same value recorded in the C, NS, and RL groups, whereas it was found to be statistically significantly lower in RL compared to the C group ($P < 0.05$, Table 3).

ROTEM Analysis

The CT and CFT values in group H were statistically significantly higher compared to the other groups (P=0.001). A10 measurement in group H was statistically significantly lower compared to the other groups (P=0.003). The MCF value measured in group H was found to be statistically significantly lower than those in the NS and RL groups (P=0.001, Table 4).

While CT and CFT in group H were statistically significantly longer than those in groups C and RL, the CT and CFT

Table 1. Comparison of Respiratory Rate Values Between Groups

	Group C (n = 5)	Group H (n = 5)	Group NS (n = 5)	Group RL (n = 5)	*P* value
Min 0 before hemorrhage	44.8±10.03	47.30±11.13	75.60±10.65	64.56±9.99	0.171[A]
Min 60 before hemorrhage	43.04±10.02*	53.0±11.28	89.36±13.0**	62.52±8.30	0.049*[A]
Min 0 of hemorrhage	44.20±11.23	59.63±13.23	83.24±13.13	71.68±11.18	0.197[A]
Min 60 of hemorrhage	46.88±11.24	59.30±11.16	77.96±8.68	61.04±6.97	0.229[A]
Min 0 of infusion	40.52±10.10	65.77±12.17	79.44±8.57	46.68±8.04	0.062[A]
Min 15 of infusion	41.52±7.11	70.60±11.78	94.20±19.91	60.04±12.27	0.090[A]
Min 30 of infusion	45.16±8.80	81.75±14.34	81.72±7.58	59.44±10.86	0.060[A]
Min 60 of infusion	51.32±15.37	76.15±20.04	77.20±6.85	67.96±14.62	0.564[A]

[A]One-way ANOVA: mean ± SD.
*$P < 0.05$: Statistically significant difference.
*< **: Reason for a statistically significant difference ($P < 0.05$).
SD, standard deviation.

Table 2. Comparison of Heart Rate Values Between Groups

	Group C (n = 5)	Group H (n = 5)	Group NS (n = 5)	Group RL (n = 5)	*P* value
Min 0 before hemorrhage	266.36±31.79	232.47±21.95	215.64±29.57	302.20±41.21	0.255[A]
Min 60 before hemorrhage	279.28±43.50	248.10±19.80	197.92±38.99	311.52±45.03	0.214[A]
Min 0 of hemorrhage	280.44±45.27	224.57±26.15	170.68±47.87	268.44±47.06	0.279[A]
Min 60 of hemorrhage	278.72±46.34**	155.27±34.55*	119.72±9.26*	162.28±16.31	0.014*[A]
Min 0 of infusion	270.76±47.98**	149.83±33.12*	158.08±12.41	166.36±11.94	0.045*[A]
Min 10 of infusion	249.08±50.42	152.47±34.71	175.12±16.49	182.16±15.51	0.229[A]
Min 15 of infusion	249.40±52.77	152.60±36.11	196.44±26.23	187.88±13.22	0.305[A]
Min 30 of infusion	256.28±51.76**	115.04±23.18*	164.84±18.42	203.88±18.77	0.035*[A]
Min 60 of infusion	246.92±52.17	138.88±36.47	160.56±16.87	190.04±17.27	0.172[A]

[A]One-way ANOVA: mean ± SD.
*$P < 0.05$: statistically significant difference.
SD, standard deviation.
*< **: Reason for a statistically significant difference ($P < 0.05$).

Table 3. Comparison of Mean Blood Pressure Values Between Groups

	Group C (n = 5)	Group H (n = 5)	Group SF (n = 5)	Group RL (n = 5)	*P* value
Min 0 before hemorrhage	99.43±8.96	92.28±7.11	74.91±8.16	97.74±4.24	0.131[A]
Min 60 before hemorrhage	104.64±9.20	93.39±8.98	73.70±11.42	95.76±5.07	0.185[A]
Min 0 of hemorrhage	104.26±9.67	68.76±10.38	63.71±11.73	69.48±3.48	0.063[A]
Min 60 of hemorrhage	114.76±10.55**	54.22±6.56*	51.54±9.39*	51.30±5.70*	0.001*[A]
Min 0 of infusion	121.36±15.55**	39.71±6.33*	71.00±4.61*	70.86±12.39*	0.001*[A]
Min 10 of infusion	114.67±17.08**	‡32.99±8.50*	‡‡76.81±4.62	65.81±11.41*	0.001*[A]
Min 15 of infusion	‡‡110.13±16.80‡‡	30.52±9.07*	77.79±3.14**	‡69.00±6.24**	0,001*[A]
Min 30 of infusion	90.82±10.12**	28.17±9.52*	68.36±4.98**	68.37±5.35**	0.001*[A]
Min 60 of infusion	84.77±10.42**	27.50±9.40*	68.34±3.54**	61.57±2.44**	0.001*[A]

[A]One-Way ANOVA: mean ± SD.
**P* < 0.05: statistically significant difference.
*<**: reason for statistically significant difference (*P* < 0.05).
‡<‡‡: reason for statistically significant difference (*P* < 0.05).
SD, standard deviation.

Table 4. Comparison of EXTEM, INTEM, and FIBTEM Values Between Groups

EXTEM	Group C (n = 5)	Group H (n = 5)	Group NS (n = 5)	Group RL (n = 5)	*P* value
CT	53.0±9.9	118.6±20.1	46.4±2.4	49.8±6.5	0.001*[A]
CFT	52.8±17.7	210.4±20.1	49.2±21.2	52.2±21.1	0.001*[A]
A10	54.8±6.5	35.8±5.0	61.2±4.3	58.2±4.9	0.001*[A]
MCF	59.6±4.9	46.6±8.7	65.4±6.5	70.6±5.1	0.001*[A]
INTEM	**Group C (n = 5)**	**Group H (n = 5)**	**Group NS (n = 5)**	**Group RL (n = 5)**	***P* value**
CT	153.6±62.7	577.8±63.2	360.2±207.5	328.4±58.3	0.001*[A]
CFT	75.8±40.8	528.4±77.8	345.8±232.9	212.8±62.2	0.001*[A]
A10	48.6±7.9	23.0±4.1	37.8±16.8	37.0±10.1	0.015*[A]
MCF	59.4±6.7	27.0±4.5	38.8±16.4	33.0±6.7	0.001*[A]
FIBTEM	**Group C (n = 5)**	**Group H (n = 5)**	**Group NS (n = 5)**	**Group RL (n = 5)**	***P* value**
A10	12.2±3.3	6.0±1.6	10.8±3.4	14.0±2.7	0.003*[A]
MCF	16.4±5.5	8.0±2.7	11.8±3.3	20.8±4.7	0.001*[A]
HEPTEM	**Group C (n = 5)**	**Group H (n = 5)**	**Group NS (n = 5)**	**Group RL (n = 5)**	***P* value**
CT	108.2±45.8	312.2±82.4	116.8±18.5	164.8±46.7	0.001*[A]

[A]One-way ANOVA: mean ± SD.
**P* < 0.05: statistically significant difference.
SD, standard deviation.

measured in group C were statistically significantly shorter compared to the RL group (*P*=0.001). A10 measurement in group H was statistically significantly lower compared to group C (*P*=0.015). Group C had a statistically significantly higher MCF value compared to those measured in the H and RL groups (*P*=0.001, Table 5). A10 and MCF measurements in the hemorrhage group were observed to be statistically significantly lower compared to the RL group (*P* < 0.05).

A10 and MCF measurements for the hemorrhage group in FIBTEM were observed to be statistically significantly lower compared to the RL group (*P* < 0.05, Table 4).

Table 5. Comparison of Renal Histopathological Evaluation Scores Between Groups

		Group C	Group H	Group NS	Group RL	
		(n = 5)	(n = 5)	(n = 5)	(n = 5)	*P* value
Proximal renal tubular injury	Zero	5	0	0	1	0.003*
	One	0	0	1	3	
	Two	0	2	2	1	
	Three	0	3	2	0	
Distal renal tubular injury	Zero	5	0	0	3	0.049*
	One	0	1	2	1	
	Two	0	3	2	0	
	Three	0	1	1	1	
Interstitial injury	Zero	4	0	0	2	0.034*
	One	1	3	4	3	
	Two	0	2	0	0	
	Three	0	0	1	0	

[k]Chi-square test: values are given as a frequency (percentage).
*$P < 0.05$: statistically significant difference, compared to the control group.

The CT measured in group H was found to be statistically significantly higher than the values measured in the K and RL groups (P=0.001, Table 4).

ELISA Analysis

The mean Annexin A5 level was 16.36±4.47 ng mL^{-1} in the hemorrhage group, which was statistically significantly higher compared to the other groups (P=0.002).

Histopathological Evaluation

In the renal histopathological evaluation, the groups were compared in terms of proximal, distal, and interstitial tubular injury scores. These scores were found to be significantly lower in the control group compared to those in the other groups ($P < 0.05$, Table 5). There was no significant difference between the NS and RL groups regarding proximal, distal, and interstitial renal tubular injuries ($P > 0.05$). No significant difference was observed when the proximal renal tubular injury scores of the hemorrhage group were compared to those of the NS and RL groups (P=0.549 and P=0.062, respectively). We did not observe any significant difference when the proximal renal tubular injury scores of the hemorrhage group were compared to those of the NS and RL groups (P=0.0766 and P=0.172, respectively). The interstitial renal tubular injury scores of the hemorrhage group were compared to those of the NS and RL groups, and no significant difference was detected (P=0.208 and P=0.135, respectively).

Correlation Analysis

A positive correlation was found between the value obtained from Annexin A5 measurement and the measurements of CT Extem, CFT Extem, CT Intem, CFT Intem, CT Heptem, and that of proximal tubular injury ($P < 0.05$). Furthermore, a negative correlation was observed between A10 Extem, MCF Extem, A10 Intem, MCF Intem, A10 Fibtem, MCF Fibtem, and the blood pressure levels measured at min 0, 10, 15, 30, and 60 of crystalloid infusion ($P < 0.05$).

Discussion

This experimental study revealed that significant hypotension and tachycardia occurred in rats following traumatic hemorrhagic shock induced by a constant volume-controlled bleeding model; additionally, as trauma-induced coagulopathy intensified and hypotension deepened, the initiation of CF was delayed. It was also observed that traumatic hemorrhage caused microcirculatory alterations, resulting in histopathological injury and apoptosis in the renal tissue. This study, in which NS and RL were compared, revealed that both crystalloids had corrective effects on the signs of shock, the development of apoptosis, CT, and the firmness, amplitude, and strength of the clot.

The selection of IV resuscitation fluid in hemorrhagic shock has been a topic of debate for more than a century. Normal saline and RL are administered as equivalent resuscitation fluids in many trauma centers. In our study, tachycardia secondary to hemorrhage was reduced more effectively in the NS compared to the RL group. There was a significant decrease in heart rate at the first hour of hemorrhage, and NS increased the blood pressure significantly at min 10 of the infusion compared to the hemorrhage group. It was also observed that an IV infusion of NS achieved a greater increase in mean arterial pressure compared to RL. Although the difference was not statistically significant, we believe that this to have been due to the small sample size and that increasing the number of samples would render the result statistically significant. We believe that this positive effect of NS in trauma patients may be due to the vasodilator effects resulting from the drop NS achieved in peripheral resistance on arterial blood pressure. Similarly, in a study comparing NS and RL on 20 swine that were given anesthesia, NS provided an increase in blood pressure.[8] Moreover, better oxygen delivery has been also reported in the NS groups. A study previously conducted reported that swine that were given NS developed hyperchloremic metabolic acidosis, leading to coagulation disorders.[9] However, in the same study, the volume of crystalloid infusion was not kept constant, and the volume of infused NS reached twice that of RL. However, another study reported that although NS caused the development of hyperchloremic metabolic acidosis, this

condition did not lead to coagulation disorder according to ROTEM analyses.[10] The main triggering factors in trauma-induced coagulopathy are coagulation pathway disorders, infection, and global disturbance of hemostasis caused by cellular dysfunction.[11] When this happens, excessive fluid resuscitation leads to dilutional coagulopathy, increasing hemorrhage. In our study, the coagulation profile was monitored with ROTEM, which enabled the accuracy of the data to be objectively proven. The values of CT, CFT, and A provided information about clotting time and the firmness and amplitude of the clot. These values were observed to be impaired in the hemorrhage group. However, there was an improvement in the coagulation parameters in the NS and RL groups compared to the hemorrhage group, and even values close to those of the controls were also obtained.

The MCF measurement values provide information on the firmness of the clot. The MCF and A10 values in this study were found to be significantly lower in the hemorrhage group, whereas these indicated an increase in both the RL and NS groups. Replacing the IV volume at the appropriate time can likely prevent the formation of coagulopathy by preventing damage to the endothelial glycocalyx and impaired perfusion. As such, it becomes possible to prevent dilutional coagulopathy by keeping the amount of fluid infused limited. One of the important characteristics of our study is that both NS and RL were administered in equal amounts and in a manner that enabled exactly meeting the amount of blood loss when needed. Thus, we were able to make an effective comparison between NS and RL. The data of our study showed that neither crystalloid caused deterioration in coagulation, provided that they were not administered in excessive amounts or in an uncontrolled manner. We believe this data to be a significant contribution to the management of trauma patients in the pre-hospital setting.

Comparing the histopathological evaluation, our study shows that the damage following hemorrhage caused injury to the proximal and distal tubules and the interstitium. It was observed that damage at the microcirculatory level could not be corrected in rats infused with a crystalloid. The NS and RL groups did not indicate any advantage over one another in this regard.

The induction of apoptosis is an area of concern in RL administration.[12] A study by Rhee et al.[13] showed that RL infusion following hemorrhagic shock caused increased apoptosis in the intestinal mucosa, smooth muscles, as well as the cells in the liver and lungs. However, no significant apoptosis was observed in fluid resuscitation procedures performed using sham, plasma, fresh blood, and hypertonic saline. The infusion of RL led to increased adhesion molecule expression, causing amplified neutrophil activation and the release of reactive oxygen species. It has been suggested that this is how apoptosis progresses. It was reported in another study analyzing a hemorrhagic shock model in 49 Yorkshire swine that RL infusion caused hepatic and pulmonary apoptosis.[14] However, there is very limited data in the literature regarding apoptosis in renal tissue. In our study, the mean Annexin A5 level was 16.36±4.47 ng mL^{-1} in the hemorrhage group, which was found to be statistically significantly higher compared to the other groups. This result indicates the presence of severe apoptosis during hemorrhage. Nevertheless, apoptosis significantly decreased in the groups that were administered RL and NS and even regressed to values close to those of the control group. On the other hand, early crystalloid infusion performed using RL or NS cannot prevent microcirculatory disorder. However, crystalloid infusion with RL or NS is promising in that it was shown to have an inhibitory effect on apoptosis. It has been demonstrated that coagulopathy and delayed CF due to traumatic hemorrhagic shock accelerate apoptosis. According to the data obtained in our study, as the coagulopathy intensified, hypotension deepened and an inversely proportional result was obtained with the onset of CF.

An RL solution is considered a balanced crystalloid mixture; conversely, NS solutions have different electrolyte contents and are associated with a risk of hyperchloremic metabolic acidosis when administered in high volumes. As a result, there is a risk of developing acute kidney injury.[15] Accordingly, it is believed that the clinical results of IV infusions may differ. However, there are not enough comparative studies to prove this assumption. In this context, our research is among the studies that have aimed to clarify this controversial issue, as it indicated that both solutions could be safely used in the emergency department. Similarly, a study compared RL and NS in non-critically ill adults treated with IV fluids in the emergency department.[16] The researchers administered an average of 1,079 mL of crystalloid fluid to 13,347 patients and found no difference in terms of length of hospital stay, which is closely related to patient prognosis. Another study compared IV NS and RL infusions in donors undergoing hepatectomy, and no significant difference was found between the solutions regarding postoperative renal outcomes and creatinine levels.[17] With an increase in the number of randomized comparative studies in this field, more extensive information can be obtained.

Study Limitations

One of this study's limitations was that, as the experiment used a rat model, it was not possible to perform non-invasive hemodynamic monitoring. While it was possible to monitor parameters such as cardiac output and extravascular lung fluid volume in studies conducted on swine, it was not possible to monitor these parameters in the present study, in which we applied fluid resuscitation.[18] Another limitation is that we did not compare the acid-base balance between the groups. Hyperchloremic metabolic acidosis has been

reported in experimental animals that were administered NS in high volumes. However, since the volume of crystalloids applied was the same as the volume of bleeding, there was no incidence of high-volume infusion in our study.

Conclusion

This study suggests that NS and RL can be safely used in the early phase of traumatic hemorrhagic shock up to the time when blood is available for transfusion. This conclusion was reached considering the improvement in the hemodynamic findings of hypovolemic shock, a reduction in apoptosis, and the improvement of the symptoms in favor of coagulopathy in bedside coagulation tests. However, there remains a need for further studies to reveal the differences specific to different resuscitation fluids.

Ethics Committee Approval: This experimental trial was approved by the Animal Experimentation Ethics Committee at University of Health Sciences Turkey (protocol number: 46418926-605.02; date: 27.06.2019; chairperson: Prof. Dr. Sadrettin Pençe).

Informed Consent: Animal experimental study.

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Role of Preoperative Oral Rehydration Solution on Myocardial Ischaemia During Orthopaedic Surgery under Spinal Anaesthesia: A Prospective Randomised Study

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Abstract

Objective: Preoperative oral rehydration solution (ORS) supplementation offers wide postoperative benefits, but its role in reducing post-spinal myocardial ischaemia is uncertain. We evaluated this aspect in elective lower limb orthopaedic surgeries and compared it to conventional preoperative fasting.

Methods: Prospectively, we randomised 126 patients aged >60 years into two groups: (A) received reconstituted ORS (1000 mL) during the overnight preoperative fasting, continued up to 2 hrs prior to spinal anaesthesia (SA) induction; (B) kept on conventional overnight preoperative fasting. This study evaluated electrocardiographic ischaemic changes at 2, 5, 10, 15, and 30 minutes after SA induction.

Results: In total, 27 patients (group A: 7; group B: 20) developed transient electrocardiographic ischaemic changes. On intergroup comparison, group B had a significantly higher incidence at all time points, with highest statistical levels at 5- and 10-minutes ($P < 0.001$). The receiver operating characteristic curve at a threshold fasting duration (fluids) of >3 hours, had an area-under-curve of 0.74 to predict such changes within 30 minutes of SA induction (sensitivity 96.30%, specificity 55.56%, accuracy 64.29%, odds ratio 32.50, relative risk 20.80, $P < 0.001$). Post-spinal hemodynamic changes were higher in group B than in A; hypotension and tachycardia were statistically significant (P=0.020). The pleth variability index was significantly higher ($P < 0.001$), while perfusion index was significantly lower ($P < 0.001$) in group B at all time points.

Conclusion: Preoperative ORS supplementation significantly reduced post-spinal transient ischaemic electrocardiographic changes in elderly patients than conventional overnight fasting.

Keywords: Fasting, geriatrics, myocardial ischaemia, ORS, orthopaedics, spinal anaesthesia

Main Points

- Preoperative oral rehydration solution supplementation significantly reduced the post-spinal ischemic electrocardiographic (ECG) changes compared to conventional overnight fasting in elderly patients undergoing elective lower limb orthopaedic surgery under spinal anaesthesia (SA).
- It was coherent with unstable haemodynamics and abnormal perfusion parameters at the same intraoperative time points.
- No patient complaint of notable anginal symptoms and the underlying ischaemic ECG changes also reverted within an hour of SA induction.
- The threshold fasting duration of >3 hours for oral fluids had an area-under-curve of 0.74 to predict ischaemic ECG changes within 30 minutes of SA induction.

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Introduction

Preoperative fasting is a prerequisite for most surgical procedures. It aims to minimise the gastric residual volume (GRV) to avoid aspiration of gastric contents, a potential cause of airway-related perioperative mortality.[1] The underlying mechanism includes reduced sympathetic tone under spinal anaesthesia (SA). However, the flip-side is increased patient hunger, anxiety, insulin resistance, hyperglycaemia, unstable intraoperative haemodynamics, cardiac ischaemia, altered thermoregulation, and decreased cardiac preload, especially in elderly patients.[2] Literature, however, shows no difference in GRV between fasted patients and those receiving preoperative fluids.[3] Guidelines also recommend fluids up to 2 hrs prior to surgery.[1] However, in clinical practice, preoperative fasting usually lasts for ≥10 hours due to early patient shifting to the preoperative area during the morning hours, insufficient staffing to look for the preoperative fasting hours, and legal fear and apprehension among surgeons for case cancellation due to inadequate fasting.[3,4]

Though preoperative clear fluids may alleviate patient dehydration, complications related to electrolyte and sugar imbalance are still unaccounted. Formulations including carbohydrate drinks and oral rehydration solution (ORS) help to preserve perioperative muscle mass, reduce anxiety, hunger, and postoperative pain, maintain nitrogen balance, and allow early patient discharge.[5,6] However, literature showing its effect on myocardial ischaemia after SA induction is relatively sparse. We hypothesised that preoperative ORS supplementation might reduce the risk of post-spinal myocardial ischaemia. We explored the effect of preoperative ORS supplementation on myocardial ischaemia at different time points during the first 30 minutes after SA induction in patients undergoing elective lower limb orthopaedic surgery, compared to traditional overnight preoperative fasting. Other parameters, including pleth variability index (PVI), perfusion index (PI) and intraoperative complications were also compared at same time points.

Methods

After All India Institute of Medical Sciences, Rishikesh, Institutional Ethics Committee approval (approval no: 331/IEC/PGM/2020, date: 20.06.2020) and written informed consent, 126 patients aged >60 years, of either sex, American Society of Anesthesiology grade I-III, undergoing elective lower limb orthopaedic surgery under SA admitted between November 2020-April 22, were included in this prospective, outcome-assessor blinded, interventional trial. We followed all ethical principles for medical research involving human subjects as per Helsinki Declaration 2013. We excluded those with known cardiac/renal disease, diabetes mellitus, body mass index >35 kg m^{-2}, requiring emergency surgery, unable to give consent, any contraindication to SA or evidence of ischaemic changes/electrocardiographic (ECG) signs mimicking myocardial ischaemia in 12-lead ECG/echocardiogram during pre-anaesthetic check-up (PAC) prior to surgery.

The included patients were randomised into two groups, "A or B" (1:1 allocation ratio), using a computer-generated random sequence, and concealed via serially numbered sealed-opaque-envelope technique. An investigator performing patient randomization, the investigator assigned to prepare ORS solution/perform preoperative work-up/gastric ultrasound, the supervising anaesthetist, and the outcome assessor remained blinded to other aspects. All patients received similar perioperative care as per standard protocols.

Group A: received 1 litre of reconstituted ORS [Oral rehydration salts sachet (Sodium chloride 2.6 g, Potassium Chloride 1.5 g, Sodium Citrate 2.9 g, Dextrose 13.5 g), Bureau of Pharma PSUs of India, mixed in 1 litre of water], administered overnight after dinner, prior to the planned day of surgery, and up to 2 hrs prior to SA induction next morning.

Group B: kept on traditional overnight fasting (solids and liquids) starting after dinner before the planned day of surgery and continued to SA induction the next morning.

In the preoperative room, IV access was established, and patients received premedication with Ranitidine 50 mg IV and Metoclopramide 10 mg IV. The GRV was measured 1/2 an hour before the scheduled surgery using a curvilinear ultrasound probe (GE parallel Design Inc. Phoenix, US, 4C-RS, Frequency range 2-5 MHz), first under supine and then right lateral position. The GRV was calculated as 27.0 + [14.6 x cross-sectional area (CSA) (cm^2)] - [1.28 x age (years)]. The antral CSA was measured using two perpendicular diameters and the area ellipse formula [CSA = (Anteroposterior diameter x craniocaudal diameter x 22/7)/4].[7] A GRV threshold ≤1.5 mL kg^{-1} was considered adequate to proceed with surgery; if observed GRV was >1.5 mL kg^{-1}, we reassessed such patients on completion of another surgery posted for the day.

Patients who met GRV criteria were shifted to the operation theatre. A multipara monitor, digital 12-lead ECG machine, and Masimo Radical 7 device (Rev E, Masimo Corp., Japan) were attached, IV fluid [Ringer lactate (RL) 15 mL kg^{-1} co-loaded over 30 minutes] started, and baseline parameter recorded. The lower limb electrodes of 12-lead ECG were placed on anterior axillary line, halfway between costal margin and iliac crest, bilaterally. With patients under a seated position, SA was induced at L3-L4/L4-L5 vertebral level with a 25G Quincke spinal needle using hyperbaric Bupivacaine 0.5% (2.5 mL) with Fentanyl 25 µg (0.5 mL) under appropriate aseptic precautions. The time point just after drug injection in a spinal block was taken as "0

min". Patients were then turned supine. The supervising anaesthetist looked after the intraoperative IV fluid need. After the RL co-load, if PVI was >13% over 5 minutes, a 250 mL IV RL bolus was administrated over 10 minutes and repeated until PVI reached ≤13%. If PVI was ≤13%, RL infusion was continued at 2 mL kg^{-1} hr^{-1} IV. Surgery was allowed to proceed after achieving a T10 sensory level to loss of cold sensation to alcohol-soaked gauge. For any hypotensive episode (MAP ≤90% of baseline), patients were treated with IV fluid augmentation (250 mL IV RL bolus) and Phenylephrine 50-100 µg IV bolus, as required. Bradycardia (heart rate ≤50 beats min^{-1}) was treated with. Atropine 0.5 mg IV. Hypoxemia (SPO_2 <94% or respiratory discomfort) was treated with free flow oxygen via facemask. Any hypertensive episode (MAP ≥10% from baseline) was treated with Labetalol 5 mg IV bolus dose.

The primary outcome included ischaemic changes in 12-lead ECG [new-onset T-wave inversion or ST-segment elevation/depression (≥0.1 mm mV)] in any cardiac lead measured at 2, 5, 10, 15 and 30 minutes after SA induction, and compared to baseline PAC ECG. The secondary outcome included PVI/PI measured at the same time points and post-spinal complications (bradycardia, tachycardia, hypotension, hypertension, hypoxia) within first 30 minutes of SA induction. Other recorded variables included preoperative fasting duration, level of sensory block at 20 min after SA induction, intraoperative IV fluid infused, surgery duration, and intraoperative blood loss.

Statistical Analysis

The sample size was calculated using Open-Epi Collection of Epidemiologic Calculator 3.01 (Andrew G. Dean, Kevin M. Sullivan, Atlanta, GA, US). The primary sample size calculation was based on expected 12-lead ECG ischaemic changes (within 30 minutes of SA induction) in 20% of patients receiving preoperative fasting and 2% in those receiving ORS during the fasting phase prior to elective lower limb orthopaedic surgery (pilot observations). Using "Fleiss with CC" model with 95% confidence level and 80% power, the sample size was calculated as 57 per group (114 patients). Considering a 10% dropout, we required 63 patients per group. For statistical analysis, we used a Statistical Package for Social Sciences software 23.0 (SPSS, IBM Corp, Armonk, NY, US). We assessed the normality of data by Kolmogorov-Smirnov test and summarised the results as mean (standard deviation), median (range), or frequency (%). Inter-group comparison for continuous variable was performed by Mann-Whitney U test or Unpaired t-test, as per Gaussian distribution. The categorical variable was analysed by chi-square test or Fisher's exact test. The value of preoperative fasting duration (fluids) in predicting myocardial ischemia (within 30 minutes after SA induction) was analysed by the receiver operating characteristic (ROC) curve. A P value < 0.05 was considered significant.

Results

We included 126 eligible patients over 18 months, with no dropouts (Figure 1). The baseline patient profile was comparable among the groups, with a majority within 60-70-year age group, predominantly males, ASA grade I-II, of average build-up, and significant comorbidity being hypertension. The major indication for surgery included total knee replacement and fracture reduction. The duration of fasting for solids was comparable, while that for fluids was statistically significant among groups. The GRV was well below the threshold criteria in all included patients and comparable among the groups (Table 1).

In total, 20 patients in group B and 7 in group A developed myocardial ECG ischaemic changes within 30 minutes after SA induction. Taking different time points individually, 16 patients in Group B had such changes at 2 and 5 minutes, 20 at 10 minutes, 15 at 15 minutes, and 10 at 30 minutes after SA induction, respectively. In group A, 5 patients had such changes at 2 minutes, 2 at 5 minutes, 4 at 10 minutes, and 3 at 15 and 30 minutes after SA induction, respectively. On intergroup comparison, statistical difference was observed at all studied time points, with highest significance achieved at 10 minutes after SA induction (P < 0.001) (Table 2). The ROC curve had an area-under-curve of 0.74 (confidence interval=0.65-0.81, P < 0.001) at a threshold fasting duration (fluids) of >3 hours to predict myocardial ECG ischaemic changes at any timepoint within 30 minutes of SA induction (sensitivity 96.30%, specificity 55.56%, accuracy 64.29%) (Figure 2). The relative risk (RR) for such changes at the above threshold was 20.80 (2.91-148.58, P=0.002).

A median sensory level of "T8" was noted 20 minutes after SA induction, which was comparable among the

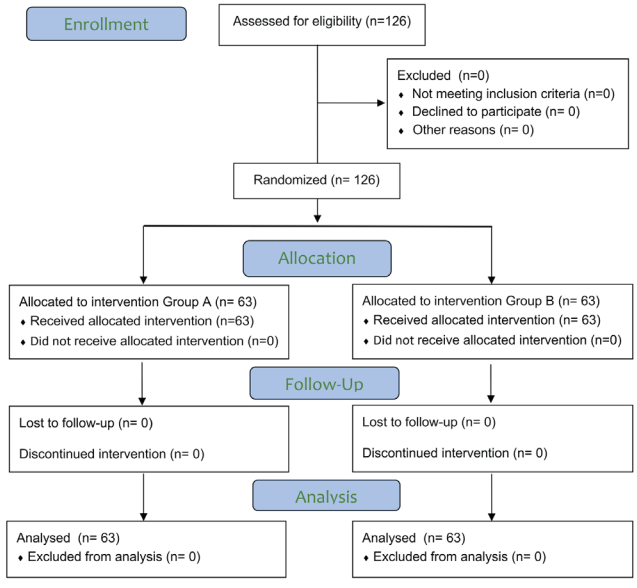

Figure 1. CONSORT flow diagram of patients studied.

groups (Table 1). The PVI was significantly higher in group B as compared to A at all time points ($P < 0.001$); On the contrary, PI was significantly higher in group A at corresponding time points ($P < 0.001$) (Table 2). The major hemodynamic changes within 30 minutes after SA induction included bradycardia in 7 versus 9 patients, tachycardia in 14 versus 26, hypotension in 13 versus 25, and hypoxia in 1 versus 4 patients in Group A and B, respectively. On intergroup comparison, only hypotension (P=0.020) and tachycardia (P=0.022) attained statistical significance (Table 2).

Table 1. The Baseline and Outcome Parameters of the Included Patients (n = 126)

Parameters		Group A	Group B	*P* value
Age (years)		66.32±6.05	66.46± 6.34	0.897
Sex (males)		39 (62%)	34 (54%)	0.367
Height (m)		1.64±0.07	1.63±0.08	0.474
Weight (kg)		62.03±6.02	61.79±8.93	0.861
Comorbidities	Cervical spondylosis	0	1 (2%)	0.482
	COPD	1 (2%)	3 (5%)	
	Hypertension	19 (30%)	24 (38%)	
	Hypothyroidism	5 (8%)	3 (5%)	
	Smoker	11 (17%)	6 (9%)	
	Hepatitis B positive	0	1 (2%)	
ASA status	I	27 (43%)	24 (38%)	0.848
	II	31 (49%)	33 (52%)	
	III	5 (8%)	6 (10%)	
Operative procedure	ACL repair	0	1 (2%)	0.346
	External fixator	1 (2%)	1 (2%)	
	BHA	9 (14%)	8 (13%)	
	Implant removal	6 (9%)	3 (5%)	
	Knee arthrodesis	1 (2%)	0	
	PFN	1 (2%)	0	
	CRIF	15 (24%)	21 (33%)	
	ORIF	7 (11%)	11 (17%)	
	THR	8 (13%)	2 (3%)	
	TKR	15 (23%)	15 (23%)	
	TAR	0	1 (2%)	
Fasting duration (solids) (hours)		12.04±1.69	12.30±2.05	0.436
Fasting duration (fluids) (hours)		2.41±0.60	10.49±2.04	<0.001
GRV before SA induction		47.52±10.34	45.11±11.44	0.217
Sensory level at 20 minutes		T8 (T6-T10)	T8 (T6-T10)	0.102
Intraoperative IV fluid infused (mL)		1784.13±419.37	2004.76±297.12	0.001
Intraoperative blood loss (mL)		510.16±194.65	503.65±191.35	0.850
Duration of surgery (minutes)		161.19±43.60	173.10±54.93	0.180

Values are presented as mean ± SD, frequency (%), or median (range). A P<0.05 is considered significant.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; ACL, anterior cruciate ligament; BHA, bipolar hemi-arthroplasty; PFN, proximal femur nailing; CRIF, closed reduction and internal fixation of fracture; ORIF, open reduction and internal fixation of fracture; THR, total hip replacement; TKR, total knee replacement; TAR, total ankle replacement; GRV, gastric residual volume; SD, standard deviation.

Table 2. Myocardial Electrocardiographic Ischaemic Changes, Perfusion Parameters and Cardiorespiratory Complications Within 30 Minutes of Spinal Anaesthesia Induction Among Included Patients (n = 126)

Parameters		Group A	Group B	*P* value
Myocardial ischaemic changes	2 minutes after SAI	5 (8%)	16 (25%)	0.009
	5 minutes after SAI	2 (3%)	16 (25%)	<0.001
	10 minutes after SAI	4 (6%)	20 (32%)	<0.001
	15 minutes after SAI	3 (5%)	15 (24%)	0.002
	30 minutes after SAI	3 (5%)	10 (16%)	0.040
Pleth variability index	0 minutes after SAI	14.76±2.97	19.87±2.67	<0.001
	2 minutes after SAI	16.14±3.20	21.65±2.32	<0.001
	5 minutes after SAI	17.95±2.96	22.79±1.92	<0.001
	10 minutes after SAI	16.86±3.10	22.97±1.72	<0.001
	15 minutes after SAI	15.54±2.87	21.56±1.63	<0.001
	30 minutes after SAI	14.03±2.42	19.86±1.69	<0.001
Perfusion index	0 minutes after SAI	3.31±4.92	1.62±0.56	<0.001
	2 minutes after SAI	2.45±0.93	1.48±0.50	<0.001
	5 minutes after SAI	2.22±0.89	1.35±0.48	<0.001
	10 minutes after SAI	2.01±0.82	1.29±0.46	<0.001
	15 minutes after SAI	2.13±0.80	1.37±0.44	<0.001
	30 minutes after SAI	2.34±0.78	1.49±0.40	<0.001
Bradycardia		7 (11%)	9 (14%)	0.593
Tachycardia		14 (22%)	26 (41%)	0.022
Hypotension		13 (21%)	25 (40%)	0.020
Hypertension		0	1 (2%)	1.000
Hypoxia		1 (2%)	4 (6%)	0.365

Values are presented as frequency (%) or mean ± standard deviation. A $P<0.05$ is considered significant.
SAI, spinal anaesthesia induction.

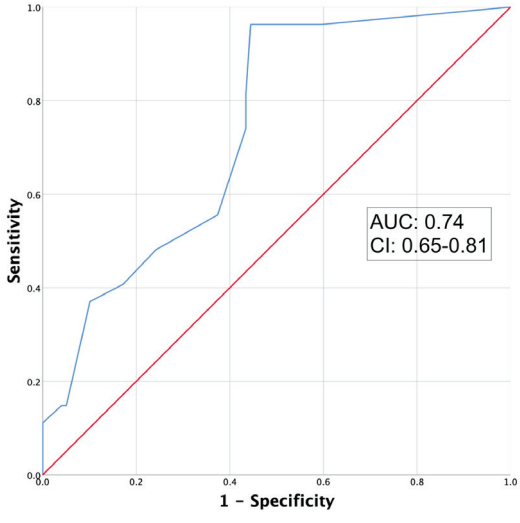

Figure 2. Receiver operating characteristic curve showing the utility of fasting duration (fluids) as predictor of myocardial electrocardiographic ischaemic changes within 30 minutes after spinal anaesthesia induction.

AUC, area under curve; CI, confidence interval.

Discussion

We observed that patients receiving ORS solution during the preoperative fasting phase (for solids) had a significantly lower incidence of transient myocardial ECG ischaemic changes during the first 30 minutes after SA induction compared to those receiving overnight preoperative fasting (both for solids and fluids) for elective lower limb orthopaedic surgery. Its coherence to unstable haemodynamics and abnormal perfusion parameters during the same studied time points further supports the above findings.

During the preoperative fasting phase, body fluids depreciate primarily via insensible fluid loss and urine production, leading to relative hypovolemia. After SA induction, this aggravates post-spinal hypotension, which causes a sudden decrease in coronary artery perfusion pressure and may trigger transient myocardial ischaemia, even if we co-load the patients with IV fluids.[4] This deviation reflects as transient T-wave inversion or ST segment changes in the ECG. An aggravated sympathetic tone resulting from preoperative anxiety and stress may further supplement such changes and consequent complications.[8] We observed that

fasting duration for fluids >3 hours significantly predicted myocardial ischaemic changes in the ECG, including all the studied time points (area under curve=0.74), with high odds ratio (32.5) and hazard ratio (20.8) to predict such changes. The observed changes were significantly high in overnight fasted patients (31.7%) having a fasting duration of 10-14 hours (solids or liquids). Yeniay et al.[4] also observed that prolonged fasting (10-18 hours) was significantly associated with intraoperative cardiac ischaemic changes (20.8%) and decreased mean arterial pressure and heart rate in a similar subset of patients. A higher incidence in our study could be related to a difference in patient demographics, ethnicity, comorbidities, anxiety level and other unaccounted factors. However, both groups were comparable regarding such differences and preoperative preparation.

The degree of dysglycemia is another independent risk factor contributing to ischaemic cardiac events during the perioperative period, especially in diabetic patients.[9] Although preoperative IV glucose supplementation is considered efficacious, a high dosage is required for sufficient insulin release that could minimise catabolic effects.[10] Moreover, IV preload/co-load over short periods, especially in elderly patients, may cause fluid overload with overt complications.[11] Oral replacement is a good alternative if rehydration solution has sufficient carbohydrate concentration (>12.5%) with lower osmolality (265 osmole L) to allow rapid insulin release and gastric emptying.[10] We chose preoperative ORS considering this assumption. Due to its comprehensive postoperative benefits, preoperative carbohydrate drink is now integral to enhanced recovery after surgery protocol for fast-track surgeries.[12] We observed significantly lower post-spinal ischaemic ECG changes in the ORS group. None of the patients in either group complained of notable anginal symptoms, and ECG changes also reverted within an hour of SA induction. Nevertheless, such changes may have particular significance in high-risk groups like diabetes mellitus and coronary artery disease, where cardiac ischaemia may progress to infarction. We noted such changes for only 30 minutes of SA induction to obviate the effects of surgical factors.

We observed a significantly higher incidence of hypotension and tachycardia in the fasted group compared to those receiving preoperative ORS; a significant difference in intraoperative IV fluid infusion further support these findings. We observed most of such episodes within 10 minutes after SA induction, coherent with ischaemic ECG changes in both groups at the "10-minute" time point. Other complications like bradycardia, and hypoxia, though higher in fasted patients, were comparable among groups. Itoh et al.[13] also observed that preoperative ORS significantly minimises a decrease in systolic blood pressure and hypotensive episodes after SA induction. To investigate the effect of dehydration on systemic tissue perfusion, we also measured PI and PVI values at the same time points. The PVI was significantly higher, and PI was significantly lower at all studied time points in fasted patients compared to the ORS group. Emektar et al.[14] also observed that moderate to severe dehydration leads to lower PI and higher PVI values in acute gastroenteritis patients. Tsutsui et al.[15] observed that preoperative ORS increases the circulating blood volume and keeps a higher cardiac index during induction of general anaesthesia, reducing any intraoperative hypotensive episodes. Thus, preoperative dehydration reduces peripheral tissue perfusion, which may also contribute to cardiac ischaemia.

Study Limitations

Our study has a few limitations. We planned to include total knee replacement patients only, but due to the ongoing coronavirus disease-2019 pandemic, we incorporated other elective lower limb orthopaedic surgeries to achieve the desired study sample in a restricted timeframe. However, in view of equivalent intraoperative parameters, this study generates sufficient data highlighting the utility of preoperative ORS in reducing post-spinal myocardial ischaemia. Secondly, preoperative anxiety could also account for such ECG changes. However, routine use of anxiolytics and preoperative counselling in all included patients minimised any intergroup differences. Finally, we could not account for various outcome parameters like perioperative insulin resistance and immune status due to logistic issues. A future trial on a larger sample size may delineate such aspects.

Conclusion

In conclusion, preoperative ORS supplementation significantly reduced the transient post-spinal ischaemic ECG changes in elderly patients compared to conventional overnight fasting, during lower limb orthopaedic surgery. A dedicated perioperative team to care for issues like patient fasting status may add a difference to perioperative outcome, especially in high-risk groups with minimal vital reserve.

Ethics Committee Approval: Ethical approval was obtained from the All India Institute of Medical Sciences, Rishikesh, Institutional Ethics Committee (approval no: 331/IEC/PGM/2020, date: 20.06.2020).

Informed Consent: All study participants gave written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.MJ., G.J.; Design - H.MJ., G.J.; Materials - H.MJ., G.J.; Data Collection and/or Processing - P.G., P.T.; Analysis and/or Interpretation - R.B.K.; Literature Review - H.MJ., G.J.; Writing - H.MJ.; Critical Review - G.J., P.G.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article
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Comparison of Two Different Methods for ProSeal™ Laryngeal Mask Fixation

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Abstract

Objective: This prospective randomized study compared 2 different methods for ProsealTM Laryngeal Mask Airway (PLMA) fixation.

Methods: Patients scheduled for ureterorenoscopic lithotripsy surgery in the lithotomy position were included in the study. General anaesthesia with PLMA was administered to the patients. To achieve PLMA fixation, patients were randomly assigned to either adjustable elastic band (Group I) or adhesive tape fixation (Group II). Fiberoptic bronchoscope (FOB) evaluation and glottic image grading (grade 1-4) and lip margin distances of PLMA (M1 and M2) were evaluated before and after the surgical procedure.

Results: We enrolled 116 patients. Surgery of 7 patients was postponed. PLMA dislocated in 2 patients in group II during positioning. For another patient who used adhesive tape in Group II, it was removed because it could not adhere to properly, and a new sticking plaster was used. The study was completed with 106 patients. In FOB evaluation, the number of patients with optimal FOB grade (FOB grade 1) after PLMA was inserted and fixed was more in Group I than in Group II ($P = 0.01$). FOB evaluation was repeated at the end of the operation, and the number of patients with the worst FOB grade (FOB grade 4) was 0 (0%) and 11 (10.5%) in Groups I and II, respectively. PLMA displaced more than 1 cm in 10 (18.9%) patients in Group I and in 30 patients (56.6%) in Group II.

Conclusion: The adjustable elastic band method is simple, easy, and convenient and can be used in any surgical procedure for PLMA fixation.

Keywords: Airway management, fiberoptic bronchoscopy, fixation, laryngeal mask airway, LMA displacement

Main Points

- Inappropriate fixation of the Proseal™ Laryngeal Mask Airway (PLMA) poses a threat to airway-related complications, such as gastric insufflation, regurgitation, aspiration of gastric contents, and hypoxemia.
- This study presents the fixation method we developed for PLMA.
- Adjustable elastic band reduces PLMA movement and prevents displacement.
- The adjustable elastic band method is simple, convenient and is superior to adhesive tape in patients with traumatized skin, edentulous mouth, or beard.

Introduction

The laryngeal mask airway (LMA) is a useful and safe device in modern anaesthesia. Although LMA insertion is more manageable than an endotracheal tube in various studies, the success rate is 80.6% for the first attempt.[1] Inappropriately placed LMAs pose a threat to airway-related complications, such as gastric regurgitation, aspiration, and hypoxemia.[2] Although the incidence of intraoperative displacement of the first-generation LMAs is 26.7%, no data were found regarding the second-generation LMAs.[3]

The gastric drainage tube and bite block in Proseal™ LMA (PLMA; Intavent Orthofix, Maidenhead, UK), a second-generation LMA, are reported to provide an advantage in keeping it in stable position.[4,5] Appropriate fixation of the PLMA can reduce the risk of device displacement with changes in patient position, especially the head and neck. Different LMA fixation approaches, such as adhesive tape, bandages, and umbilical tape, are used

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with it.[6,7] Inappropriate fixation may cause regurgitation, displacement, and undesirable adverse effects due to adhesive tape or ligation.

Successful PLMA insertion is primarily evaluated clinically, given suitable and sufficient chest excursion, using a capnogram, without a leak at a peak inspiratory pressure of 20 cmH_2O.[2] However, these clinical signs do not guarantee correct positioning and continuity. The direct visual technique using a fiberoptic bronchoscope (FOB) is considered a better alternative for placement than the classic method.[2,8-10]

Our study compared 2 different PLMA fixation methods with FOB examination.

Methods

The study was approved by the Clinical Research Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, University of Health Sciences Turkey (ref: 134/13) on April 4, 2022. Written informed consent was obtained from all patients participating in the trial. In addition, this trial was registered at ClinicalTrials.gov (NCT05433740). This prospective randomized study was conducted between 30 August 2022 and 30 September 2022.

In this prospective randomized single-center study, we included American Society of Anesthesiologists (ASA) I-III patients with Mallampati scores I-II, and ≥18 years of age who underwent elective ureterorenoscopic (URS) lithotripsy surgery. We chose URS to observe the risk of PLMA displacement due to the patients being placed in the lithotomy position. The exclusion criteria were: risk of regurgitation or aspiration (e.g., dysphagia), pulmonary diseases (e.g., chronic bronchitis), body mass index (BMI) of ≥35 kg m^{2-1}, head and neck anomalies, neck movement limitations, inability to open mouth, obstructive sleep apnea, abnormal or loose teeth, mandibular joint movement limitation, and beard.

The patients were transferred to the operating room without premedication. Standard monitoring included noninvasive arterial blood pressure, electrocardiography, and peripheral O_2 saturation. Pre-oxygenation was performed with 100% O_2 with tidal-volume ventilation for 3 min. Induction was performed with intravenous fentanyl 1 μg kg^{-1} and propofol 2 μg kg^{-1}. A neuromuscular blocker was not administered. PLMA size was determined on the basis of patient weight. PLMAs were lubricated using a water-soluble gel and inserted using the index finger. A maximum of 3 attempts were allowed. After 3 failed attempts, the airway was secured as per the decision of the anaesthesiologist. These patients were excluded from the study. PLMA cuffs were inflated as recommended by the manufacturer. Patients were randomized into two groups using the closed envelope method. PLMA was fixed with an adjustable elastic band we designed for Group I and adhesive tape for Group II.

Following LMA insertion, placement was confirmed with clinical tests (chest and bag movement with ventilation, no leak at 20 cmH_2O of airway pressure, and capnogram). Afterwards, LMA was fixed according to the group selection while the patient was in the neutral position. The adjustable elastic band was for single use. With this method, a lacing strap with a button at one end and buttonholes along the band are looped around the bite block section of the outer end of the PLMA. The ends were brought between the tubes over the outer end of the bite block, adjusted at or above the ear (excluding neck vessels), and secured by buttoning in the appropriate hole (Figure 1). In Group II, adhesive tape was fixed to the maxilla (Figure 2). FOB (Karl Storz / Germany, Tuttlingen, Germany, 11302BD2) evaluation and glottic image grading (grade 1-4) and lip margin distances of PLMA (M1 and M2) were assessed before and after the surgical procedure. The same anaesthesiologist performed all PLMA insertions and fixations. However, it was a second anaesthetist who did the FOB review. All fiberoptic evaluations were performed while the tip of the FOB was 1 cm at the end of the ventilation port of the PLMA. The position of the LMA was graded as per the fiber optic scoring system described: 1-glottis seen, 2-epiglottis and glottis seen, 3-epiglottis impinging on the grille, glottis seen, 4-epiglottis

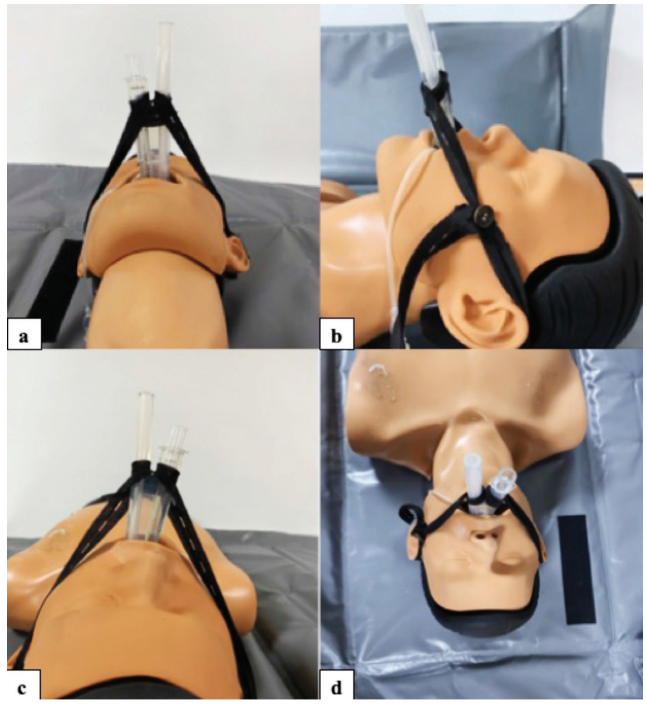

Figure 1. Application of adjustable elastic band method on mannequin; a) Bottom view of adjustable elastic band method, b) Left side view of adjustable elastic band method, c) Top view of adjustable elastic band method, d) Front view of the adjustable elastic band method.

Figure 2. Fixing the PLMA with the adhesive tape method. PLMA, Proseal™ Laryngeal Mask Airway.

downfolded, glottis not seen.[11] After proper placement and fixation of the LMA, the FOB grade was recorded (G1). Then, the lip level measurement of PLMA (M1) was recorded. To avoid the weight of the anaesthesia circuit, the y part of the circuit was connected to the shield separating the anesthesia and surgical areas. Patients were placed in the lithotomy position for surgery. Patients were ventilated with a tidal volume of 6-8 mL kg^{-1} at a rate of 10-14 breaths min^{-1} to maintain $ETCO_2$ between 35 and 40 mmHg. Anaesthesia was maintained with 2 to 2.5% sevoflurane in an oxygen-air (50-50%) mixture. For perioperative analgesia, 0.05 to 0.1 µg kg^{-1} min^{-1} remifentanil infusion was used. PLMA was removed and reinserted in case of a leak at 20 cmH_2O of airway pressure and absence of capnogram, if there was no chest and bag movement with ventilation during the surgery. These patients were excluded from the study. At the end of the surgery, before awakening the patient, on the same anaesthetic depth, after the operating table was taken to the neutral position, FOB grade (G2) and PLMA lip level (M2) measurements were repeated. FOB grade changes between 2 measurements were calculated as G2-G1. The displacement of the PLMA was measured by the difference between M2 and M1.

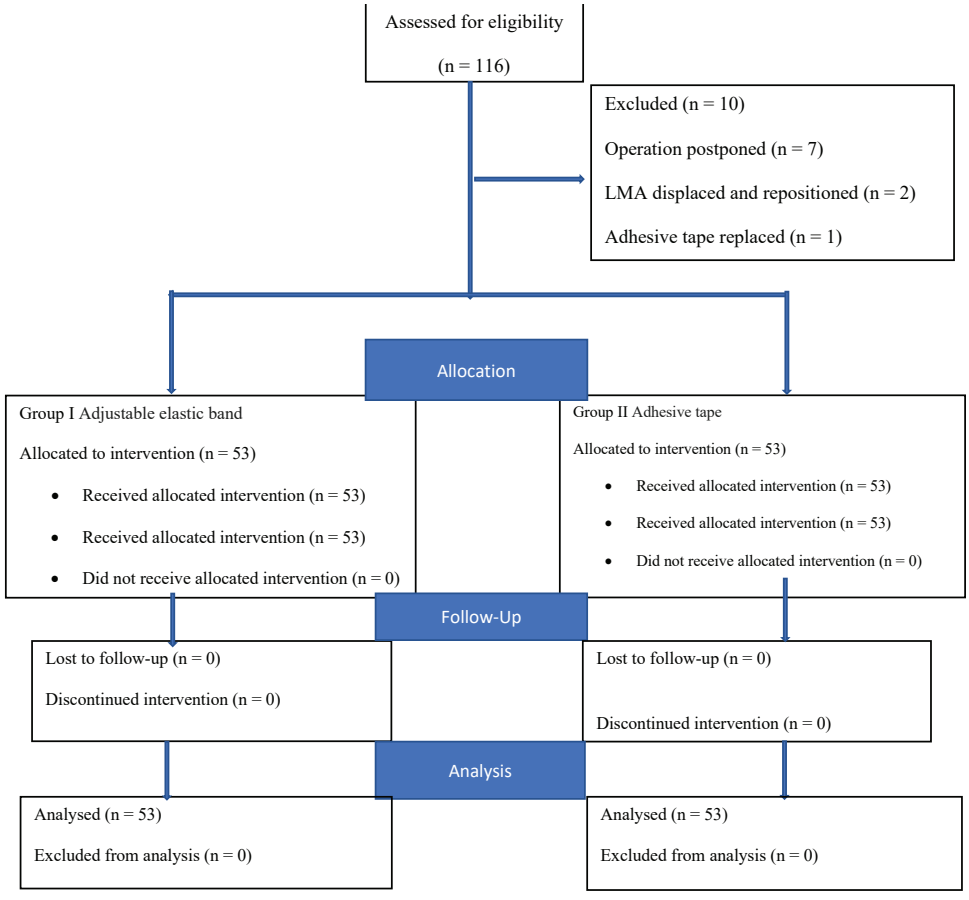

Figure 3. Flow diagram of patients recruitmens.

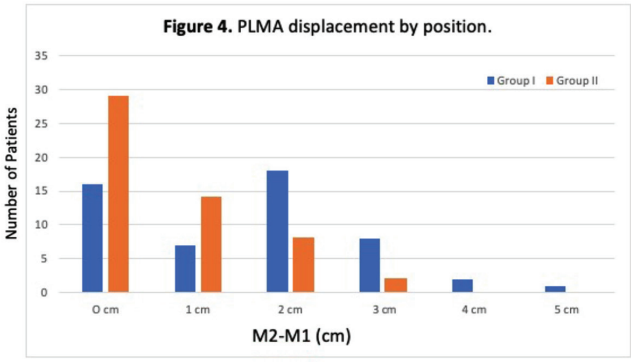

Figure 4. LMA displacement by position.
LMA, laryngeal mask airway; PLMA, Proseal™ Laryngeal Mask Airway.

Age, gender, BMI, ASA score, comorbidity, number of LMA insertion attempts, hemodynamic data, leak volume, peak airway pressure values, FOB grades, PLMA lip alignment levels, and complications related to fixation were recorded for all patients. The difference between the set tidal and exhaled volumes gave the leak volume. Surgery completed, lithotomy position turned to normal position, measurement of the anesthesia team (G2 and M2) done, and after that anesthesia discontinued.

No previous study has used different PLMA stabilization techniques, so the necessary sample size for research was determined with the G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) program before data collection. The minimum sample size was estimated to be 53 patients for each group, with an effect size of 0.5, a power of 80%, and a type I error of 0.05.[12]

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, v. 25.0 (IBM Corp., Armonk, N.Y., USA). Normality assumptions of the data were checked by the Kolmogorov-Smirnov test. Descriptive statistics were presented mean ± SD, median (IQR), frequency (n), and percentage (%) for numerical variables. For the data analysis, an independent 2-group t-test (Student's t-test) was used to compare the two groups, and the Mann-Whitney U test was used when prerequisites were not met. Categorical data were analyzed using Fisher's exact and chi-square tests. After PLMA insertion and removal, parameters were compared for paired ratios using the McNemar and Wilcoxon signed rank tests. $P < 0.05$ was considered to be the statistically significant for these tests.

Results

A total of 116 patients, 58 per group, were registered to allow for dropouts (Figure 3). The surgery of 5 patients in Group I and 2 in Group II was postponed. In two patients in Group II, LMA was displaced and repositioned in attempting to position the patient. For another patient who used adhesive tape in Group II, it was removed because it could not adhere to properly, and a new sticking plaster was used. These patients were excluded; therefore, the study was completed with 106 patients. No intergroup differences were observed in terms of demographic data, ASA classification, and comorbidities. The duration of operations was 48±16.1 min and 47.5±23.5 min for Group I and Group II, respectively (P=0.753) (Table 1). There were no differences in hemodynamic parameters, peak airway pressures, and leak volumes among groups ($P > 0.05$, Table 1). In the FOB evaluation, the vocal cords were more visible in Group I than in Group II at the time of insertion (P=0.01) (Tables 2 and 3). At the end of surgery the FOB evaluation was repeated, and we found that the epiglottis was downfolded in 0 (0%) and 11 (10.5%) patients in Groups I and II, respectively (Tables

Table 1. Characteristics of Patients, Comparison of Hemodynamic Parameters, and Characteristics of Successful Airway Insertion (n = 106)

	Group I (n = 53)	Group II (n = 53)	*P*
Age (year)	51.8±14.9	52.01±16.0	0.935
BMI (kg m$^{2-1}$)	28.2±5.1	28.1±4.9	0.852
Gender			
Male/Female	40/13	38/15	0.410
ASA Classification			
ASA I/II/III	9/38/6	11/37/5	0.659
Comorbidities	30	22	0.120
Cerebrovascular disease	1	0	1.00
Chronic obstructive lung disease	5	2	0.437
Diabetes mellitus	14	10	0.353
Hypertension	9	11	0.620
Coronary artery disease	4	6	0.506
Chronic kidney disease	3	1	0.618
Goiter	2	0	0.495
Systolic Blood Pressure (mmHg)			
After placing the PLMA	120.9±26.2	115.1±25.8	0.256
At the end of surgery	107.8±18.8	111.2±21.6	0.388
Diastolic Blood Pressure (mmHg)			
After placing the PLMA	70.4±16.8	69.1±15.0	0.680
At the end of surgery	66.4±14.7	68.5±15.0	0.481
Mean Blood Pressure (mmHg)			
After placing the PLMA	70.4±16.8	82.5±18.1	0.099
At the end of surgery	66.4±14.7	81.0±16.9	0.448

Table 1. Continued			
Heart rate (beat/min)			
After placing the PLMA	74.1±13.1	71.6±13.2	0.343
At the end of surgery	66.3±12.3	68.5±13.2	0.501
Peripheral oxygen saturation			
After placing the PLMA	98.6±1.1	98.2±1.2	0.399
At the end of surgery	98.8±0.8	98.5±1.6	0.928
End-tidal carbon dioxide			
After placing the PLMA	34.3±2.9	34.3±4.3	0.507
At the end of surgery	33.5±3.5	34.2±4.0	0.410
Peak inspiratory pressure (mmHg)			
After placing the PLMA	14 (13;17)	14 (12;16.5)	0.294
At the end of surgery	16 (14;19)	16 (14;19)	0.427
Leak volume (mL)			
After placing the PLMA	3 (0;10)	5 (0;10)	0.680
At the end of surgery	8 (0;10.5)	10 (0;14)	0.480
Duration of surgery (min)	48.6±16.1	47.5±23.5	0.753

*Pearson chi-square test †Fisher-Freeman-Halton test results. Values are mean ± SD, median (min; max), or frequency.
ASA, American Society of Anesthesiologists; BMI, body mass index; PLMA, proseal laryngeal mask; SD, standard deviation, min, minimum; max, maximum.

Table 2. FOB Evaluation After Insertion Within the Groups			
FOB evaluation after insertion[a]	**Group I (n = 53)**	**Group II (n = 53)**	***P***
Grade 1	43 (81.1%)	30 (56.6%)	0.06
Grade 2	10 (18.9%)	23 (43.4%)	

Values are number (%).
[a]The glottic view via fiberoptic examination was scored using the following: Grade 1, glottis seen; 2, epiglottis and glottis seen; 3, epiglottis impinging on the grille, glottis seen; 4, epiglottis downfolded, glottis not seen.
FOB, fiberoptic bronchoscopy.

Table 3. FOB Evaluation Before LMA Removal Within the Groups			
FOB evaluation before LMA removal[a]	**Group I (n = 53)**	**Group II (n = 53)**	***P***
Grade 1	37 (69.8%)	16 (30.2%)	<0.001
Grade 2	15 (28.3%)	12 (22.6%)	
Grade 3	1 (1.9%)	14 (26.4%)	
Grade 4	0	11 (20.8%)	

Values are number (%).
[a]The glottic view via fiberoptic examination was scored using the following: Grade 1, glottis seen; 2, epiglottis and glottis seen; 3, epiglottis impinging on the grille, glottis seen; 4, epiglottis downfolded, glottis not seen.
PLMA, proseal laryngeal mask; FOB, fiberoptic bronchoscopy.

2 and 3). The G2-G1 difference was significantly higher in Group II than in Group I (86.8%, 41.5%, $P < 0.001$, respectively) (Table 4). The PLMA displacement distances for each fixation method are graphically shown in Figure 4. The adjustable elastic band significantly reduced PLMA movement compared with adhesive tape. Thirty patients (46.6%) experienced more than 1 cm PLMA movement when adhesive tape was used to secure the LMA against 10 (18.9%) when an adjustable elastic band was used ($P < 0.001$). No complications were observed in patients who used adjustable elastic bands.

Table 4. Comparison of FOB Grade Within the Groups			
G2-G1	**Grup I (n = 53)**	**Grup II (n = 53)**	***P***
0	46 (86.8%)	22 (41.5%)	0.016
1	7 (13.2%)	12 (22.6%)	
2	0 (0)	18 (34%)	
3	0 (0)	1 (1.9%)	

Values are number (%). G1, FOB evaluation after insertion; G2, FOB evaluation before LMA removal. G2-G1, FOB grade differences between FOB evaluations.
LMA, laryngeal mask airway; FOB, fiberoptic bronchoscopy.

Discussion

In this study, we compared the adjustable elastic band that we designed for PLMA fixation with adhesive tape. This band significantly reduced the mobility of the PLMA and provided better fixation than the adhesive tape.

Studies have emphasized that proper initial LMA insertion and fixation are important in maintaining the LMA position.[8] In our study, even at the fixation stage, the visibility of the vocal cords was better after PLMA insertion with adjustable elastic band fixation than that with adhesive tape. For proper placement, the distal end of the LMA must fit tightly against the upper esophageal sphincter (UOS).[7] Inward force with PLMA fixation reduces the possibility of extrusion and misplacement.[7] As such, the correct approach for fixing the PLMA in place is to apply the ends of the adhesive tape to the maxilla.[7] Our study fixed the PLMA to the maxilla in the adhesive tape group. However, when evaluated with FOB, we observed that the vocal cords were visible in only 56.6% of patients with adhesive tape, whereas visibility was 81.1% with the adjustable elastic band method. These results suggest that the adjustable elastic band method is more effective for PLMA fixation. Studies investigating ideal positioning of LMA by FOB in children show that although ventilation is clinically normal, only 12 to 50% of LMAs are properly positioned.[13-15] These studies did not investigate different fixation methods but only different LMA placement methods. They used adhesive tape for all patients. As a result, we think the bands may not have exerted pressure in the required inward direction to

ensure that the distal end of the mask was pressed against the UOS.

In our study, we observed that the fiberoptic view changed less in the adjustable elastic band group than in the adhesive tape group at the end of surgery. All patients' vocal cords were visible in the adjustable elastic band group after surgery. However, visibility of the vocal cords could not be attained with FOB in 11 (10.5%) patients in the adhesive tape group, suggesting that the elastic band does not fully prevent displacement: deviation of the LMA cuff to one side can cause this issue.[3] However, there were no symptoms of leakage, and ventilation was optimal in both groups. Chandan et al.[10] reported that ventilation was clinically optimal in all patients, although the cuff position was optimal in only 56.7% of patients at the time of insertion. Another study examined how head and neck position affected the cuff position and oropharyngeal sealing pressure of the LMA in children; it was observed that airway patency was not adversely affected in 97% of patients.[16] However, complete or partial obstruction of the glottic aperture by the epiglottis might result in increased work of breathing, especially in spontaneous breathing cases or children.[17] Although the FOB view changed within groups, no audible leak was detected at a pressure of 20 cmH_2O, and no negative effect on ventilation was observed. Nevertheless, these patients were adults, and spontaneous breathing was not permitted. We cannot generalize the results of this study to spontaneously breathing adults or children, since hypopharyngeal muscular tension can alter LMA positioning; it may be thought that adequate clinical ventilation parameters do not indicate an anatomically or properly placed LMA.

In our study, the adjustable elastic band reduced extreme (>1 cm) PLMA movements, in contrast to the adhesive tape. During anaesthesia maintenance, PLMA ordinarily provides an appropriate airway; position adjustment is infrequently necessary. Nevertheless, displacement may occur, especially if anaesthesia becomes light, the patient moves, or the surgical position changes. Major intraoperative LMA displacement is not frequent, but minor events can occur; which can cause regurgitation, aspiration, or partial laryngeal obstruction.[15] When positive pressure ventilation is used, the increased airflow resistance may lead to higher airway pressure and opening of the UOS, increasing the risk of regurgitation.[13] Thus, it can be assumed that the fixation method affects the major or minor displacement of the PLMA.

Inappropriate fixation of the PLMA can lead to complications such as device displacement, increased work of breathing, hypoxemia, gastric inflation, regurgitation, and aspiration. In this study, no complications related to the fixation method were observed in the adjustable elastic ligament group. In the adhesive tape group, for 3 patients, the PLMA was removed from the patient during positioning or the sticking plaster was repeated.

This may be caused by contamination of the adhesive tape by patient secretions or by the weight of the breathing circuit and loosening of the tape. Studies comparing endotracheal tube fixation methods have shown that adhesive tape may not provide adequate protection for unintentional extubation.[18-22] There are case reports about LMA fixation methods in the literature, but we could not find studies comparing them. Our study found that the adjustable elastic band did not allow outward displacement of the PLMA and fixed it more securely than the adhesive tape. Adhesive tape allergy, burned, traumatized or loose skin, edentation of the mouth as in the elderly, or facial hair may limit the use of adhesive tape for PLMA fixation.[6] Forces applied to a taped PLMA deform and pull facial tissues, causing important PLMA movements without adhesive failure.[22] This may cause displacement of the PLMA. PLMA secured with adjustable elastic ligament was fixed between bony structures that did not move under such loads, while protecting venous neck structures. We believe that this may be an advantage in patients with loose skin, edentulous mouth, or beards. Along with avoiding the disadvantages of adhesive tape, we found that this method offered better control over the applied pressure.

Study Limitations

The inability to hide the PLMA fixation method from the observer can be considered a limitation of our study. In addition, this method may not be applicable to every patient due to economic reasons and the lack of materials. Observing only patients in the lithotomy position is another limitation. The positive contribution of this fixation method to PLMA mobility can be supported by creating different surgical positions, longer surgery times, or patients with different BMIs.

Conclusion

To our knowledge, this is the first study to compare LMA fixation methods. Our results indicate that the adjustable elastic band reduces PLMA movement and may prevent displacement. The adjustable elastic band method is simple, easy, and convenient and can be used in any surgical procedure for PLMA fixation. In addition, we believe that the method is superior to adhesive tape in patients with adhesive tape allergy, burnt or traumatized skin, edentulous mouth, or beard, and in cases in which PLMA fixation can be challenging due to blood, sweat, mouth, and facial secretions. In addition, this method can make a significant contribution in cases where the lithotomy position or the table position is frequently changed during the procedure.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, University of Health Sciences Turkey (ref: 134/13) on April 4, 2022.

Informed Consent: Written informed consent was obtained from all patients participating in the trial.

Peer-review: Internally and externally peer-reviewed.

Author Contributions: Concept - G.K.; Design - A.D.; Supervision - G.K.; Fundings - F.A.; Materials - G.K.; Data Collection and/or Processing - F.A., Y.E.; Analysis and/or Interpretation - A.D.; Literature Review - F.K.A.; Writing - F.A.; Critical Review - A.D.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

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Continuous Serratus - Intercostal Plane Block for Perioperative Analgesia in Upper Abdominal Surgeries: A Prospective Randomized Controlled Study

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Abstract

Objective: Acute pain management after open abdominal surgeries is an essential goal in perioperative management.. Recently, serratus-intercostal plane block (SIPB) was suggested as an analgesic technique for upper abdominal surgeries.

Methods: This prospective, randomized, controlled study included sixty adult patients scheduled for open upper abdominal surgeries. Patients were allocated into two equal groups: SIPB group (S group, n = 30) and control group (the C group, n = 30). In the S group, SIPB was performed in the midaxillary line at the eighth rib level followed by continuous infusion of local anaesthetic for the first postoperative day. In the C group, no block was done. The primary objective of the study was to control postoperative pain on the first postoperative day as assessed by the numerical rating scale (NRS). Secondary outcomes included perioperative hemodynamics, total postoperative analgesic consumption, number of analgesic requests, and incidence of postoperative nausea and vomiting.

Results: The mean postoperative NRS reported in group S was statistically lower than that in group C (2.4±0.7, 3.9±0.31, $P < 0.001$). The postoperative morphine consumption was lower in the S group than in the C group [(0 (0-4), 3 (1-4), respectively, $P < 0.001$]. The incidence of PONV was significantly lower in the S group than in the C group (16.7% and 40%, $P < 0.045$).

Conclusion: SIPB was associated with a better analgesic profile compared with the control group after upper abdominal surgeries. Further studies are recommended to determine block safety in special patient groups, including bariatric and laparoscopic surgeries.

Keywords: Abdominal surgery, analgesia, block, pain, regional anaesthesia

Main Points

- Upper abdominal incisions are associated with substantial postoperative pain.
- Technical difficulties, hemodynamic effects, and contraindications in certain groups of patients limit the use of most regional techniques.
- Recently, the serratus-intercostal plane block (SIPB) was reported as an effective analgesic technique for upper abdominal surgeries.
- This study investigated the perioperative analgesic effect of continuous SIPB plane block with the hypothesis that the block will offer an adequate analgesic option for patients undergoing elective open abdominal surgeries.

Introduction

Upper abdominal incisions are associated with a substantial degree of postoperative pain, which is associated with higher rates of postoperative complications, delayed ambulation, and prolonged hospital stay. Diverse analgesic modalities have been used to control pain after abdominal surgeries; including neuraxial techniques, abdominal wall block, and systemic analgesics.[1,2]

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The epidural technique, which is the gold standard analgesia technique for abdominal surgeries, is limited by technical difficulties, hemodynamic effects, and contraindications in certain groups of patients.[3] As an alternative, abdominal wall blocks have been used for different open and laparoscopic abdominal surgeries; however, the ambiguity of the sonographic view in obese patients and the fear of iatrogenic injury to the viscera could complicate the procedure.[4]

Recently, few studies have reported serratus-intercostal plane block (SIPB) as an effective analgesic technique for upper abdominal surgeries. The diffusion of local anaesthetic (LA) in this fascial plane blocks the cutaneous branches of the 7th to the 11th intercostal nerves, providing adequate analgesia for the control of pain after upper abdominal surgeries.[5] The suggested advantages of SIPB include the ease of the technique, the solid landmarks, and the possible administration in the supine position.[6]

In this study, continuous SIPB; using catheter technique was investigated as an adequate analgesic option for patients undergoing elective open abdominal surgeries. The primary objective of the study was to control postoperative pain assessed by the numerical rating scale (NRS) on the first postoperative day. Secondary outcomes included perioperative hemodynamics, postoperative analgesic consumption, number of postoperative analgesic requests, and postoperative nausea and vomiting (PONV).

Methods

This prospective, randomized, controlled study was conducted after Medical Research Ethics Committee, Institutional Review Board of Mansoura University approval (approval no: R.21.02.1217, date: 03.04.2021) and clinical trial registry (PACTR202105543447214). Informed consent was obtained from eligible candidates, including all adult patients of American Society of Anaesthesiologists physical status I and II, who were scheduled for open abdominal surgeries through a unilateral incision. Patients with chest wall deformities, neuromuscular disease, and a known allergy to the study medications were excluded from the study.

Randomization

A randomization list, in blocks of 10, was used to allocate patients into two equal groups (Sealed Envelope.com, Seed no. 64866366541202)[7]; SIPB Group (S group, n = 30) and control group (C group, n = 30). All patients were subjected to routine preoperative assessment, including medical history, physical examination, and laboratory investigations, and additional assessment was performed as per attending anaesthesiologist's recommendations. All included patients were educated about the use of a 10-mm NRS for pain assessment (0 mm= no pain, and 10= the worst possible pain).

General Anaesthesia

Upon arrival to the operative room, patients were monitored using basic monitors [heart rate (HR), non-invasive arterial blood pressure, and peripheral oxygen saturation]. General anaesthesia was induced by intravenous (IV) administration of 2 μ kg^{-1} of fentanyl, 1-2 mg kg^{-1} of propofol, and 0.5 mg kg^{-1} of atracurium. A properly sized endotracheal tube was inserted and fixed in place after confirmation of correct positioning. Anaesthesia was maintained using sevoflurane in 40% oxygen-air mixture.

Block Procedure

After ensuring patient stability, the study protocol was applied according to the allocation sequence. In the S group, under aseptic conditions, with the patient lying supine, the linear probe (Toshiba Xario, Japan, PLT 805AT transducer) was placed sagittally at the 8th rib in the midaxillary line. An 80-mm Tuohy needle was introduced via an in-plane approach until the needle tip was adjacent to the 8th rib between the serratus and external intercostal muscles. A test for correct placement of the needle was performed using 2-3 mL of normal saline, and then 20 mL of 0.25% bupivacaine was injected between the external intercostal and the serratus anterior muscle after negative blood aspiration. After bolus injection, a 20-gauge catheter (Perifix® Epidural anaesthesia catheter, Braun Medical Inc., USA) was inserted into the interfacial plane and fixed in place using adhesive tape (Figure 1).

Perioperative Analgesia

After catheter insertion and fixation, a continuous infusion of 0.125% bupivacaine was initiated, at a rate of 4 mL h, through the catheter using an elastomeric infusion pump

(Disposable infusion pump, Zhejiang Fert medical device Co., China- 100 mL capacity, 0.5 mL bolus, lock time 15 minutes), with no injection was performed in C group.

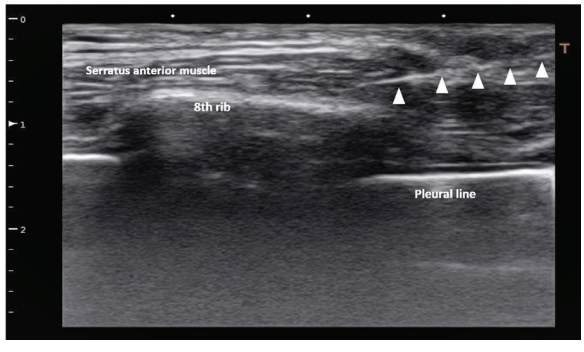

Figure 1. Ultrasound view for the SIPB block, showing the 8th rib with the covering Serratus muscle layer, and the tip of the catheter floating in the local anaesthesia bolus.

SIPB, serratus-intercostal plane block.

For both groups, IV 50 µg fentanyl bolus was administered when intraoperative rescue analgesia was deemed indicated by the attending anaesthetist or if the hemodynamic measurements increased by >20% of the basal recording (in the absence of other causes). Additionally, 1 g of acetaminophen was given 30-minutes before skin closure in both groups. After skin closure, the patient was extubated upon fulfilling the extubation criteria and adequate reversal of the muscle relaxant. The postoperative analgesia order included regular IV paracetamol (1 g/6 h) administered to all patients. If postoperative NRS ≥4, a rescue dose of IV morphine (0.02 mg kg^{-1}) was administered. Patients were admitted to a high dependency unit for 24 h monitoring after surgery. Thereafter, the catheter was removed and its site was inspected for any sign of edema, redness, hematoma, or discharge.

Outcomes

The collected data included patient age, weight, height, gender, type of surgery, perioperative hemodynamics (HR, MAP) measured at induction, 15 min, 30 min, and hourly until end of surgery, analgesic bolus requirements, NRS (at 0, 2, 4, 8, 12, and 24 h after surgery), analgesic bolus requirements, incidence of PONV, and any catheter site complications. Data were collected and recorded by an independent nurse trained in the study protocol.

Sample Size Calculation and Statistical Analysis

Depending on the results of a previous study,[8] the mean postoperative pain score after upper abdominal surgeries was (NRS 4.8±1.6). Adopting a 25% reduction of the mean pain score after SIPB as an accepted effect size to attain a study power of 0.80 with an alpha error of 0.05; 27 patients per group were required. Adapting for 10% dropout, 30 patients were sufficient. G*power software version 3.1.9.7 was used for the sample size calculation.

IBM SPSS (USA) version 22 was used for statistical analysis of the collected data. Data were explored for normality of distribution and presented as mean ± standard deviation, median (minimum-maximum), or number (percentage). Statistical differences between the two studied groups were analyzed using the independent samples t-test, Mann-Whitney test, or chi-square test as appropriate. *P* value was considered significant if less than 0.05.

Results

In this study, 63 patients scheduled for open upper abdominal surgery through a unilateral incision were recruited from the study from May 2021 to July 2022. As shown in Figure 2, three patients were excluded from the study. The included patients were randomly divided into two groups: 30 patients each.

Patient basal data and perioperative characteristics, duration, incision type, and type of surgery were comparable between the two groups (Table 1). Perioperative hemodynamics are shown in Figures 3 and 4. Intraoperative hemodynamics [HR and mean blood pressure (MBP)] showed statistically significant lower readings in group S. Postoperative hemodynamic readings continued to be lower in group S despite could not reach statistical significance except for the MBP reading for the second postoperative hour.

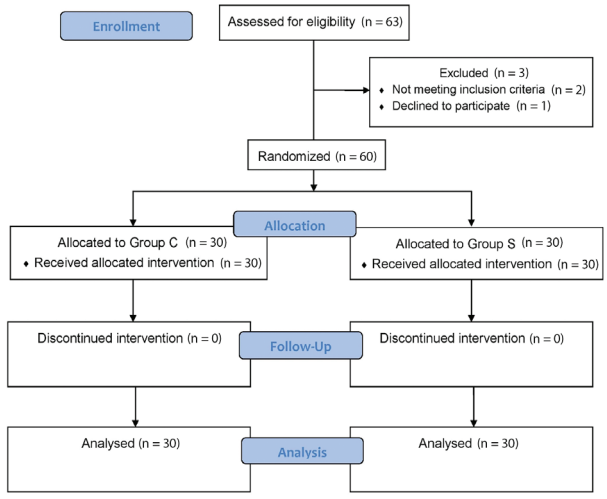

Figure 2. Study consort chart.

Table 1. Patients' Basal Characteristics, Duration and Type of Surgery in the Two Studied Groups

	Group S (n = 30)	Group C (n = 30)
Age (years)	51.4±15.1	54.8±13.7
Weight (kg)	78.2±13.1	79±9.9
Height (cm)	164.9±6.4	166.6±4.8
Gender (M/F) (n)	16/14	18/12
ASA physical status (I/II)	19/11	20/10
Type of incision n (%)		
- Right transverse incision	23 (76.6%)	24 (80%)
- Left transverse incision	7 (24%)	6 (20%)
Type of surgery n (%)		
- Hepatobiliary surgery	15 (50%)	12 (40%)
- Pancreatic surgery	3 (10%)	4 (13.3%)
- Splenic surgery	7 (23.3%)	11 (36.7%)
- Parietal surgery	5 (16.7%)	3 (10%)
Duration of surgery (min)	130.6±38.9	151.9±54.6

Data are presented as mean ± standard deviation, numbers, or numbers (percentage).
M, male; F, female; n, absolute number.

Table 2 shows the intraoperative and postoperative analgesic profiles for the two studied groups. The number of intraoperative analgesic boluses was statistically lower in group S [0 (0-1), 1 (0-2), *P < 0.001*]. Postoperatively, the reported NRS was statistically lower in group S than in group C at 0, 2, 4, 8 hours after surgery. Likewise, a statistically significant reduction in both the mean postoperative NRS value and the total postoperative morphine consumption (mg) was noticed lower in group S than in group C [(2.4±0.7 vs. 3.9±0.31, *P < 0.001*, 0 (0-4) 3 (1.4-4.1), *P < 0.001*, respectively]. In addition, Table 2 shows a statistically lower incidence of PONV in group S than in group C (16.7% and 40%, *P* 0.045 respectively).

None of the cases in group S showed any edema, redness, hematoma, or discharge at the site of catheter insertion.

Table 2. Analgesic Profile and the Incidence of PONV in the Two Studied Groups

	Group S (n = 30)	Group C (n = 30)	*P* value
Number of intraoperative fentanyl boluses (n)	0 (0-1)*	1 (0-2)	<0.001
Postoperative pain scores			
- NRS 1h	1.5±0.8*	2.4±0.5	<0.001
- NRS 2h	1.9±1*	3.3±0.61	<0.001
- NRS 4h	2.6±1.1*	5.4±0.7	<0.001
- NRS 8h	2.9±1*	6.3±0.65	<0.001
- NRS 12h	3.2±0.98	3.4±0.56	0.204
- NRS 24h	2.3±0.95	2.7±0.56	0.081
Mean postoperative NRS	2.4±0.7*	3.9±0.31	<0.001
Postoperative morphine consumption (mg)	0 (0-4)*	3 (1.4-4.1)	<0.001
PONV n (%)	5 (17%)*	12 (40%)	0.045

Data are presented as median (minimum-maximum), mean ± SD. **P* value is significant if <0.05.
PONV, postoperative nausea and vomiting; n, absolute number; NRS, numerical rating scale for pain.

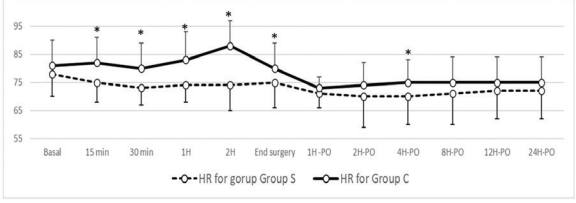

Figure 3. Perioperative heart rate in the two studied groups.

***Indicates *P* value of less than 0.05.**
Bpm, beat per minute; HR, heart rate.

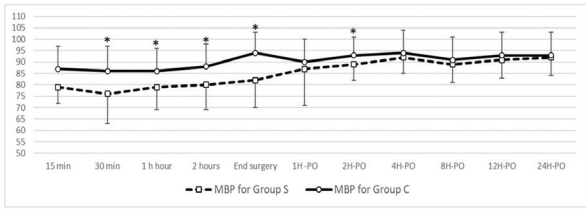

Figure 4. Perioperative mean arterial pressure in the two studied groups.

***Indicates *P* value of less than 0.05.**
MBP, mean blood pressure.

Discussion

In this study, continuous SIPB was used for perioperative analgesia open abdominal surgeries through a unilateral incision. Compared with IV opioid, SIPB showed a better analgesia profile, less postoperative morphine consumption and decreased incidence of PONV. To the best of our knowledge, this is the first study to apply continuous SIPB for analgesia after unilateral abdominal incisions.

Acute pain management after open abdominal surgeries is an essential goal in perioperative management, especially in the era of enhanced recovery programs.[9,10] Inadequate analgesia is associated with higher rates of postoperative complications, delayed ambulation, and prolonged hospital stay.[11]

Analgesic practices for abdominal incisions include a wide range of techniques. IV analgesics either bolus or continuous infusion were associated with respiratory depression, delayed intestinal motility, and PONV. Opioid crisis worldwide have triggered the use of opioid-saving strategies, including neuraxial, regional, and facial plane blocks.[1,8,10,12-15]

Neuraxial analgesic techniques, including intrathecal, epidural and paravertebral blocks, have proven to have great analgesic efficacy. Nevertheless, neuraxial procedures are considered technically difficult, and they also carry some risk in special groups of patients, e.g., stenotic valve diseaser receiving anticoagulants.[16,17]

Facial plane blocks, such as transversus abdominal plane (TAP) and rectus sheath blocks, have been proven to decrease pain scores after abdominal surgeries, especially with the evolution of ultrasound technology. However, difficulties are usually encountered in obese patients and in patients with previous incisions that obscure the proper visualization of the interfacial planes or are even disturbing. In addition, preemptive use of TAP block can cause escape of LA outside the targeted space after surgical incision. In addition, serious complications such as vascular injury, abdominal visceral injury, liver trauma, and nerve injuries have been reported.[18-20]

The first description of SIPB was in 2013[21] using the acronym BRILMA block (Blocking the branches of intercostal nerves in the middle axillary line). Advancement of the technique follows, with subsequent modification to target the lower intercostal nerves at the level of the 8th rib; modified BRILMA block. The block was effective for somatic analgesia after gastrectomy and cholecystectomy in a small series of cases.[21,22] Afterwards, more than one study reported the effectiveness of SIPB for open upper abdominal surgeries.[5,8,23] SIPB lacks an analgesic effect on visceral pain, yet control of the somatic component of postoperative pain can result in satisfactory pain scores and minimize the required rescue analgesics.

Several studies have used the SIPB bolus technique for analgesia after unilateral abdominal surgeries.[5,8,21,22,24] Compared with the oblique subcostal TAB block; SIPB compared with the rectus sheath block significantly improved the quality of analgesia and lowered the analgesic requirement in patients undergoing laparoscopic cholecystectomy.[5] Interestingly, bilateral SIPB was effectively used as a rescue analgesia after bariatric surgery, achieving an adequate NRS pain score after 10 min and lasting for 46 hours.[24]

In a prospective randomized study, 102 patients were divided into a control group receiving IV morphine and an interventional group receiving SIPB. The SIPB group showed lower pain scores, lower postoperative opioid consumption and improved quality of recovery (QoR-15 scores) 24 h postoperatively.[23]

PONV is an important patient outcome that was recorded in our study and was found to be significantly lower in patients who received SIPB. This can be explained by the lower postoperative opioid consumption, which is included in the Apfel score as one of the risk factors for PONV.[25] Lower PONV can increase patient satisfaction and shorten the in-hospital length of stay.[26]

Study Limitations

Limitations of the study included the heterogeneous group of patients with different surgical approaches and incisions and variable pain profiles. However, this can support the wide applicability and effectiveness of the SIPB. Secondly, the use of an elastomeric pump, which has a fixed preset infusion rate, should be used in all patients, rather than individualized. Nevertheless, simplicity, non-electricity, and better patient mobilization motivated the authors to use an elastomeric pump instead of electricity-driven syringe pumps. Assessment of dermatomal distribution of analgesia was limited by the surgical wound and dressing. The serum level of LA was not measured in our study, the LA concentration reached after bolus and continuous infusion in SIPB can assess the degree of systemic absorption, verify block safety, and help determine the mechanism of action of the block. A double-blind protocol could avoid data collection bias and the placebo effect; nevertheless, this could not be achieved in this study because of the nature of the intervention.

Conclusion

Continuous SIPB can be added to the arsenal of analgesic techniques used for analgesia after abdominal surgeries with a unilateral incision. In our study, SIPB was associated with a better analgesic profile and lower analgesic consumption. Further studies are recommended to determine block safety in special patient groups, including bariatric and laparoscopic surgeries.

Ethics Committee Approval: Ethical clearance was given by the Medical Research Ethics Committee, Institutional Review Board of Mansoura University (approval no: R.21.02.1217, date: 03.04.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.K.A., M.M.M.; Design - A.K.A., M.M.M.; Data Collection and/or Processing - M.M.M.; Analysis and/or Interpretation - A.K.A., M.M.M.; Literature Review - M.A.A.; Writing - A.K.A., M.A.A.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article
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Serum Cholinesterase, C-reactive Protein, Interleukin 6, and Procalcitonin Levels as Predictors of Mortality in Patients in the Intensive Care Unit

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Abstract

Objective: The prognostic utility of inflammatory markers in survival has been suggested in patients with cancer; however, evidence on their prognostic value in severely ill patients is very limited. We aimed to explore the prognostic value of cholinesterase (ChE), C-reactive protein (CRP), interleukin-6 (IL-6), and procalcitonin (PCT) in predicting mortality in patients from the intensive care unit (ICU).

Methods: Serum levels of ChE, CRP, IL-6 and PCT were measured in ICU patients from December 13th, 2019 to June 28th, 2022. We assessed the predictive power of ChE, CRP, IL-6, and PCT using the receiver operating characteristic (ROC) curves. Furthermore, we evaluated their diagnostic accuracy by comparing the areas under the ROC curve (AUCs) along with their corresponding 95% confidence intervals (CIs). The cut-off values were determined to dichotomise these biomarkers, which were then included in multivariable logistic regression models to examine their relationship with ICU mortality.

Results: Among 253 ICU patients included in the study, 66 (26%) died during the ICU stay. The AUCs to predict ICU mortality were 0.643 (95% CI, 0.566-0.719), 0.648 (95% CI, 0.633-0.735), 0.643 (95% CI, 0.563-0.723) and 0.735 (95% CI, 0.664-0.807) for ChE, CRP, IL-6 and PCT, respectively. After adjusting for age, sex and disease severity, lower ChE level ($<3.668 \times 10^3$ U L^{-1}) and higher levels of CRP (>10.546 mg dL^{-1}), IL-6 (>986.245 pg mL^{-1}) and PCT (>0.505 µg L^{-1}) were associated with higher mortality risk, with odd ratios of 2.70 (95% CI, 1.32-5.54), 4.99 (95% CI, 2.41-10.38), 3.24 (95% CI, 1.54-6.78) and 3.67 (95% CI, 1.45-9.95), respectively.

Conclusion: ChE, CRP, IL-6 and PCT were independent ICU mortality risk factors in severely ill patients. Elevated PCT levels exhibited better predictive value than the other three biomarkers that were evaluated.

Keywords: Cholinesterase, C-reactive protein, intensive care, interleukin-6, procalcitonin

Main Points

- Critically ill patients who did not survive in the intensive care unit exhibited elevated levels of C-reactive protein (CRP), interleukin-6 (IL-6), and procalcitonin (PCT), while their cholinesterase (ChE) levels were decreased.
- Serum PCT levels may have a better prognostic value compared to ChE, CRP and IL-6 in critically ill patients.
- Special attention should be given to the quality of care for critically ill patients at high risk of nosocomial infection.

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Introduction

Patients who are hospitalized in the intensive care unit (ICU) as a result of severe illness or injury face a greater risk of mortality when compared to other patients receiving inpatient care. One prospective, multi-centre study in China reported a hospital mortality rate of 20.3% in ICU settings.[1] Patients in the ICU consume a large proportion of medical resources; therefore, identifying critically ill patients with higher likelihood of mortality is important for resource allocation as well as for improvement in quality of care in clinical practice. Nosocomial infections and severe sepsis are major contributors to mortality in patients in the ICU and provide better access points for interventions compared to other mortality risk factors such as advanced age, disease severity, and mechanical ventilation.[2] Thus, identifying biomarkers of infection and sepsis are important for initiating appropriate treatments at an early stage and predicting prognosis.

The traditionally used markers of infection and sepsis include C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin (PCT). CRP, the most commonly used marker of acute inflammation, is a valuable tool in monitoring treatment response.[3] IL-6 is an early predictor that can indicate inflammation before the elevation of circulating CRP levels.[4] In addition, PCT has been proposed as the most valuable marker of infection as it is a better indicator of the severity of systemic inflammatory response compared to other biomarkers.[5] Although PCT, IL-6 and several other inflammatory markers have been regarded as prognostic indicators of survival in patients with cancer, evidence on their prognostic value in septic patients in the ICU is very limited and inconsistent.[6,7]

In addition to the classic inflammatory biomarkers, several novel markers such as cholinesterase (ChE) have been considered as predictive factors for mortality. Serum ChE is primarily synthesised in hepatocytes before its release into peripheral blood.[8] ChE activity is reduced in severe clinical conditions such as liver dysfunction, malnutrition, heart disease, sepsis, inflammation, stress and cancer.[8,9] The serum level of ChE has been reported to inversely correlate with levels of inflammatory biomarkers such as IL-6 and tumour necrosis factor α.[10] Furthermore, ChE has been demonstrated to be related with mortality and complications in patients with stroke,[11] cancer[12] or in those undergoing surgery.[13] Therefore, serum ChE level is often used as a routine biochemical parameter in clinical diagnostic procedures. However, no study to date has examined changes in serum ChE level in ICU patients and its prognostic value for mortality remains unclear.

In the present study involving patients admitted to the ICU, we measured serum ChE levels and examined its correlation with CRP, IL-6 and PCT. We also compared the prognostic value of these biomarkers in predicting mortality among ICU patients.

Methods

Study Population

From December 13th, 2019 to June 28th, 2022, we conducted a cohort study in the ICU of Shengli Oilfield Central Hospital, Shangdong, China. A total of 299 ICU patients were randomly selected. Patients who were under 18 years of age; those who were immunocompromised due to malignancy, human immunodeficiency virus infection or other reasons; those who were pregnant; and those who were without legal representatives or were unable to provide written informed consent were excluded. The final study cohort included 253 patients, who were followed from the date of ICU admission until death due to any cause or until ICU discharge. The study was approved by the Ethics Committee of Shengli Oilfield Central Hospital (no. Q/ZXYY-ZY-YWB-LL202149).

Sample Collection and Laboratory Tests

After ICU admission, a 5 mL peripheral venous blood sample was collected from each patient via venipuncture. The collected samples were then centrifuged at 3500 r min for 5 min, and the resulting serum samples were stored at a temperature of -80 °C for subsequent analyses. To determine serum CRP levels, we used a commercially available CRP test kit (Mindray, Shenzhen, China) based on the immunoturbidimetric method. IL-6 and PCT levels were measured by electrochemiluminescence using the Elecsys IL-6 and BRAHMS PCT (Roche) kits, respectively. Serum ChE levels were determined using a kit from Shanghai Gao Chuang Medical Technology, Shanghai, China based on the butyrylthiocholine method.

Data Collection

The following data were collected: dates of ICU admission and discharge, age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score and underlying indications for ICU admission. The outcome of interest was all-cause ICU mortality.

Statistical Analysis

Comparisons of continuous variables between the survival and non-survival groups were performed using the Mann-Whitney U or Student's t-test, and comparisons of categorical variables between the two groups were performed using the χ^2 test or Fisher's exact test. Correlations of ChE with CRP, IL-6, and PCT was evaluated by Spearman's nonparametric correlation coefficient (rho).

The ability of CRP, IL-6, PCT and ChE levels to predict mortality was measured by using receiver operation characteristic curves (ROCs). The cutoff values were determined by maximum area under the ROC curve (AUC), and sensitivity and specificity were calculated for each biomarker. ROC comparisons were conducted using a nonparametric method.

Cutoff values were used to dichotomise CRP, IL-6, PCT and ChE, which were then included in the logistic regression model to examine their relationship with all-cause ICU mortality. The multivariable logistic regression model was adjusted for patient age, sex and disease severity determined by APACHE II score. To investigate whether the relationship of inflammatory markers with ICU mortality differed by sex, the study patients were stratified by sex and its interaction with biomarkers was analysed by including the interaction term.

All statistical tests were two-sided with an α-level of 0.05. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 5.3.0.

Results

Overall Cohort Characteristics

In the present study, 66 of the 253 patients (26%) did not survive. Compared to the survivors, the non-survivors were more likely to be older males and to have higher APACHE II scores (Table 1). Median serum ChE level was lower in the non-survivors than in the survivors [2.93 (2.23-3.83) × 10^3 U L^{-1} vs. 3.87 (2.80-5.41) × 10^3 U L^{-1}). In contrast, compared to the survivors, the non-survivors had significantly higher serum levels of CRP [11.48 (6.87-16.99) vs. 8.24 (4.37-10.72) mg dL^{-1}], IL-6 [815.86 (100.01-3916.66) vs. 190.67 (44.68-799.97) pg mL^{-1}] and PCT [0.81 (0.53-1.93) vs. 0.25 (0.07-0.72) μg L^{-1}]. Serum ChE level was significantly correlated with CRP (rho, -0.22; $P < 0.001$), IL-6 (rho, -0.16; $P=0.009$) and PCT (rho, -0.15; $P=0.01$).

ROC Analysis

In analyses to evaluate the ability of inflammatory biomarkers in predicting ICU mortality revealed that the AUCs of ChE, CRP, IL-6 and PCT were 0.643 [95% confidence interval (CI), 0.566-0.719], 0.648 (95% CI, 0.633-0.735), 0.643 (95% CI, 0.563-0.723) and 0.735 (95% CI, 0.664-0.807), respectively (Figure 1). The optimal cut-off values of ChE, CRP, IL-6 and PCT for ICU mortality were 3.668 × 10^3 U L^{-1} (sensitivity, 74.2%; specificity, 55.6%), 10.546 mg dL^{-1} (sensitivity, 59.1%; specificity, 73.8%), 986.245 pg mL^{-1} (sensitivity, 50.0%; specificity, 79.1%) and 0.505 μg L^{-1} (sensitivity, 78.8%; specificity, 70.1%), respectively. Comparison of the ROC curves revealed no significant difference in the clinical values of ChE and CRP ($P=0.93$) or those of cholinesterase and IL-6 ($P=0.99$), although the clinical values of ChE and PCT exhibited a marginally significant difference ($P=0.06$).

Relationship Between Inflammatory Markers and Mortality

In logistic regression including the dichotomised values of study biomarkers according to the optimal cutoff values

Table 1. Characteristics of Survivors and Non-Survivors in the Intensive Care Unit

Variables	Survivors (n = 187)	Non-Survivors (n = 66)	*P* value
Age (years)	65 (51-73)	79 (72-83)	0.03
Sex, n (%)			
Male	115 (61.5)	50 (75.8)	0.04
Female	71 (38.5)	16 (24.2)	
APACHE II score, median (IQR)	26 (20-33)	40 (32-47)	<0.001
Infection type, n (%)			
Respiratory infection	95 (50.8)	37 (56.1)	0.11
Abdominal infection	42 (22.5)	17 (25.8)	
Urinary tract infection	17 (0.09)	6 (0.1)	
Inflammatory biomarkers, median (IQR)			
ChE (×103 U L^{-1})	3.87 (2.80-5.41)	2.93 (2.23-3.83)	<0.001
CRP (mg dL^{-1})	8.24 (4.37-10.72)	11.48 (6.87-16.99)	<0.001
IL-6 (pg mL^{-1})	190.67 (44.68-799.97)	815.86 (100.01-3916.66)	<0.001
PCT (μg L^{-1})	0.25 (0.07-0.72)	0.81 (0.53-1.93)	<0.001

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; IQR, interquartile range; ChE, cholinesterase; IL-6, interleukin-6; CRP, C-reactive protein; PCT procalcitonin.

revealed that patients with low ChE levels (≤3.668 × 10^3 U L^{-1}) were at higher risk of ICU mortality than these with high ChE levels [adjusted odds ratio (OR), 2.70; 95% CI, 1.32-5.54] (Table 2). Additionally, patients with higher serum levels of CRP (>10.546 mg dL^{-1}), IL-6 (>986.245 pg mL^{-1}) or PCT (>0.505 µg L^{-1}) were at higher risk of ICU mortality than those with low levels of these biomarkers, with adjusted ORs of 4.99 (2.41-10.38), 3.24 (1.54-6.78) and 3.67 (1.45-9.95), respectively.

Analysis of ICU Mortality Stratified by Sex

Cholinesterase, IL-6 and PCT did not significantly interact with patient sex for ICU mortality risk (*P*=0.94, *P*=0.50 and *P*=0.25, respectively), whereas CRP did (*P*=0.04) (Table 3). The adjusted ORs for ChE and CRP were higher in female patients than in male patients, although the 95% CIs were wider due to limited number of women. Moreover, the relationship between IL-6 and ICU mortality risk was slightly stronger in male patients than in female patients.

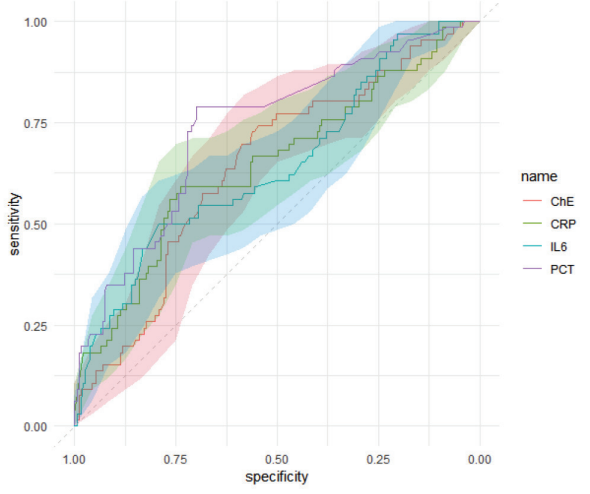

Figure 1. Receiver operating characteristic curve analysis for predicting mortality in the intensive care unit according to serum levels of cholinesterase, interleukin-6, C-reactive protein and procalcitonin.

ChE, cholinesterase; IL-6, interleukin-6; CRP, C-reactive protein; PCT, procalcitonin.

Table 2. Relationship of ChE, CRP, IL-6 and PCT With Mortality in Patients in the Intensive Care Unit

Inflammatory markers	Cut-off value	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
ChE (×10^3 U L^{-1})	3.668	3.61 (1.94-6.73)	2.70 (1.32-5.54)
CRP (mg dL^{-1})	10.546	4.07 (2.26-7.33)	4.99 (2.41-10.38)
IL-6 (pg mL^{-1})	986.245	3.79 (2.09-6.90)	3.24 (1.54-6.78)
PCT (µg L^{-1})	0.505	4.69 (2.45-8.95)	3.67 (1.45-9.95)

[a]Adjusted for age, sex, and Acute Physiology and Chronic Health Evaluation II score.
ChE, cholinesterase; IL-6, interleukin-6; CRP, C-reactive protein; PCT procalcitonin; AUC, area under the receiver operating characteristic curve; OR, odds ratio; CI, confidence interval.

Discussion

In the present study evaluating critically ill patients in the ICU, the mortality rate was 26%, which was comparable to that reported in other countries (17-38%).[1,14] Nosocomial infection is a major contributor of ICU mortality. Therefore, special attention should be given to the quality of care for patients who are at high risk of nosocomial infection. The utilization of inflammatory biomarkers in screening procedures can aid in evaluating the risk of mortality among ICU patients.

In the present study, we explored the clinical diagnostic value of CRP, IL-6 and PCT in ICU patients, as well as that of ChE as a potential novel biomarker. In our findings, we observed higher serum levels of CRP, IL-6, and PCT, along with lower levels of ChE, in non-surviving patients when compared to the survivors. The ROC curve analyses revealed that the AUC was greatest for PCT. Patients with ChE, CRP, IL-6 or PCT levels of <3.67 × 10^3 U L^{-1}, >10.55 mg dL^{-1}, >986.25 pg mL^{-1} or >0.51 µg L^{-1}, respectively, were at increased risk of ICU mortality even after taking control of patients' age, sex and the APACHE II score. In addition, the risk magnitudes for ChE and CRP were stronger in female patients than in male patients.

In patients with liver dysfunction, the activity of ChE, a crucial enzyme, is decreased due to reduced synthesis, in contrast to other serum enzymes whose activity levels are elevated due to cell membrane damage and the subsequent cellular release.[15] Additionally, decreased ChE activity was recently reported to be closely associated with malnutrition, cancer and severe inflammation.[9,12,13] However, the value of ChE activity as a diagnostic tool for mortality prognosis is often overlooked in ICU settings. To our best of knowledge, the present study is the first to investigate the association between serum ChE levels and ICU mortality risk. Our results demonstrating the significant and inverse correlation of ChE with the other three inflammatory biomarkers, i.e. CRP, IL-6 and PCT, are in line with the findings of a previous study.[10] Surprisingly, serum ChE levels were not decreased in the non-survivor patients in the present study. The ROC curve analysis indicated that the sensitivity and specificity of ChE at a cut-off value of <3.67 × 10^3 U L^{-1} were not high enough for its utility as a diagnostic marker in the ICU. Nevertheless, ChE, as a dichotomised variable, was associated with increased ICU mortality risk regardless of age, sex or disease severity. Therefore, ChE might be considered as a potential tool to assist clinicians in the prognostic evaluation of patients in the ICU.

Table 3. Relationship of ChE, CRP, IL-6 and PCT with Mortality in the Intensive Care Unit in Patients Stratified by Sex

Inflammatory markers	Median (IQR)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Male patients (n = 165)			
ChE ($\times 10^3$ U L^{-1})	3.67 (2.48-5.07)	3.86 (1.88-7.94)	2.57 (1.13-5.86)
CRP (mg dL^{-1})	8.41 (4.71-13.67)	2.81 (1.41-5.59)	2.85 (1.24-6.56)
IL-6 (pg mL^{-1})	214.34 (75.07-1100.00)	4.33 (2.11-8.89)	3.61 (1.50-8.72)
PCT (µg L^{-1})	0.32 (0.16-1.00)	5.93 (2.63-10.34)	4.75 (1.91-11.95)
Female patients (n = 88)			
ChE ($\times 10^3$ U L^{-1})	3.41 (2.42-5.10)	4.10 (1.08-15.61)	3.45 (0.75-15.86)
CRP (mg dL^{-1})	9.67 (6.22-14.45)	7.02 (3.57-12.07)	7.59 (5.40-15.77)
IL-6 (pg mL^{-1})	181.53 (44.35-999.00)	2.72 (0.88-8.45)	2.52 (0.64-9.78)
PCT (µg L^{-1})	0.43 (0.17-1.06)	2.25 (1.23-8.53)	4.61 (0.75-12.11)

[a]Adjusted for age and Acute Physiology and Chronic Health Evaluation II score.
IQR, interquartile range; ChE, cholinesterase; IL-6, interleukin-6; CRP, C-reactive protein; PCT procalcitonin; AUC, area under the receiver operating characteristic curve; OR, odds ratio; CI, confidence interval.

CRP, IL-6 and PCT are well-known inflammatory markers; however, evidence on their potential as predictors of ICU mortality is limited. In one study including four ICUs in China, the serum level of CRP, but not PCT, was associated with mortality.[6] Furthermore, the inclusion of serum CRP as a prognostic predictor improved risk reclassification. The cut-off CRP and PCT values used in that study were slightly lower than those found in the present study, which might be due to the higher rate of infection in the current study cohort. Another study in Germany reported that IL-6, rather than PCT or CRP, might potentially serve as a reliable predictor of mortality during the early stage of ICU patients with the early onset of fever;[4] however, the authors also stated that the prognostic value of PCT might be better than that of IL-6 in patients with established SIRS and sepsis. In the present study, the sensitivity and specificity of PCT in predicting ICU mortality were 78.8% and 70.1% at a cutoff value of 0.5 µg L^{-1}, which was comparable to that reported by the study in Germany. Therefore, our findings suggest that PCT has better prognostic value than ChE, CRP and IL-6 in critically ill patients. Nevertheless, our analyses also suggest serum CRP, IL-6 and PCT as plausible risk factors based on their association with increased ICU mortality risk after controlling for potential confounders.

Study Limitations

This study has several limitations to be noted. First, this was a single-centre study with a small sample size and lacked power to evaluate the predictive value of these four biomarkers when used in combination. Second, information on some important confounders, such as socio-economic status, body mass index, preexisting clinical conditions and relevant treatments, was not available for analyses in the present study.

Conclusion

Altered serum levels of ChE, CRP, IL-6 and PCT were associated with increased risk of ICU mortality in severely ill patients. Elevated PCT level may be useful as a prognostic marker in these patients. Further studies with larger cohorts are warranted to improve the predictive values of these four biomarkers used in combination.

Ethics Committee Approval: The study was approved by the Ethics Committee of Shengli Oilfield Central Hospital (no. Q/ZXYY-ZY-YWB-LL202149)

Informed Consent: All study participants gave written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - X.W.; Concept - N.W., L.Q.; Design - N.W., L.Q.; Data Collection and/or Processing - Q.L.; Analysis and/or Interpretation - X.F., Z.Z.; Literature Review - W.C.; Writing - Q.L., X.F.

Declaration of Interests: The authors have no conflict of interest to declare.

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Effect of Preoperative Anxiety on Depth of Anaesthesia and In Vitro Fertilization Success

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Abstract

Objective: Infertility anxiety may have a harmful effect on embryo quality and fertilization during in vitro fertilization (IVF). Monitoring brain function gives real-time information about the depth of anaesthesia of a patient. This study examined the effect of preoperative anxiety on the depth of anaesthesia and IVF success.

Methods: One hundred thirty-one patients who had undergone oocyte retrieval were divided into two groups according to the Beck Anxiety Inventory (BAI): the low-anxious Group L (n = 71) and high-anxious Group H (n = 60). Hemodynamic stability, intraoperative total propofol and fentanyl consumption, good quality embryo (GQE) rate, and fertilization rate were recorded.

Results: Fertilization and GQE rates were not significant between groups L and H. Total propofol consumption was significantly higher in group H than in group L. Heart rate (HR) preoperatively and postoperatively and systolic arterial pressure (SAP) preoperatively and diastolic arterial pressure (DAP) postoperatively were significantly increased in group H than in group L. The time for the modified Aldrete score to reach 9 (MAS 9) in group H was significantly higher than that in group L. The effect of variables that were found significantly in the univariate analysis (Propofol, HRpreop, HRpostop, SAPpreop, DAPpostop, and MAS 9) on BAI score.

Conclusion: Total propofol consumption was higher in patients with high anxiety levels, but it did not have a negative effect on IVF success.

Keywords: Anxiety, depth of anaesthesia, monitoring of brain function, oocyte retrieval, sedation

Main Points

- Infertility is usually accompanied by psychological and behavioral changes and can result in postoperative anxiety.
- Monitoring brain function gives real-time information about the depth of anaesthesia of a patient.
- The increased total anaesthetic drug consumption under monitoring brain function does not have any negative effect on the fertilization rate, embryo quality, and/or pregnancy rate.

Introduction

Anxiety is common in women undergoing infertility treatment. Psychological and behavioral changes can often accompany infertility and cause pre-operative anxiety.[1] Therefore, when these women are hospitalized for oocyte retrieval, the degree of anxiety can be much higher. The absence of premedication before oocyte retrieval may further increase anxiety. In addition, this situation can negatively affect the total consumption of analgesics and

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anaesthetic drugs and recovery from anaesthesia. The impact of anaesthetic agents on embryo quality and fertilization has not been clearly definite until today. Previous studies have described different results concerning the negative effects of anaesthetic drugs on fertilization and embryo development.[2-7]

Propofol is an excellent drug for outpatient surgery. The level of propofol that is spread in follicular fluid is indicated to increase in proportion to the total dose of propofol consumed.[2,4] Studies examining the effect of propofol on in vitro fertilization (IVF) technologies have reported conflicting results during the studies.[8,9]

Opiates are generally used with propofol for sedation during oocyte retrieval. Soussis et al.[6] reported low follicular fluid concentrations of fentanyl and alfentanil during transvaginal oocyte retrieval in patients, but they did not find any difference between the groups in terms of fertilization rate or pregnancy rate. In a study, general anaesthesia versus sedation with remifentanil for assisted reproduction was compared, and the pregnancy rate in the group under general anaesthesia was found to be significantly lower.[10]

Monitoring brain function gives real-time information about the depth of anaesthesia of a patient. Brain function monitoring helps reduce anxiety by prevention awareness and the harmful effects of a low dose of anaesthesia. Previous studies have demonstrated the effects of many factors on pregnancy rates and oocyte number during IVF treatment.[11,12] However, the effect of anxiety level with anaesthetic drugs on embryo and oocyte quality during IVF in women undergoing sedation has not yet been studied. We aimed to examine the effect of preoperative anxiety on depth of anaesthesia, embryo quality, fertilization, and pregnancy rates.

Methods

This prospective, single-center, double-blind study was approved by the local ethical committee, was conducted in patients who underwent surgery at Trakya University (ClinicalTrials.gov Identifier: NCT03134651). The patients were informed about the study and their written approval was obtained. A total of 131 adult patients with American Society of Anesthesiologists physical status I-II, aged 25-43 years, and who were scheduled for oocyte retrieval under sedation were enrolled in this study. The exclusion criteria were; (1) unable to communicate well in the native language, (2) secondary infertility can be surgically corrected, (3) history of psychiatric illness, (4) women who necessitated general anaesthesia.

Clinical Evaluation and the Method

The anaesthesiologists evaluated all patients the day before the surgery at the surgical clinic. Patient characteristics (age, body mass index, duration of surgery, smoker, alcohol, reason for infertility, etc.) were recorded. Beck's Anxiety Inventory (BAI) consists of questions concerning 21 symptoms of cognitive and somatic anxiety. The responses of the patients were rated on a scale from 0 to 3, and the highest score was 63. The validity and reliability of this test translated into the Turkish has been approved by Ulusoy et al.[13] The cut-off score of 17 was determined for BAI. All data from the study were gathered by two anaesthesiologists. The first anaesthetist evaluated the BAI score in patients and recorded the results. Patients were separated into two groups according to the pre- procedure BAI score: Group L (low-anxiety group) and Group H (the high-anxiety group). The BAI scores of the low-anxiety group are equal to or less than 17 and those of the high-anxiety group are more than 17.[13,14] Intraoperative and postoperative data were recorded by a second anaesthetist.

All women in this study were fasting for 8 h and none received premedication (opioid, antiemetic, sedative). Electrocardiogram, pulse oximetry (SpO_2 in %), non-invasive blood pressure, axillary temperature (T), and end-tidal carbon dioxide were used for standard monitoring in the operating room. The Patient State Index (PSI) SEDLine (Masimo Inc., California, USA) sensor was placed simultaneously with other standard monitors before the induction of anaesthesia. In all women, pre-oxygenation was administered via face mask during the procedure. After preoxygenation, all patients received 1.5 mcg kg^{-1} fentanyl and a 2-3 mg kg^{-1} propofol bolus for induction. Anaesthesia was maintained with an infusion of 150 µg kg^{-1} min propofol. The anaesthesiologist applied 0.5-1.0 mg kg^{-1} propofol boluses to keep PSI values between 40 and 60. Respiration was supported by manual ventilation or oxygenation during the procedure.

PSI, heart rate (HR), SpO2, diastolic arterial pressure (DAP), and systolic arterial pressure (SAP) were recorded at baseline, 15 min, and postoperatively. The postoperative sedation score was evaluated using the Ramsay Sedation Scale (RSS). At the end of the process, the operation time and total propofol and fentanyl consumption were recorded.

Propofol infusion was discontinued 5 min before the completion of the surgical procedure. The patients were sent to the recovery unit after spontaneous breathing and cognitive functions were assessed. Nausea, vomiting, agitation, and tremors were recorded by an independent investigator throughout the procedure.

The modified Aldrete score (MAS) was used to assess patients' recovery from anaesthesia. These parameters are rated on a scale from 0 to 2. MAS was recorded every 3 min in the recovery unit. When the MAS was equal to or more than 9, patients were transferred to the clinic. The time for MAS to reach 9 was recorded. Patients were assessed

for pain using the visual analog scale (VAS) at 1, 2, and 4 h postoperatively by an anaesthesiologist who was not included in this study. Oral acetaminophen at 500 mg was used as a rescue analgesic when VAS scores were more than 4 in each of the two groups within 4 h.

Ovarian Stimulation

Antagonist cycles were performed in all women. When adequate stimulation was achieved, human chorionic gonadotropin was administered. The oocyte retrieval procedure was performed using a single lumen aspiration needle (Reproline, Rheinbach, Germany). All cycles were intracytoplasmic sperm injection cycles. After 2-5 days, one or two embryos were transferred. A pregnancy test was performed on the 12th day after embryo transfer. Clinical pregnancy was evaluated and confirmed by ultrasound, 3 weeks after embryo transfer.

In this study, the fertilization rate and good quality embryo (GQE) rate were investigated in patients who had undergone oocyte retrieval. The fertilization rate was described as follows: number of fertilized oocytes (=2 pronuclei, PN)/ The number of retrieved oocytes. The GQE rate was calculated as follows: the number of GQEs/The number of 2 PN zygotes. A GQE was described as having one to four to six cells on the 2nd day, 6-10 cells on the 3rd day with <20% fragmentation and no multinucleation, and finally a tightly packed inner cell mass and trophectoderm cells in a cohesive layer on the 5th day.[7] The fertilization and GQE rates were calculated per patient. Pregnancy rate was the secondary outcome.

Statistical Analysis

The sample size was 64 patients in each group to detect a middle effect size (d=0.5) in the number of oocytes retrieved between the high and low BAI score groups with an alpha level of 5% and power of 80%. The normality distribution of all numeric variables was tested using the one-sample Kolmogorov-Smirnov test. Variables that were normally distributed between the high and low BAI score groups were compared using Student's t-test. Categorical data were compared using the chi-square test. Variables that were non-normally distributed between the high and low BAI score groups were compared using the Mann-Whitney U test. The effect of variables that were found to be significant in the univariate analysis (Propofol, HR_{preop}, HR_{postop}, SAP_{preop}, DAP_{postop}, and MAS 9) on BAI score was investigated using multivariate logistic regression analysis. A *P* value of 0.05 was set as statistically significant.

Results

One hundred thirty-five patients were included in this study, four patients dropped out because of the necessity of general anaesthesia. Therefore, 131 patients were analyzed according to the protocol (Figure 1). There was no statistically significant difference between the groups with respect to body mass index, age, duration of surgery, and patient characteristics (Table 1).

HR preoperatively and postoperatively and SAP preoperatively and DAP postoperatively were significantly increased in group H than in group L (P=0.002, P < 0.046, P < 0.040, and P < 0.025, respectively). PSI values and SpO_2 preoperatively were similar in groups L and H.

Total propofol consumption was significantly higher in group H than in group L (P=0.006). Total fentanyl consumption and VAS scores were not significantly different between the groups (Table 2).

MAS 9 was significantly increased in group H than in group L (P < 0.001). Postoperative RSS was not significant between groups (Table 3). The side effects are presented in Table 3. The groups were similar with respect to nausea, agitation, and shivering. None of the patients in the two groups suffered other side effects (rash, dizziness, headache, or allergic reaction).

The effects of propofol, HR_{preop}, HR_{postop}, SAP_{preop}, DAP_{postop}, and the time for MAS to reach 9 on the BAI score were investigated through multivariate logistic regression analysis. HR_{preop} and MAS to reach 9 were found to be related factors with a high BAI score (P=0.020 and P=0.001, respectively). According to the results of the multivariate logistic regression model, when HR_{preop} [odds ratio (OR)=1.049: 95% confidence interval (CI): 1.008-1.092] and MAS reach time 9 (OR=1.503; 95% CI: 1.179-1.916) increases the risk of high BAI score increases.

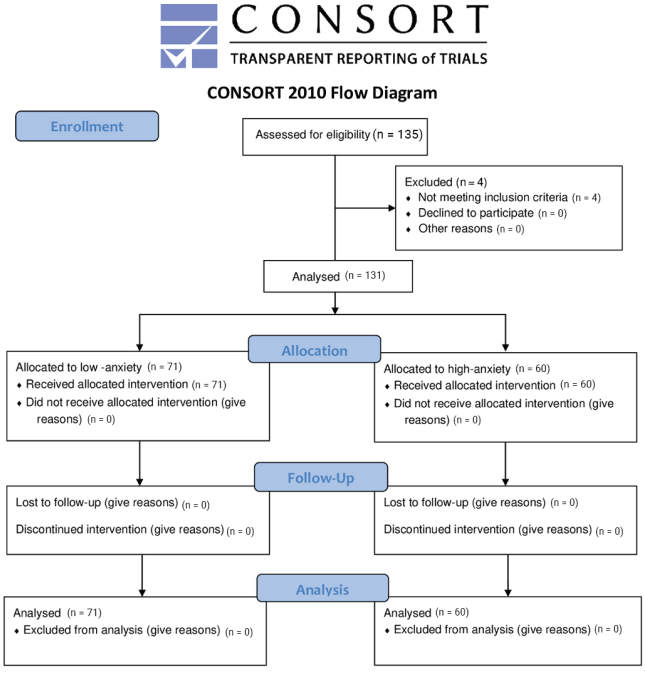

Figure 1. Flow diagram.

The fertilization and GQE rates were not significantly different between groups L and H (*P*=0.848, *P*=0.349, respectively). The mean number of embryos transferred, day of embryo transfer, and pregnancy rate was similar between the groups (Table 4).

Table 1. Demographic, Surgery Data and Patient Characteristics

	Group L (n = 71)	Group H (n = 60)	*P* value
Age (years)	33.8±5.2	34.4±5.6	0.583
BMI (kg m^2)	25.2±3.7	24.3±3.6	0.181
Duration of surgery (min)	17.9±3.3	18.4±3.8	0.547
Smoker, (yes/no)	15/56	12/48	1.000
Alcohol, (yes/no)	5/66	1/59	0.218
Reason for infertility			
Tubal factor, (yes/no)	10/61	8/52	1.000
Endometriosis, (yes/no)	2/69	0/60	0.500
Ovulatory factor, (yes/no)	0/71	3/57	0.093
Male factor, (yes/no)	16/55	11/49	0.707
Unexplained, (yes/no)	28/43	17/43	0.251
Low oocyte reserve, (yes/no)	17/54	23/37	0.112
Previously IVF, (yes/no)	18/44	10/42	0.355
Previously miscarriages, (yes/no)	12/56	4/54	0.325
Previously pregnancies, (yes/no)	12/55	4/53	0.387
Previously deliveries, (yes/no)	2/68	1/17	0.590

Data are mean ± SD or number of patients. No significant differences were noted between the groups.
BMI, Body Mass Index; IVF, in vitro fertilization

Table 2. Total Intraoperative Propofol and Fentanyl Consumption and Post-Operative VAS Scores

	Group L (n = 71)	Group H (n = 60)	*P* value
Total propofol consumption (mg)	199±32.8	217.8±37.3	0.006*
Total fentanyl consumption (mg)	46.8±8.4	49.2±4.5	0.056
VAS 0 h	0.8±0.7	0.8±0.7	0.864
VAS 1 h	0.7±0.5	0.8±0.5	0.862
VAS 2 h	0.7±0.7	0.7±0.8	0.672
VAS 4 h	0.6±0.7	0.9±0.9	0.109

Data are mean ± SD. *Statistically significant.
VAS, visual analogue scale; SD, standard deviation.

Table 3. Postoperative Recovery and Side Effects by Groups

	Group L (n = 71)	Group H (n = 60)	*P* value
MAS 9 time (min)	9.6±1.6	11.4±2.3	<0.001*
RSS (Postoperative)	1.9±0.8	1.9±0.6	0.584
Nausea	2/69	2/58	1.000
Vomiting	0/71	0/60	-
Agitation	0/71	3/57	0.093
Shivering	2/69	5/55	0.246
Other	0/71	0/60	-

Data are mean ± SD or number of patients. *Statistically significant.
MAS, modified Aldrete score; RSS, Ramsay sedation scale.

Table 4. Oocyte and Embryo Quality by Groups

	Group L (n = 71)	Group H (n = 60)	*P* value
No. of oocytes retrieved	6.2±5.5	6.2±6.5	0.570
No. of 2PN	3.6±3.3	3.4±4.1	0.230
Fertilization Rate (No. 2PN/No. of oocytes retrieved)	0.8±0.2	0.7±0.3	0.848
No.of embryos transfered	1.1±0.6	1±0.7	0.487
No.of frozen embryos	0.7±1.7	0.5±1.3	0.424
Day of embryo transfer	2.3±1.1	2.2±1.2	0.833
No.of GQE (No. of embryos transfered + No. of frozen embryos)	1.8±1.9	1.5±1.5	0.457
GQE rate (No. of GQE/No. of 2PN)	0.6±0.4	0.6±0.3	0.349
e1-c	6.2±2.2	6.3±2.2	0.707
e2-c	5.8±2	5.1±2.6	0.402
e1-g	1.1±0.3	1.1±0.3	0.673
e2-g	1.2±0.4	1.2±0.4	0.931
Pregnancy	14/57	10/50	0.823
Pregnancy rate/Embryo transfer (%)	14/77 (18.1%)	11/60 (16.1)	0.841

Values are numbers or mean ± SD.
Fertilization Rate; No. 2PN/No. of oocytes retrieved
No. of GQE: Number. of embryos transfered + Number. of frozen embryos
GQE rate: Number of GQE/Number of 2PN
e1-c: The number of cells of the first best embryo
e2-c: The number of cells of the second best embryo
e1-g: Grade of the first best embryo
e2-g: Grade of the second best embryo
GQE, good quality embryo; PN, pronuclei.

Discussion

The most valuable result of this study was that the increased total propofol consumption in the high-anxiety group did not have any negative effect on the fertilization rate, embryo quality, and/or pregnancy rate. Moreover, MAS 9 was significantly higher in group H than in group L.

Anaesthetic management is very difficult in women with high levels of anxiety due to the lack of any premedication. The absence of premedication, due to significant surgical stimulation during needle insertion and prevention of awareness, may require increased total consumption of analgesic and anaesthetic drugs and deeper levels of sedation to provide optimal patient comfort and surgical status.[15] Patients undergoing brain function monitoring can be protected from the harmful effects of over- or low-dose anaesthesia.

Oocyte retrieval is generally performed using sedation in an ambulatory setting and is a short operation. There are many studies investigating the effects of various anaesthetic drugs used on fertilization and embryo quality or pregnancy rate during oocyte retrieval.[16-19] In animal studies in mice, exposure of mouse oocytes to propofol caused toxic effects on fertilization.[20,21] Human studies have reported conflicting results regarding the side effects of anaesthetic agents on fertilization and embryo quality.[7,22,23] Conscious sedation and general anaesthesia are well tolerated by propofol, opioids, benzodiazepines, nitrous oxide, or other drugs for women and oocytes, but further studies are needed to find the ideal drug or technique combination for women and oocytes.[24] In our study, we did not observe any negative effects on fertilization and embryo quality or the pregnancy rate in women who required high-doses of propofol because of preoperative anxiety. Unlike our study, Wilhelm et al.[10] retrospectively compared the effects of remifentanil versus general anaesthesia during oocyte retrieval on fertility and embryo quality in 251 women. In this study, general anaesthesia induction was performed using propofol and nitrous oxide and was maintained with isoflurane or a propofol infusion. In the other group, all patients received standardized under monitored anaesthesia care with remifentanil infusion, but local anaesthetics were not used. They reported that the rate of pregnancy in the general anaesthesia group was significantly lower. Christiaens et al.[4] reported that the time-dependent diffusion and accumulation of propofol in follicular fluid were related to the dose of propofol used. They suggested that the total dose of propofol administered during anaesthesia should be limited. A study by Coetsier et al.[2] supports these informations, and furthermore, they reported higher blood and follicular fluid concentrations of propofol because of the administration of a smaller dose of alfentanil. They recommend that the oocyte retrieval procedure should be as short as possible to reduce anaesthetic drug accumulation in the follicular fluid. Although the total amount of propofol consumed in these studies was not reported, the protocol for propofol sedation was similar to ours. In our study, total propofol consumption was significantly higher in the high-anxiety group 217.8 (37.3) than in the low-anxiety group 199 (32.8). Nevertheless, these values were not considered to be clinically meaningful as neither the fertilization rate nor the GQE rate were found to be significantly different between the groups.

There are studies investigating the effect of emotional anxiety on reproductive success in infertile women without evaluating anaesthesia.[1,25,26] Anderheim et al.[26] investigated the effect of psychological stress on IVF outcomes before and during IVF treatment. They obtained no evidence that psychological stress had an effect on the IVF outcome. The authors did not report any anaesthetic drugs used in this study. To the best of our knowledge, the effect of preoperative anxiety on depth of anaesthesia and IVF success has not been compared during oocyte retrieval. In this study, reduced total propofol consumption in the low-anxiety group did not increase fertility success. However, the time for anaesthesia recovery was significantly increased in the high-anxiety group. In addition, brain function monitoring could be helpful in preventing awareness and preventing the harmful effects of an overdose of anaesthesia. Sedation depth is important for preventing anxiety. We believe that brain function monitoring in our study is important in assessing the validity of our data.

Serious side effects related to propofol and fentanyl were not observed during oocyte retrieval in our study. The high and low anxiety groups were clinically similar with respect to hemodynamic state, postoperative VAS scores for pain, nausea, and vomiting. However, the time for anaesthesia recovery increased in the group with high anxiety.

Study Limitations

There are several factors that limit this study. First, the results of our study cannot be generalized to other anaesthesia techniques. Second, oocyte retrieval is not performed without anaesthesia for comparison. Third, this study is important at first in assessing embryo quality but second in assessing the pregnancy rate because many factors influence the pregnancy rate after sedation. Fortunately, the two groups in this study detected homogeneous results relating to gender, age, and ASA preoperatively.

Conclusion

In conclusion, preoperative anxiety can commonly be observed before oocyte retrieval. In this study, it can be said that propofol and fentanyl can safely be administered with monitoring brain function to prevent preoperative anxiety during oocyte retrieval, so high level of anxiety will not have negative effect on embryo quality, fertilization, and pregnancy rates.

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Ethics Committee Approval: Ethical committee approval was received from the Trakya University Faculty of Medicine (no: 2014/115).

Informed Consent: Written informed consent was obtained from patients and/or their relatives who participated in this study.

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Effect of Intravenous Ketamine Infusion on Hemodynamics of Patients Undergoing Cesarean Delivery after Spinal Anaesthesia: A Randomized, Double-Blind, Controlled Trial

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Abstract

Objective: Hypotension is the most frequent side effect of intrathecal anaesthesia, with an incidence of more than 80%. Following neuraxial anaesthesia, perioperative shivering is a serious complication affecting 40-60% of patients undergoing surgery. This study aimed to determine the effectiveness of low-dose ketamine on blood pressure in patients undergoing cesarean delivery after spinal anaesthesia.

Methods: We included 126 female patients undergoing cesarean deliveries, American Society of Anesthesiologists (ASA)-(II and III), and aged 21-40 selected from the outpatient clinics of the anaesthesia department. Patients were randomized to two groups; Group K (63 patients), who received 0.3 mg kg^{-1} of ketamine IV diluted to 10 mL, followed by an infusion of 0.1 mg kg^{-1} h^{-1}. Group C (Controlled) (63 patients) received 10 mL of normal saline, followed by an infusion of 0.1 mL kg^{-1} h^{-1}, which started before spinal anaesthesia.

Results: Compared with the saline group, the average heart rate, blood pressure, and level of sedation were significantly higher in the ketamine group ($P < 0.05$). The ketamine group reported a significantly lower incidence of shivering ($P < 0.01$). The ketamine groups exhibited significantly less mild or severe hypotension ($P < 0.05$). There was no significant difference between the two groups in terms of nystagmus, diplopia, hallucinations, or neonatal outcomes ($P > 0.05$).

Conclusion: Ketamine decreases the incidence of hypotension and shivering in patients undergoing spinal anaesthesia during cesarean delivery. In addition, it resulted in improved sedation for the mother and prolonged postoperative analgesia without neonatal illness.

Keywords: Hypotension, obstetric anaesthesia, pain, perioperative care, regional anaesthesia

Main Points

- The effect of ketamine on intraoperative blood pressure during cesarean delivery after spinal anaesthesia.
- Neonatal outcome after ketamine use in patients undergoing cesarean delivery after spinal anaesthesia.
- The effect of ketamine on shivering, sedation, and postoperative analgesia.

Introduction

Hypotension is the most prevalent side effect of intrathecal anaesthesia, with an incidence of more than 80%. The negative effects of hypotension during spinal anaesthesia for cesarean delivery include reduced uteroplacental blood flow, impaired fetal oxygenation with asphyxia stress, and fetal acidosis, as well as maternal symptoms of low cardiac output, such as nausea, vomiting, dizziness, and decreased consciousness. These adverse effects can harm

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both the mother and newborn. Methods for preventing and managing hypotension in obstetric anaesthesia have garnered significant interest in the literature. However, there is controversy over the utility of IV fluid preload. Uterine displacement is common. Despite these precautions, it is frequently necessary to administer a vasopressor. Ephedrine effectively demonstrated effectiveness in restoring maternal arterial pressure following hypotension and is typically prescribed in such cases.[1]

Ketamine increases the release and inhibits the reuptake of catecholamines, thereby preserving arterial blood pressure and vascular resistance, making it the optimal anaesthetic agent for hypotensive conditions.[2] The sympathetic nervous system is stimulated by ketamine, which results in an elevated heart rate (HR) and hypertension. It can raise intraocular and intracranial pressures, and its use is restricted in conditions where such an increase in pressure could be harmful (eye injury, head trauma, vascular disease, and hydrocephalus, for example).[3]

Shivering during surgery is a prevalent issue in anaesthesia practice, resulting in discomfort and life-threatening issues if not effectively controlled and prevented, especially in cardiorespiratory patients. Surgical patients may experience shivering for various reasons, including surgery, anaesthesia, skin exposure in a cool operating room, and receiving unwarmed fluids. Numerous pharmacological and non-pharmacological methods exist to prevent and treat this issue. Methods for preventing and treating shivering include prewarming the patient for 15 min prior to anaesthetic administration and administering modest doses (e.g., ketamine, clonidine, pethidine, dexamethasone, dexmedetomidine, tramadol, and magnesium sulfate).[2] Therefore, beneficial analgesic effects can be achieved without psychoactive side effects such as hallucinations and blockade of excitatory synaptic activity caused by loss of responsiveness associated with clinical ketamine anaesthesia.[4] However, subsequent research revealed that ketamine exhibits several different molecular effects and plays a role in the management of a wide range of conditions, including acute and chronic pain, and rapidly acting antidepressant.[5]

We hypothesize that ketamine decreases the incidence of spinal-induced hypotension in cesarean delivery by a ketamine sympathhomimetic effect.

This study aimed to determine the effectiveness of ketamine infusion on hemodynamic parameters in patients undergoing cesarean delivery after spinal anaesthesia.

Methods

We included 126 female patients, aged 21-41 years, undergoing cesarean deliveries with an American Society of Anesthesiologists (ASA)-(II and III). Subjects were recruited from the outpatient clinics of the Anaesthesia Department Outpatient Clinics in Al-Azhar University Hospitals from September 2022 to February 2023. Patients were randomly assigned to two groups; Group K (63 patients), who received 0.3 mg kg^{-1} of ketamine IV diluted to 10 mL, followed by an infusion of 0.1 mg kg^{-1} h^{-1} as 20 mL solution. Group C (Controlled) (63 patients) received 10 mL of normal saline, followed by an infusion of 0.1 mL kg^{-1} h^{-1} as a 20 mL solution.

The type of study: Randomized, double-blind, prospective, controlled study.

Study Outcomes

Primary outcomes: Hemodynamic parameters (MAP and HR).

Secondary outcomes

1. Incidence of intraoperative shivering
2. Postoperative pain was assessed by VAS score.
3. Sedation score between groups.
4. Fetuse evaluated using the Apgar score.
5. Postoperative side effects include nausea, vomiting, nystagmus, diplopia, and hallucinations.

Ethical Considerations

The Research Ethics Committee approved the study protocol at Al-Azhar University (approval no: 00328/2022). Written informed consent was obtained from each patient before the operation. This research is registered in the Clinical Trials Register (NCT05865080).

Inclusion criteria

Female patients and full-term, between (21 and 40), with (ASA)-II or III, and undergoing a cesarean section.

Exclusion criteria

1. Twins and preterm birth.
2. Hypertensive and preeclamptic patients.
3. Morbidly obese patients.
4. Spinal anaesthesia contraindication because the patient refused severe mitral or tricuspid stenosis and local sepsis.

Randomization

Ten minutes before the start of anaesthesia, the patients were equally randomized into two groups using computer-generated random numbers placed in separate opaque envelopes. The researcher opened the envelopes immediately before administering spinal anaesthesia, as depicted in the consort chart (Figure 1). An anaesthetist blinded to the study groups prepared two syringes, one containing ketamine (5 mg mL^{-1}, Ketalar, Pfizer, New York) and the other containing 0.9% saline. Both syringes were labeled "study drug" to maintain the double-blind design of the study.

Anaesthetic procedure:

All patients underwent preoperative planning before surgery, which included history taking, tests, and examinations. The patient was connected to standard monitoring devices such as noninvasive arterial blood pressure, electrocardiogram, and pulse oximeter, with baseline parameters measured and recorded in the pre-operative holding area. A wide-pore IV cannula was placed with preoperative Ringer lactate (500 mL) as preload. No pre-medical treatment was administered. At the L4-5 level, spinal anaesthesia was administered using a paramedian approach while seated. A 25 G Quinke needle and 2 mL of 0.5% heavy bupivacaine mixed with 25 g of fentanyl were used. A 2-liter nasal cannula was used to connect all patients. Ketamine was administered prior to the administration of spinal anaesthesia and was discontinued at the end of surgery.

Surgical procedures

Before administering spinal anaesthesia, the obstetrician and nurse disinfected their hands with betadine and sterilized the patient. The assessment of the patient's lower limb motor block and bilateral loss of sensation with a pinprick to the T4 dermatomes indicated that the patient had adequate surgical anaesthesia. After ensuring the absence of sensation, the operation began, and the newborn was evaluated at 1 and 5 min using the Apgar score by the pediatrician. Following delivery and clamping of the umbilical cord, oxytocin was administered. According to the obstetrician's recommendation, incremental doses of 10 units of oxytocin were administered, followed by increments of 2 units, depending on the contractility of the uterus. After completion of the operation, the patient was transferred to the recovery room.

Measurements

1. The baseline data included the duration of the procedure, the patient's height, weight, age, gestational age, and an indication of the cesarean section.

2. Intraoperative hemodynamics.

3. Incidence of shivering among groups.

4. Evaluation of sedation by Ramsay sedation score at 5, 10, 20, 30, and 40 min after surgery.

5. At four, eight, twelve, sixteen, twenty, and twenty-four hours, the visual analog scale (VAS) was evaluated.

6. Fetus Apgar score in the 1st and 5th min.

7. Postoperative side effects, such as nausea, vomiting, nystagmus, diplopia, and hallucinations.

Ramsay sedation score

1. Anxious, agitated, and restless.

2. Oriented, tranquil.

3. Responds to commands.

4. Brisk response to light glabellar tap.

5. Sluggish response to light glabellar tap.

6. No response (deep sedation).

Sample size justification

Using Epi-info TM version 7.2.4.0 (2020), the sample size was determined on the basis of the following factors:

- Level of tow-side confidence: 95%
- 80% of the test power.
- 5% error rate.

According to the findings of the study by Salah and Alansary[6] on hemodynamic affection, a minimum sample size of 140 subjects was required, plus an additional 15% (or approximately 24 patients) to account for dropouts. Therefore, the study included 63 patients in each group to test the hypothesis.

Statistical Analysis

The collected data were coded, processed, and analyzed using SPSS (Version 25) for Windows. Descriptive statistics were calculated to include mean, standard deviation, median, range, and percentage. For continuous variables, independent t-tests were performed to compare the means of normally distributed data. The Mann-Whitney U test was used to compare the median differences in non-normally distributed data, whereas the chi-square test was used for categorical data. The t-test and Wilcoxon signed-rank test were used for independent groups. The level of statistical significance was set at P values <0.05.

Results

One hundred forty patients passed the eligibility criteria. There were 14 patients excluded from the exclusion criteria. A total of 126 patients were randomly assigned to two groups, as depicted in the CONSORT flowchart (Figure 1).

There were statistically significant differences between the groups with regard to age, weight, ASA, gestational age, height, length of the procedure, and an indication of cesarean section ($P > 0.05$) as shown in Table 1.

According to Tables 2 and 3, there were statistically significant differences between the groups in terms of HR and blood pressure ($P < 0.05$), with the ketamine groups exhibiting greater hemodynamic stability.

There were statistically significant differences between the groups regarding intraoperative sedation and the frequency of shivering ($P < 0.05$), as depicted in Table 4. There were statistically significant differences between the groups in terms of pain score (VAS) postoperatively, which was lower in the ketamine groups ($P < 0.05$), as illustrated in (Table 5).

Table 1. Basic Data on the Study Population

Parameters	Group K (n = 63)	Group C (n = 63)	*P* value
Age (years)	29.12±2.9	27.25±3.16	0.35
GA (weeks)	38±1.15	37±1.25	0.27
Weight (kg)	8 2±5.43	88±6.74	0.45
Height (cm)	155±8.68	158±2.53	0.17
ASA (II: III)	49:14	45:18	0.25
Duration of operation (mean ± SD)	45.44±7.76	51.65±5.48	0.23
Indication Previous CS: failed induction: Cephalopelvic Disproportion	28:10:25	32:12:19	0.55

Data represented by (mean ± SD), numbers and percentage.
Group K: Received ketamine. Group C: Received normal saline.

Table 2. Heart Rate Changes at Different Time (Mean ± SD) in (b min^{-1})

Group Time	Group K (n = 63)	Group C (n = 63)	*P* value
Baseline	78.2±7.2	72.1±9.5	0.43
10 min	105.8±8.6	94.2±5.9	0.04*
20 min	114.5±6.2	85±5.7	0.02*
30 min	99.5±7.6	83.6±3.1	0.04*
40 min	93.5±5.6	81.6±5.31	0.16
40 min	89.5±7.3	86.6±2.7	0.32
At the end	86.5±6.8	80.7±6.5	0.24

*Statistically significant at *P* value ≤ 0.05.
Group K: Received ketamine. Group S: Received normal saline.

Table 3. Mean Arterial Blood Pressure Changes (Mean ± SD) in mmHg

Group Time	Group K (n = 63)	Group C (n = 63)	*P* value
Baseline	85.7±7.2	88.1±6.8	0.51
10 min	115.5±8.6	65.3±5.6	0.02*
20 min	90.7±6.4	75.2±7.4	0.004*
30 min	98.7±5.9	83.2±5.4	0.002*
40 min	89.7±5.9	76.2±7.1	0.34
50 min	92.7±5.9	81.2±8.5	0.25
At the end	82.3±5.7	87.2±7.1	0.12

*Statistically significant at *P* value ≤ 0.05.
Group K: Received ketamine. Group S: Received normal saline

There were statistically significant differences between the groups in terms of hypotension, nausea, and vomiting (Figure 1).

Table 4. Sedation Scores and Number of Patients with Shivering

Groups Parameters	Group K (n = 63)	Group C (n = 63)	*P* value
Minute-5	4 (3-4)	2(1-2)	<0.01*
Minute-10	4 (3-4)	2 (1-2)	<0.01*
Minute-15	3 (3-4)	3 (2-3)	<0.01*
Minute-30	3 (2-3)	2 (1-2)	0.17
Minute-45	2 (1-2)	1 (1-2)	0.11
End	2 (1-2)	1 (1-2)	0.13
Number of patients with shivering	5 (7.94%)	22 (38.1%)	<0.001*

Data represented by (IQR), numbers and percentage.
*Statistically significant at *P* value ≤ 0.05.
Group K: Received ketamine. Group S: Received normal saline.

Table 5. Postoperative Pain Score (VAS) Between Two Groups

Groups Parameter	Group K (n = 63)	Group C (n = 63)	*P* value
2 hrs.	1 (0-1)	0 (0-1)	<0.01*
4 hrs.	2 (2-3)	1 (1-2)	<0.05*
8 hrs.	3 (2-3)	2 (1-2)	<0.05*
12 hrs.	4 (3-4)	3 (1-2)	<0.01*
16 hrs.	5 (4-5)	4 (2-4)	<0.05*
20 hrs.	5 (4-5)	4 (4-5)	0.13
24 hrs.	6 (5-6)	6 (5-6)	0.12

Data represented by (IQR).
*Statistically significant at *P* value ≤ 0.05.
Group K: Received ketamine. Group C: Received normal saline.

There was no significant difference between the groups in terms of nystagmus, diplopia, hallucinations, or neonatal outcomes ($P > 0.05$) with respect to postoperative side effects, as demonstrated in (Figure 2).

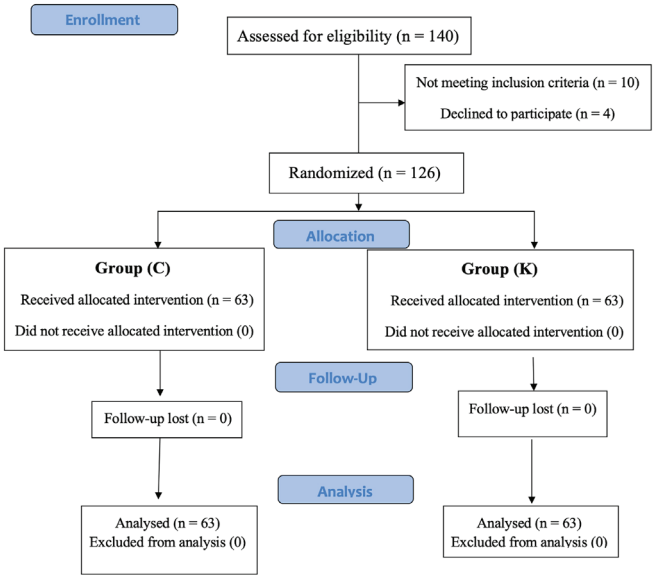

Figure 1. CONSORT diagram chart

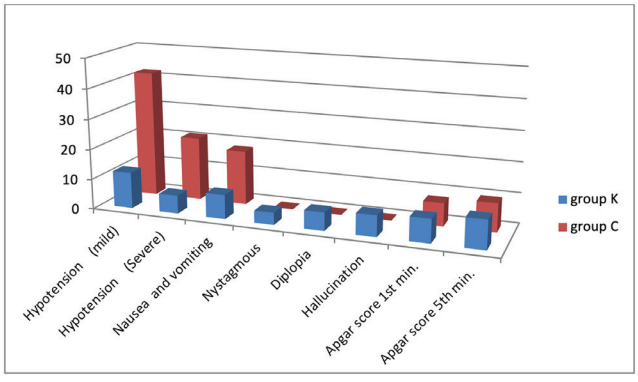

Figure 2. The two groups' side effects.

Discussion

Spinal anaesthesia applications, particularly during cesarean section in pregnant women, have been found to cause both hypotension and tremor with sympathetic blockade and are accompanied by some complications. This study avoided the common adverse effects associated with obstetric anaesthesia.

When compared with the control group, the ketamine patients in the current study demonstrated hemodynamic stability in terms of mean blood pressure and HR ($P < 0.05$). These findings agree with those of Salah and Alansary[6] study, which reported that a minimal amount of ketamine could be used to prevent hypotension following intrathecal anaesthesia in CS.

With a frequency of between 40% and 60% in patients undergoing surgery, perioperative shivering is a severe adverse effect frequently following neuraxial anaesthesia. In particular, in patients with cardiorespiratory issues, it causes excruciating discomfort and negative outcomes. Many techniques have been devised to avoid and manage shivering during and after neuraxial anaesthesia.[7,8]

In spinal anaesthesia, hypotension is caused by sympathetic nervous system blockade, and aortic and inferior vena cava compression during pregnancy is typically treated with ephedrine, intravenous fluid, and left lateral tilt.[9]

In the present study, 38.1% of patients in the saline group experienced postoperative shivering, compared with 7.94% in the ketamine group. The percentage of patients recovering from anaesthesia who experienced postoperative shivering ranged from 5-65%,[10] and numerous studies have reported that ketamine plays a role in reducing postsurgical shivering.[11]

Thangavelu et al.,[12] reported that only 4 cases (13.79%) of intraoperative shivering were observed in the ketamine group compared with 80 cases (58.06%) in the group receiving saline. In addition, the ketamine group showed significantly less postoperative shivering than the saline group. A small bolus of low-dose ketamine followed by an infusion prevented intraoperative and postoperative shivering. In the current study, intraoperative sedation was superior in the ketamine group compared with that in the control group. Also postoperative analgesia was better in the ketamine group than in the control group. Brinck et al.[13] studies on intravenous ketamine during surgery to treat severe postoperative pain in adults revealed a reduction in opioid dependance (an average decrease of 14.38 mg of intravenous morphine equivalents in 24 h).

Pendi et al.,[14] studies on patients who underwent spine surgery using perioperative ketamine as an analgesic and found that it reduced opioid-related side effects such as postoperative nausea and vomiting and respiratory sedation and improved engagement in recovery-oriented activities such as postoperative physiotherapy. In this study, there were significant differences in VAS between the groups postoperatively, with the ketamine group experiencing prolonged analgesia. These findings are consistent with those of Seman et al.,[15] studies in patients with morbid obesity undergoing laparoscopic gastric bypass surgery. They reported that infusions of ketamine significantly reduced the need for opioids in the ketamine group compared with the control group.

In the current study, 8 (14.28%) patients in the ketamine group and 18 (60.32%) patients in the saline group experienced nausea and vomiting. Nystagmus was reported in four patients (6.3%), diplopia in six (9.5%) patients and hallucinations in seven patients (11.11%) in the ketamine group, but none of these side effects were reported in the saline group. In more than 80% of cases, the most frequent side effect of intrathecal anaesthesia is hypotension, which

can negatively impact uterine blood flow and the health and outcome of the fetus as measured by Apgar scores.[16] In the compared groups of this study, Apgar scores remained unchanged.

Adhikari et al.,[17] illustrated that in patients who undergo nonelective cesarean deliveries, intravenous administration of a small dose of ketamine before surgical incision significantly decreases the need for opioid usage in the first 24 h post-surgery.

Karacaer et al.,[18] reported that a continuous infusion of ketamine and deflurane inhalation in patients with chronic obstructive pulmonary disease during one-lung ventilation increased arterial oxygenation and decreased shunting by ketamine effect on the catecholamine reuptake inhibitor mechanism. Therefore, there was no risk of respiratory depression when using a small dose of ketamine, and there were no cases of desaturation.

In this study, the incidence of mild or severe hypotension was significantly lower in the ketamine group than in the saline group.

Dhiman et al.,[19] reported that a small nebulized dose of ketamine with dexmedetomidine was superior to sedation with enhanced ease of intravenous line and postoperative analgesia in children.

Ketamine increases the release and inhibits the reuptake of catecholamines in circulation, thereby aiding in the preservation of vascular resistance and arterial blood pressure, making it the optimal anaesthetic method for hypotensive patients.[20]

Numerous clinical and pharmacological properties of ketamine have recently been reported. There are numerous applications of ketamine in anaesthesia, pain management, and intensive care.[21]

Intravenous low-dose ketamine combined with midazolam for sedation during spinal anaesthesia for elective cesarean section provides more effective and long-lasting pain relief than the control group.[22]

Spinal anaesthesia applications, especially during cesarean section in pregnant women, cause both hypotension and tremor with sympathetic blockade and result in many complications. This study will provide an opportunity to avoid undesirable effects frequently encountered in obstetric anaesthesia.

Study Limitations

In this research, the study was conducted on some cases, and patient satisfaction was not evaluated.

Conclusion

Ketamine decreases the incidence of hypotension and shivering in patients undergoing spinal anaesthesia during cesarean delivery. In addition, it resulted in improved sedation for the mother and prolonged postoperative analgesia without neonatal illness.

Ethics Committee Approval: The Research Ethics Committee approved the study protocol at Al-Azhar University (approval no: 00328/2022).

Informed Consent: Written informed consent was obtained from each patient before the operation.

Author Contributions: Concept - M.A.A.A.; Design - M.M.H.A.; Supervision - T.A.A.A.A.; Fundings - M.A.A.A.; Materials - M.I.A.E; Data Collection and/or Processing - A.S.A.E.; Analysis and/or Interpretation - M.M.H.A.; Literature Review - A.M.A.E.; Writing - T.A.A.A.A.; Critical Review - A.M.A.E.

Declaration of Interests: Nil

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Original Article
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Evaluation of Anaesthetic Approaches in Transcatheter Aortic Valv Implantation Procedures

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Abstract

Objective: Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement and has become a popular treatment modality for inoperable or patients at high surgical risk with severe aortic stenosis. We aimed to evaluate our perioperative anaesthetic experiences with patients undergoing TAVI under sedation or general anaesthesia (GA).

Methods: One hundred and fifty-nine patients who underwent TAVI procedures were enrolled. Effects on TAVI outcomes of sedation and GA were compared.

Results: The duration of surgery and anaesthesia was significantly longer in patients who received GA. Insertion site complication and post-TAVI pacemaker implantation rates were similar between the groups, but the frequency of intraoperative complications (10% vs. 0.8%; P=0.015), intraoperative hypotension (35.3% vs. 70%; $P < 0.001$), and acute kidney injury (12.6% vs. 27.5%; P=0.028) was significantly higher in the GA group. Stroke occurred in seven patients, and all were in the sedation group.

Conclusion: GA is related to increased procedure time and acute kidney injury; therefore, local anaesthesia and sedation may be the first option in patients undergoing TAVI.

Keywords: Aortic stenosis, general anaesthesia, perioperative care, sedation, transcatheter aortic valve implantation (TAVI)

Main Points

- Evaluation of perioperative anaesthetic experience with patients undergoing transcatheter aortic valv implantation (TAVI) under sedation or general anaesthesia (GA) is aimed.
- Using local anaesthetics with sedation is a more popular modality than GA with endotracheal intubation due to the advantages of sedation.
- Acute kidney injury is a frequent complication after TAVI.
- Local anaesthesia with sedation can be safely performed during transfemoral TAVI procedures.

Introduction

Aortic stenosis is a common valvular disease and valvular replacement is required in symptomatic patients with severe aortic stenosis. Surgical aortic valve replacement is the gold standard treatment in patients who are fit for surgery, but a significant proportion of patients carry high perioperative mortality risk or refuse surgery. Transcatheter aortic valve implantation (TAVI) has emerged as an alternative option to surgical aortic valve

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replacement in recent years and has become a popular treatment modality for inoperable or patients at high surgical risk with severe aortic stenosis. The procedure should be performed with general anaesthesia (GA)/ sedation under the guidance of anaesthesiologists for patient safety and comfort. The choice of anaesthesia technique for TAVI may vary depending on the nature of the selected procedure, the additional comorbidities of the patient, and the experience of the team performing the procedure. GA is advantageous for respiratory control, patient immobility, hemodynamic stability, enabling the use of transesophageal echocardiography (TEE), facilitating the management of procedural complications, and arterial interventions. As the experience of the team increases, the choice of a local anaesthesia-sedation (LAS) combination becomes more prominent. The LAS combination has advantages such as the early detection of neurologic complications, short procedure time, rapid recovery, and reduced postoperative care requirements. The main limitations of sedation are the invasiveness of the procedure and the difficulty of obtaining stable hemodynamics.[1,2]

We aimed to evaluate our perioperative anaesthetic experience with patients undergoing TAVI under sedation or GA.

Methods

After obtaining approval from the Hacettepe University Non-Invasive Clinical Research Ethics Committee (approval no: 2019/24-16, date: 15.10.2019), a retrospective review of anaesthesia management data for TAVI procedures was conducted. All patients (n = 159) who underwent percutaneous TAVI procedures in our hospital from 2013 to 2018 were included in the study.

Patients' characteristics such as age, sex, comorbidities, and data including echocardiographic parameters, anaesthesia method, anaesthetic drugs used, surgical duration, hospitalization time in the cardiac intensive care unit (ICU), and total hospitalization time, perioperative complications, and mortality were recorded for all patients. Patients' perioperative mortality risk was assessed using the Society of Thoracic Surgeons and Logistic EURO score models.

The pre-anaesthetic evaluation was performed one to two days before the procedure. Following a fasting period of 8 hours, standard monitoring with a 5-lead electrocardiogram, non-invasive blood pressure, pulse oximeter, and capnography were performed on all patients. After the femoral arterial sheath side port was placed, invasive arterial blood pressure was also monitored. GA was induced with intravenous (IV) anaesthetics from the IV catheter placed and the maintenance of GA was provided with 2% sevoflurane in a 50% oxygen - N_2O mixture through an anaesthesia device (Datex Ohmeda ADU S - 5, Finland). Induction for sedation was performed with midazolam and fentanyl and the maintenance of sedation was provided with iv infusion of propofol with bolus doses of ketamine or fentanyl if needed.

The time from induction of anaesthesia to tracheal extubation was recorded as the anaesthesia time for patients who underwent the procedure under GA. The duration of anaesthesia for patients who underwent the procedure under LAS was defined as the time from the administration of sedative agents until the decision to take the patient out of the operating room. The time from the initiation of vascular cannulation by the cardiologist to the removal of the catheters was recorded as the surgical time.

We aimed to evaluate and compare outcomes in patients who underwent TAVI under either GA or sedation. Outcomes were defined as periprocedural complication rates and mortality rates. Periprocedural complications were defined as insertion site complications, stroke, permanent pacemaker implantation, acute kidney injury (AKI), and intraoperative hypotension. The AKI was identified as an increase in creatinine level of 1.5-1.9 times that of baseline or ≥0.3 mg dL^{-1} (≥26.5 mmol L). Intraoperative hypotension was defined as a mean arterial pressure <65 mmHg for at least one minute.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS, Inc., Chicago, IL) statistical software. Mean, standard deviation, median, lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for the analysis of quantitative independent data. A chi-square test was used for the analysis of qualitative independent data.

Results

A total of 197 patients were screened and 159 patients (58 males, 101 females) with accessible data were included. The mean age of the study population was 76.6±10.1 years. Hypertension was present in 119 (74.8%) patients and diabetes was present in 46 (28.9%). Baseline characteristics are presented in Table 1. The median follow-up after TAVI was 36.3 (0-77.4) months. All procedures were performed under deep sedation or GA. GA was preferred in 40 (25.1%) patients. Twenty-seven (17%) patients were intubated via an endotracheal tube and a laryngeal mask airway was used in 13 (8.2%) patients. The most used IV agents during the procedures were midazolam (94.3%) and propofol (83%). The median surgical time was 70 (30-270) minutes and the median anaesthesia time was 80 (45-300) minutes. The procedure was completed without any complications in 154 (96.8%) patients. Five (3.1%) patients had intraoperative

Table 1. Baseline Characteristics

	Entire Population (n = 159)	Sedation (n = 119)	General Anaesthesia (n = 40)	*P* value
Age, years	76.6±10.1	75.7±10.6	79.1±8.1	**0.072**
Sex, male, n (%)	58 (36.5%)	43 (36.1%)	15 (37.5%)	**0.877**
Comorbidities, n (%)				
- Diabetes	46 (28.9%)	38 (31.9%)	8 (20%)	**0.216**
- Hypertension	119 (74.8%)	89 (74.8%)	30 (75%)	**0.979**
- Coronary artery disease	66 (41.5%)	49 (41.2%)	17 (42.5%)	**0.883**
- Chronic obstructive pulmonary disease	39 (24.5%)	27 (22.7%)	12 (30%)	**0.473**
- Heart failure	23 (14.5%)	21 (17.6%)	2 (5%)	**0.067**
- Cerebrovascular disease	7 (4.4%)	6 (5%)	1 (2.5%)	**0.680**
- Chronic kidney disease	11 (6.9%)	9 (7.6%)	2 (5%)	**0.732**
Laboratory parameters;				
- Hemoglobin	11.9±1.84	12.1±1.8	11.2±1.7	**0.008***
- Creatinine	0.92 (0.22-8.3)	0.9 (0.71-1.19)	0.96 (0.78-1.12)	**0.587**
- Glomerular filtration rate	69.7 (5.8-128.5)	72.2 (51.3-84.6)	63.3 (52.7-76.3)	**0.499**
- BNP	372 (10-9934)	372 (140-1054)	352 (177-2537)	**0.192**
Echocardiographic parameters;				
- LVEDD, mm	48.6±6.1	48.6±6.5	48.6±5.1	**0.973**
- LVEF, (%)	54.9±11.6	55.2±11.5	53.9±11.8	**0.549**
- Interventricular septum, mm	12.7±2.1	12.8±2.1	12.4±1.8	**0.314**
- Aortic valvular area, cm^2	0.77±0.23	0.79±0.25	0.72±0.15	**0.087**
- Mean aortic valvular gradient, mmHg	47.3±15.09	47.3±15.0	47.5±15.3	**0.953**
- sPAP, mmHg	48.6±16.0	48.4±15.4	49.0±17.8	**0.862**
STS score	8 (4-20)	8 (4-20)	9 (4-14.5)	**0.127**
Logistic EURO score	30 (10-65)	31 (10-65)	28 (14-64)	**0.548**

**P* values < 0.05 were accepted as statistically significant.
BNP, brain-type natriuretic peptide; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons.

complications including cardiac arrest (n = 3), femoral artery injury requiring surgery (n = 1), and ventricular rupture (n = 1). One of the patients with cardiac arrest died. Procedural characteristics are presented in Table 2.

Patients were classified into two groups according to the performed anaesthesia modality; GA or deep sedation. Baseline characteristics were similar between the groups except for hemoglobin (Hb) levels (Table 1), which were significantly lower in the GA group (12.1±1.8 vs. 11.2±1.7 g dL^{-1} *P*=0.008). Midazolam, fentanyl, and ketamine use were significantly higher in the sedation group, whereas remifentanil use was higher in the GA group (Table 2). Anaesthesia duration, surgical duration, amount of given fluid, and intraoperative complication rates were higher in patients who underwent GA compared with sedation (Table 2).

The median length of ICU stay was higher in the GA group (6 vs. 9.5 days; *P*=0.047), but the length of hospital stay was similar between the groups. Insertion site complications and post-TAVI pacemaker implantation rates were similar between the groups, whereas the frequency of intraoperative complications (0.8% vs. 10%; *P*=0.015), intraoperative hypotension (35.3% vs 70%; *P* < 0.001), and AKI (12.6% vs. 27.5%; *P*=0.028) was significantly higher in the GA group. Stroke occurred in seven patients, and all were in the sedation group. In-hospital (1.7% vs. 10%; *P*=0.035) and all-cause mortality rates (35.3% vs. 52.5%; *P*=0.045) were higher in the GA group (Table 3). However, we realized that a significant proportion of deaths occurred in the earlier patients as GA was preferred more in the preliminary cases. Therefore, we thought that it might be due to the effect of learning curve and we reassessed the survival analysis after excluding the patients who took place in the first 30 cases of our cohort. Ten cases in the GA group and 11 cases in the sedation group were excluded. In addition, 9 of these 30 patients were in the excluded group because their data could not be reached. Both in-hospital and overall all-cause mortality rates were similar between the two arms (Table 3). Survival was assessed using Kaplan-Meier analysis curve and survival chart (after the learning curve affect eliminated) is presented in Figure 1.

Table 2. Procedural Characteristics				
	Entire Population (n = 159)	**Sedation (n = 119)**	**General Anaesthesia (n = 40)**	***P* value**
Anaesthetic drugs;				
- Midazolam	150 (94.3%)	118 (99.2%)	32 (80%)	**<0.001***
- Propofol	132 (83.0%)	97 (81.5%)	35 (87.5%)	**0.471**
- Fentanyl	111 (69.8%)	91 (76.5%)	20 (50%)	**0.002***
- Rocuronium	31 (19.5%)	0 (0%)	31 (77.5%)	**<0.001***
- Ketamine	102 (64.2%)	82 (68.9%)	20 (50%)	**0.031***
- Remifentanil	3 (1.9%)	0 (0%)	3 (7.5%)	**0.015***
- Morphine	21 (13.2%)	13 (10.9%)	8 (20%)	**0.142**
- Thiopental	2 (1.3%)	0 (0%)	2 (5%)	**0.062**
Intraoperative complication, n	5 (3.1%)	1 (0.8%)	4 (10%)	**0.015***
Duration of anaesthesia, min	80 (45-300)	75 (45-180)	120 (45-300)	**<0.001****
Surgical time, min	70 (30-270)	70 (30-160)	100 (40-270)	**<0.001****
Fluid volume, mL	1000 (250-4000)	100 (250-4000)	2000 (1000-3500)	**<0.001****
**P* values < 0.05 were accepted as statistically significant				

Table 3. Follow-up and Outcomes				
	Entire Population (n = 159)	**Sedation (n = 119)**	**General Anaesthesia (n = 40)**	***P* value**
ICU stay, days	6 (1-70)	6 (1-70)	9.5 (1-43)	**0.047***
Hospital stay, days	9 (3-71)	8 (3-71)	11.5 (4-43)	**0.139**
Follow-up, months	36.3 (0-77.4)	36.5 (0.1-72.0)	29.4 (0-77.4)	**0.210**
Complications, n (%)				
* Insertion site complications	26 (16.4%)	17 (14.3%)	9 (22.5%)	**0.224**
* AKI	26 (16.4%)	15 (12.6%)	11 (27.5%)	**0.028***
* Stroke	7 (4.4%)	7 (5.9%)	0 (0%)	**0.041***
* Pacemaker implantation	32 (20.1%)	27 (22.7%)	12.5 (12.5%)	**0.253**
* Intraoperative complication	5 (3.1%)	1 (0.8%)	4 (10%)	**0.015***
* Intraoperative hypotension	70 (44%)	42 (35.3%)	28 (70%)	**<0.001***
Mortality, n (%)				
- Intraoperative	1 (0.6%)	0 (0%)	1 (2.5%)	**0.252**
- In-hospital mortality	6 (3.7%)	2 (1.7%)	4 (10%)	**0.035***
- All-cause mortality	63 (39.6%)	42 (35.3%)	21 (52.5%)	**0.045***
Mortality, n (%) - (After learning curve effect eliminated)	(n = 138)	(n = 108)	(n = 30)	
- In-hospital mortality	4 (2.8 %)	2 (1.9 %)	2 (6.7%)	**0.206**
- All-cause mortality	58 (42.0 %)	42 (38.9 %)	16 (53.3%)	**0.167**
**P* values < 0.05 were accepted as statistically significant. All-cause mortality analysis was performed with Kaplan-Meier analysis and log-rank analysis. ICU, intensive care unit; AKI, acute kidney injury.				

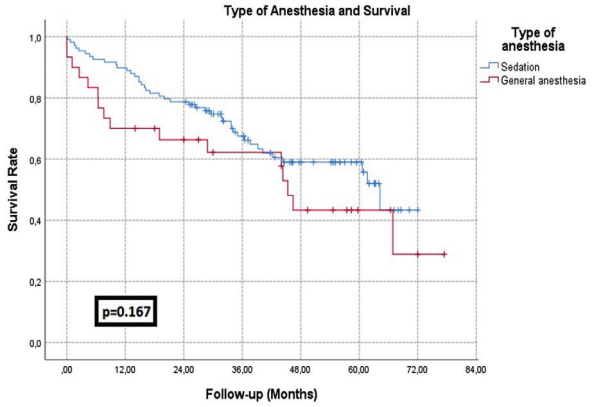

Figure 1. The survival curves of the sedation group and general anaesthesia group.

Discussion

Recently, the TAVI procedure is more preferred over surgical aortic valve replacement for high-risk patients with symptomatic and severe aortic stenosis.[3,4] The anaesthetic management of patients undergoing TAVI has become more important nowadays. Using local anaesthetics with sedation is a more popular modality than GA with endotracheal intubation due to the advantages of sedation.[1,2,5-7] In our study, sedation was more preferred than GA during TAVI procedures in accordance with the literature. The use of GA was reduced over time due to the increasing experience of the team in our unit, as described in the literature. If TEE should not be performed or there are no other indications for GA with endotracheal intubation during TAVI procedures, sedation is a good alternative for this process. It was shown that procedures performed with sedation were related to shorter-duration surgical time, anaesthesia time, hospital and ICU stays, and a lower incidence of respiratory complications and hypotension than with GA.[6-8] The results of our study are compatible with the literature.

The safest environment for TAVI procedures is a hybrid operating room that includes imaging equipment for faster intervention if surgical intervention is needed during the procedure. In many centers, TAVI procedures are performed in a cardiac catheterization laboratory (CCL). In our center, TAVI procedures are currently performed in a CCL, but it is close to the cardiac surgery operating room. The anaesthetist should have all the critical drugs and equipment required for intervention should any emergency condition occur due to complications of the procedure. In our center, we have all the drugs we would need in an emergency in a Pyxis unit and all anaesthetic equipment in the CCL.

In the selection of anaesthetic agents to be used for GA and sedation, it is recommended to use drugs that ensure the stability of hemodynamics, generally comprising agents such as etomidate, propofol, and ketamine.[9] Moderate-acting agents such as rocuronium can be used as muscle relaxants during intubation. It is emphasized that dose titration is more important than drug choice in keeping hemodynamics stable.[1] In this study, we used midazolam for most patients to reduce the dose of other anaesthetic drugs to keep the hemodynamics stable. We used propofol infusion for sedation to achieve a stable drug plasma concentration.

Several studies compared the effects of anaesthesia methods on TAVI outcomes. It is reported in all of the studies that surgical time and hospital stay are longer in patients who undergo GA when compared with sedation, as in our study. There are controversial results regarding the effects of the anaesthesia method on in-hospital mortality rates after TAVI; however, it is expressed in all studies that the anaesthesia method does not affect mid to long-term all-cause mortality rates.[10] Harjai et al.[11] reported that in-hospital and all-cause mortality rates were similar among the patients who underwent TAVI under GA and sedation during a median 365 day follow-up. A review including 13 non-randomized trials and in-hospital mortality rates concluded to be similar between the two anaesthesia methods.[12] In our study, we first found that in-hospital and all-cause mortality rates were higher in the GA group. However, we realized that a significant proportion of deaths occurred in the early period of our TAVI experience. The possible explanation for the diverse mortality rates between the anaesthesia type is the impact of the operator's learning curve on outcomes. We used to prefer GA in the beginning stages of our TAVI experience and by the time we switched our approach to sedation. Therefore, the GA group mostly underwent TAVI in the early experience period, which might have resulted in higher mortality rates. It is reported that operators performing TAVI need about 30 cases to become "better" and the cut-off value was determined as 30 cases.[13] Hence, we excluded the cases who were included in the first 30 cases of our TAVI cohort, and we reassessed the mortality analysis after eliminating the learning curve effect. There were not any differences in both overall all-cause and in-hospital mortality rates between the two-anaesthesia type. After interpreting these results, our findings suggest that anaesthesia type has no impact on mortality rates after TAVI as compatible with the previous data.

Intraoperative hypotension is defined as having a mean arterial pressure <65 mmHg for at least one minute. It is shown that intraoperative hypotension is associated with an increased risk of postoperative AKI and mortality.[14,15] In our study, intraoperative hypotension occurred in 70 (44%) patients, the frequency of intraoperative hypotension was significantly higher in the GA group despite left ventricular dimensions and wall thickness parameters being similar between the groups.

AKI is a frequent complication after TAVI and it is reported in ranges from 8.3% to 58%.[16,17] There are several defined risk factors for post-TAVI AKI including contrast media volume, red blood cell transfusion, post-procedural leukocyte count, peripheral artery disease, and intraoperative hypotension.[18] In our study, AKI developed in 26 (16.4%) patients and significantly more in the GA group. This finding might be due to higher rates of intraoperative hypotension and the lower Hb levels in the GA group.

Perioperative stroke is defined as a cerebral infarction that develops during or after an interventional procedure, with the postoperative period being up to 30 days.[19] In our study, stroke occurred in 7 (4.4%) patients, and all were in the sedation group. This finding should not be interpreted as a clinically significant result because all the strokes occurred more than 1 month after the procedures and despite it not being statistically significant, follow-up was longer in the sedation group. We also did not evaluate the patients' preoperative stroke-related risk factors such as the presence of atrial fibrillation.

Due to the retrospective design of the study, we could not obtain some data including the contrast media volume used, American Society of Anesthesiologists (ASA) scores, and causes of mortality. Using propensity score matching could have extinguished the effects of confounding factors on outcomes and would be better preferred; however, the absence of significant differences in age, gender, and comorbidities among both groups reduces the impact of these confounding factors on outcomes.

Conclusion

TAVI is a great option for patients with severe aortic stenosis who are at high risk for surgical repair. We observed that LAS can be safely performed during transfemoral TAVI procedures and may be an appropriate option in these patients. The anaesthesia method should be selected according to the medical condition of the patient and the experience of the team; however, LAS may be the first option in suitable patients due to the shorter surgical duration. We believe that close follow-up, dose titration, and equipment preparation are important for both methods, and caution is needed in terms of complications that may develop intraoperatively.

Ethics Committee Approval: Ethical approval was obtained from the Hacettepe University Non-Invasive Clinical Research Ethics Committee (approval no: 2019/24-16, date: 15.10.2019).

Informed Consent: Retrospective sutdy.

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Original Article
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Accuracy of Sonographic Airway Parameters in Difficult Laryngoscopy Prediction: A Prospective Observational Cohort Study from Central India

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Abstract

Objective: Though airway ultrasonography (USG) is used to assess difficult laryngoscopy (DL), there is still ambiguity about approach followed and parameters assessed. There is need of a simple, stepwise sonographic assessment with clearly defined parameters for DL prediction. The primary objective of this study was to find diagnostic accuracy of sonographic parameters measured by a stepwise Airway-USG in DL prediction (DLP).

Methods: This prospective, observational cohort study was done in 217 elective surgical adult patients administered general anaesthesia with tracheal intubation using conventional laryngoscopy from 1st May 2019 to 31st July 2020, after ethical approval. A sagittal Airway-USG was done using 2-6 Hz transducer in three steps specifying probe placement and head position. Demographic, clinical and Airway-USG measurements were noted. Correlation of the clinical/sonographic parameters was made with Cormack-Lehane score on DL. After receiver operating characteristic curve plotting, the sensitivity, specificity, positive predictive value, negative predictive value (NPV) of DL was calculated for each parameter using open-epi software.

Results: DL was observed in 19/217 patients. Airway-USG parameters of skin to epiglottis distance >2.45 cm, hyomental distance with head extension <5.13 cm, head neutral <4.5 cm, their ratio <1.18, maximum tongue thickness >3.93 cm and maximum skin to tongue distance >5.45 cm were statistically significant in predicting DL. DLP score with presence of >3 positive parameters showed 98% specificity, 98% NPV and 96% diagnostic accuracy to predict DL.

Conclusion: DLP score derived from Airway-USG may be used as a screening and diagnostic tool for DL.

Keywords: Airway management, airway ultrasonography, difficult airway screening test, difficult laryngoscopy, preoperative airway assessment

Main Points

- Three-step Airway-ultrasonography (USG) can be used to assess occipital-atlantoaxial extension, submandibular space compliance, epiglottis position and tongue size.
- Difficult laryngoscopy (DL) predictor (DLP) score can be derived from measured parameters of Airway-USG.
- DLP score has a good screening and diagnostic potential to predict DL when more than 2 and 3 parameters, respectively are positive.

Introduction

Airway associated complications are the most common anaesthesia-related adverse outcomes.[1] Intubation failure is usually attributed to difficult laryngoscopy (DL).[2,3] The low sensitivity, high inter-observer variation of morphometric screening tests like Mallampati classification, upper lip bite test, thyromental distance, cervical spine

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movements has led to continued search for more accurate airway examination tool.[4,5] Airway-ultrasonography (USG) is a non-invasive, portable bedside method which can visualize anatomical airway structures, confirm placement of endotracheal (ET)/double-lumen tube and guide invasive procedures like percutaneous tracheostomy and cricothyroidotomy.[6-10]

A recent meta-analysis has highlighted the heterogeneity in performance of airway sonography.[11-14] There needs to be more literature on accuracy of a step-wise sonographic airway assessment to predict DL better. With this research gap, we conducted this study with the primary objective of studying accuracy of sonographic airway assessment using a three-step approach of protocolized stepwise Airway-USG examination in prediction of DL seen by Cormack-Lehane (CL) Scoring system in patients administered general anaesthesia with ET intubation for elective surgery.

Methods

Subjects and Methods

This single-centre, prospective observational study was conducted in an academic tertiary care hospital in Central India in American Society of Anesthesiologists Physical Status (ASA-PS) I-III patients, aged 18-70 years, undergoing elective surgery under general anaesthesia with ET intubation from 1st May 2019 to 31st July 2020. Ethical clearance was given by the Institutional Ethics Committee (IHEC-LOP/2019/MD0049). All study participants gave written informed consent. We excluded patients with any airway abnormality preventing the use of clinical screening tests and Airway-USG like head and neck surgery/trauma/tumors/burns/scars/radiotherapy injuries/neck abscess/hematoma/beard, medical conditions like rheumatoid arthritis, ankylosing spondylitis, pregnancy, extreme obesity [body mass index (BMI) ≥40 kg m^{2-1}], previous history of DL and where laryngoscopy was not part of anaesthesia plan.

Data Collection

On the preoperative day, a trained anaesthesiologist collected the demographic variables and clinical airway parameters like inter-incisor gap, modified Mallampati score and thyromental distance. A single trained study investigator, blinded to the clinical airway parameters, performed the Airway-USG examination using a 2-6 Hz curvilinear transducer of the SonoSite M Turbo portable ultrasound machine. During Airway-USG, all patients were positioned supine with mouth closed and were instructed to keep their tongue relaxed and touch the lower incisors, without phonation or deglutination.

Several upper airway anatomical components influence the glottic view during laryngoscopy. Tongue and oral cavity volume, submandibular space compliance, epiglottis and extension at occipito-atlanto-axial joint are important. To assess and quantify these components ultrasonographically, yet keep it simple to perform, we proposed a three-step approach of protocolized step-wise Airway-USG examination. The three steps of as follows:

Step 1: With the patient's head in a neutral position, the transducer was placed in the midline of suprahyoid region in sagittal plane, as shown in Figure 1a, and adjusted to bring the hyoid bone, muscles of the floor of the mouth (geniohyoid and mylohyoid), the entire tongue and mentum in a single frame (Figure 1b). The following parameters were measured.

Tongue thickness was measured at the base of tongue (TT_B) and at a maximum vertical distance (TT_M), from the tongue's dorsum to the geniohyoid muscle's dorsum.

Skin-to-tongue distance was measured at the base of tongue (STD_B), and a maximum vertical distance (STD_M), from the dorsum of the tongue to the skin surface.

The hyomental distance also measured in a neutral position (HMD_N) from the hyoid bone's upper border to the mentum's lower border.

Step 2: The patient's head was extended (Figure 2a) without changing the probe position. Hyomental distance in extension (HMD_E) was measured from hyoid bone's upper border to mentum's lower border (Figure 2b).

Step 3: With the head back in a neutral position, the transducer was slowly moved caudally in the midline to the infrahyoid region, keeping the hyoid bone in frame (Figure 3a), to trace the entire length of epiglottis, which appeared as a hypoechoic structure with hyperechoic air-mucosa interface on its posterior surface. Distance from

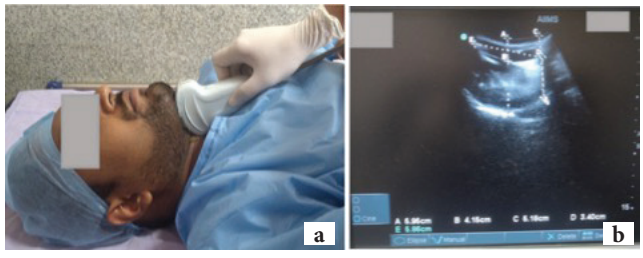

Figure 1. a) First step Airway-USG-patient head in neutral position with curvilinear transducer placed in suprahyoid region at the midline in sagittal plane, adjusted to bring the hyoid bone, muscles of floor of the mouth, the entire tongue and mentum in one frame. b) Ultrasonographic image at first step. A=Skin to tongue distance-maximum, B=Tongue thickness-maximum, C=Skin to tongue distance at base, D=Tongue thickness at base of tongue, E=Hyomental distance in neutral (Note hyperechoic air-mucosa interface at dorsum of tongue).

USG, ultrasonography.

skin to epiglottis (DSE) was measured just below the hyoid bone from skin surface to the posterior surface of epiglottis (Figure 3b).

On the day of surgery, standard institutional protocols were followed for induction of general anaesthesia with ET intubation done by an independent conventionally trained anaesthesiologist with more than 5 years of experience using Macintosh laryngoscopes of appropriate size blinded to preoperative airway sonography findings. The CL grading was noted.[15]

For each case, the study's end point was the difficulty in laryngoscopy judged by the CL grading, where Grades 1 or 2 and Grades 3 or 4 were considered easy and DL, respectively. The demographic, clinical and Airway-USG parameters were compared between easy and DL patients.

Statistical Analysis

Based on previous studies, the sensitivity of USG parameters was reported from 65% to 85% (average 75%) and clinical screening tests was reported from 20-62% (average 41%).[16,17] To estimate at least 30% higher sensitivity of USG over clinical parameters with 80% power to detect this change, considering a prevalence of 9.5% to 12% (average of 11) DL for the Indian population, with 95% confidence interval (CI), the estimated sample size calculated using PASS software was 200. We assumed an attrition rate of 10% and calculated the final sample size as 220 patients.

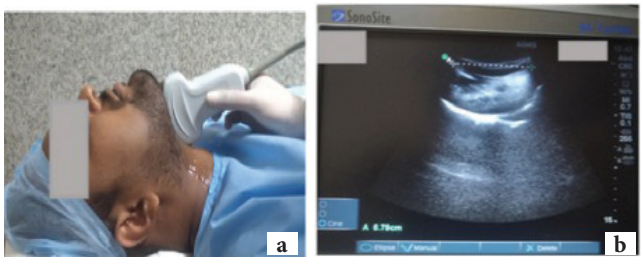

Figure 2. a) Second step Airway-USG-patient head in extended position with curvilinear transducer placed in suprahyoid region at midline in sagittal plane, adjusted to bring the hyoid bone and mentum in one frame. b) Ultrasonographic image at second step. A=Hyomental distance in extension.

USG, ultrasonography.

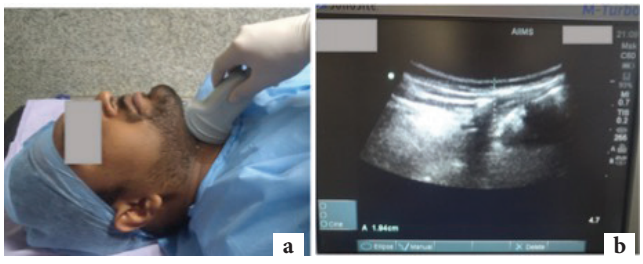

Figure 3. a) Third step Airway-USG-patient head in neutral position with curvilinear transducer placed in Infrahyoid region at the midline in sagittal plane (Note the transducer is moved caudally from step-1 to trace the epiglottis still keeping the hyoid bone in plane). b) Ultrasonographic image at third step. A=Distance from skin to posterior surface of epiglottis, measured just below hyoid bone (Note Hyperechoic air-mucosa interface at posterior surface of epiglottis).

USG, ultrasonography.

Data was entered, cleaned, and coded in Microsoft Excel 2013. Data was analysed using IBM Statistical Package for the Social Sciences version 23. The Shapiro-Wilk method was used to test the distribution normalcy of numerical variables and presented as mean [standard deviation (SD)] when normally distributed, while non-normally distributed variables presented as median [interquartile range (IQR)]. Categorical variables were expressed as absolute numbers and percentages. Ratios were expressed as values and their 95% CI.

Pearson's chi-square and Fisher's exact tests were used as significance tests for the association between categorical variables. Using Levene's test for equality of variances, numerical variables were checked for homogeneity between the difficult and easy laryngoscopy groups. Independent samples t-test and ANOVA test were used as tests of significance for homogenous numerical variables, while Mann-Whitney U test was used as test of significance for non-homogenous numerical variables. Correlation analysis was performed using the Pearson test. Receiver operating characteristic (ROC) curves were plotted and optimal cut-off values were determined using Youden's index.

Four derived parameters were calculated from the measured values.

Hyomental distance ratio (HMD_R) is defined as the ratio of HMD_E divided by HMD_N head position.

Delta_HMD is defined as percentage change in Hyomental distance during Occipito-Atlanto-Axial joint (Neck) extension.

$$\Delta_{HMD} = \left[\frac{HMDE - HMDN}{HMDE}\right] \times 100$$

R1 defined as ratio of tongue thickness (TT_M) to skin to tongue distance (STD_M) at maximum tongue width.

R2 defined as ratio of tongue thickness (TT_B) to skin to tongue distance (STD_B) at base of the tongue.

"Difficult Laryngoscopy Prediction (DLP)" Scoring System

Since DL is influenced by complex upper airway anatomy, a composite DLP score was developed using statistically significant USG parameters measuring different static and dynamic upper airway components. Diagnostic parameters

such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (LR) and diagnostic accuracy were calculated for individual and composite parameters using open-epi software.

Results

During the study period, 280 patients were assessed for eligibility, 220 patients were enrolled, and data analysis was possible in 217 patients. (Figure 4). The median age of this study population was 37 (IQR: 22) years, 60% of them female. The study included general surgical (25.8%), gynecological (17.1%), neuro-surgical (13.8%) and onco-surgical (10.6%) patients operated under general anaesthesia. We observed an 8.8% incidence of DL (19/217). The measured and derived sonographic parameters were noted to have a normal distribution, and homogenous variance except TT_B, STD_B and R2.

Association of DL with Demographic and Clinical Airway Parameters

Patients with DL were observed to have higher age [43 (IQR: 16) years vs 36 (IQR: 20) years, P=0.002] and BMI [26.62±3.13 (95% CI: 25.11-27.12) kg m^{2-1} vs 22.77±3.91 (95% CI: 22.31-23.31) kg m^{2-1}, P=0.002] in comparison to those with easy laryngoscopy.

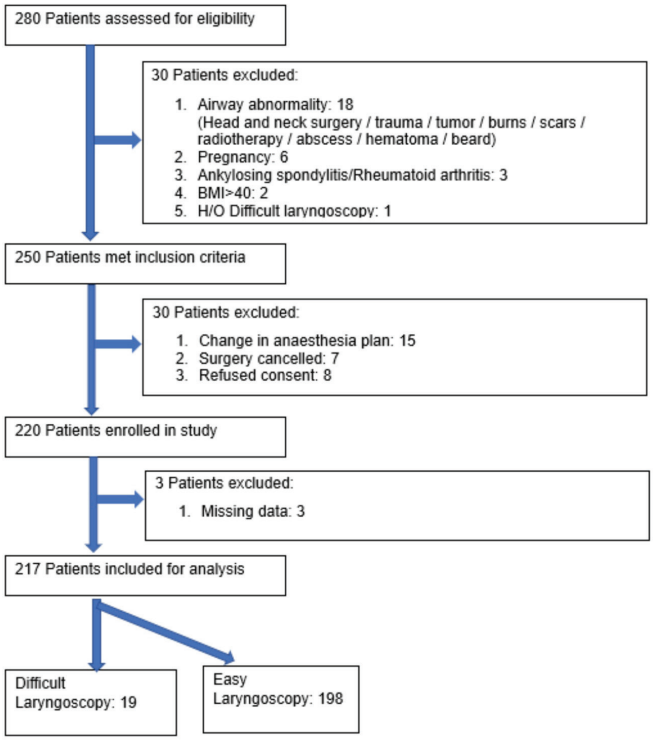

Figure 4. Study flow chart and outcome.

BMI, body mass index.

MMP and TMD were the only clinical test observed to be statistically significant in patients with DL. Though both parameters showed poor sensitivity, the specificity was good (Table 1).

Association of DL with Protocolized Stepwise Airway-USG Examination Parameters

Amongst the measured parameters, HMD_N, HMD_E, skin-to-tongue distance maximum (STD_M), tongue thickness maximum (TT_M), and DSE were statistically significant in differentiating easy and DL. Pearson correlation analysis showed a strong positive correlation between DL and DSE (r=0.71, $P < 0.001$), moderate negative correlation between DL and HMD_E (r=-0.42, $P < 0.001$), small correlation between DL and STD_M (r=0.27 P=0.01) but minimal correlation between DL and TT_M, HMD_N. Amongst the derived, HMD_R and delta hyomental distance (Delta_HMD) were statistically significant in differentiating easy and DL. Mean±SD, area under the ROC curve, optimal cut-off value along with their sensitivity, specificity and odds ratio of statistically significant measured and derived variable is mentioned in Table 2 and Table 3, respectively.

One-way ANOVA test and post-hoc analysis (using Dunnett's t3 multiple comparisons of means) revealed two Airway-USG parameters, namely HMD_E and DSE, exhibited statistically significant difference between different CL grades (Table 4).

Predictor of Difficult Laryngoscopy on Logistic Regression

Multivariate logistic regression showed DSE, HMD_E, STD_M and Delta_HMD were independent predictors of DL, their cut-off values were used to develop the Difficult Laryngoscopy Prediction Score. Each of them scored 1 and 0 for satisfying and not satisfying the cut-off criteria, respectively. DLP score=DSE + HMD_E + STD_M + Delta_HMD. The diagnostic profile of DLP score ≥2 and ≥3 shown in Table 5.

Discussion

Several anatomical and pathophysiological components, independently or in combination, can influence the laryngoscopic view. The main anatomical structures obscuring the glottic vision are the tongue, hyoid bone, and epiglottis.[18] Extension at Occipito-Atlanto-Axial (OAA) joint during laryngoscopy brings the oral axis in near alignment with laryngopharyngeal axes, aiding the glottic vison.[19] The morphometric screening tests investigate one or a few of these components, hence need better sensitivity. A meta-analysis by Shiga et al.[5] have confirmed their poor sensitivity with fair specificity. Our results for modified Mallampati score, thyromental distance, and inter-incisor distance were consistent with Shiga et al.[5] study.

Table 1. Comparison of Morphometric Difficult Airway Screening Tests in Difficult and Easy Laryngoscopy Groups

Parameters		Total (217)	Difficult laryngoscopy (19)	Easy laryngoscopy (198)	Significance	Sensitivity and specificity
MMP	MMP1	71 (32.7%)	0 (0%)	71 (35.8%)	*P*=0.001[a]	Sensitivity-32% Specificity-85%
	MMP2	111 (51.2%)	13 (68.4%)	98 (49.5%)		
	MMP3	35 (16.1%)	6 (31.6%)	29 (14.6%)		
TMD	<6 cm	14 (6.5%)	7 (36.8%)	7 (3.5%)	*P*=0.001[b]	Sensitivity-36% Specificity-96%
	>6 cm	203 (93.5%)	12 (63.1%)	191 (96.4%)		
IID	<3 fingers	4 (1.8%)	1 (5.2%)	3 (1.5%)	*P*=0.247[a]	Insignificant *P* value
	>3 fingers	213 (98.2%)	18 (94.7)	195 (98.5%)		

MMP, modified Mallampati grade; TMD, thyromental distance; IID, inter incisor distance.
a, Fisher's exact test; b, Pearson's chi-square test.

Table 2. Comparison of Measured USG-Airway Parameters in Difficult and Easy Laryngoscopy Groups

Parameters	Difficult laryngoscopy (19) Mean±SD (95% CI) (cm)	Easy laryngoscopy (198) Mean±SD (95% CI) (cm)	Significance	Area under curve of ROC (95% CI)	Cut-off value (cm)	Sensitivity (95% CI)	Specificity (95% CI)	Odds ratio (95% CI)
HMD_N	4.43±0.59 (4.14-4.65)	4.70±0.52 (4.63-4.77)	*P*=0.032[a]	0.82 (0.72-0.93)	<4.50	63.2% (41.0-80.8)	62.6% (55.7-69.0)	2.87 (1.08-7.64)
HMD_E	5.10±0.53 (4.85-5.36)	5.79±0.54 (5.71-5.86)	*P* < 0.001[a]	0.63 (0.50-0.77)	<5.13	63.8% (40.2-76.8)	90.9% (86.0-94.1)	13.75 (4.90-38.58)
DSE	2.60±0.31 (2.45-2.75)	1.97±0.27 (1.93-2.10)	*P* < 0.001[a]	0.95 (0.90-0.99)	>2.45	78.9% (56.6-91.5)	97.4% (93.5-98.6)	120.0 (30.49-472)
TT_M	4.10±0.36 (3.92-4.26)	3.89±0.39 (3.83-3.94)	*P*=0.026[a]	0.66 (0.54-0.78)	>3.93	63.2% (40.0-80.5)	60.1% (53.1-66.6)	2.58 (0.98-6.84)
STD_M	5.75±0.32 (5.60-5.90)	5.40±0.44 (5.43-5.55)	*P*=0.013[a]	0.68 (0.58-0.78)	>5.45	89.5% (68.6-97.0)	47.0% (40.1-53.9)	7.52 (1.69-33.41)
TT_B	2.46±0.48 (2.22-2.69)	2.35±0.33 (2.30-2.40)	*P*=0.215[b]	0.61 (0.46-0.76)	Insignificant *P* value			
STD_B	4.11±0.47 (3.89-4.34)	3.93±0.49 (3.86-3.99)	*P*=0.113[b]	0.63 (0.51-0.76)	Insignificant *P* value			

SD, standard deviation; CI, confidence interval; USG, ultrasonography; HMD_N, hyomental distance in neutral head position; HMD_E, hyo-mental distance in head extension position; DSE, distance from skin to epiglottis; TT_M, tongue thickness maximum; STD_M, skin to tongue distance maximum; TT_B, tongue thickness at base; STD_B, skin to tongue distance at base of tongue.
a, Independent sample T test; b, Mann-Whitney U test.

USG has been studied to visualize and quantify upper airway anatomical structures with good precision.[11,12,17] In our study, we have demonstrated the accuracy of a simple, three step approach of protocolized step-wise Airway-USG examination in anticipating DL. The measured sonographic parameters of HMD_N, HMD_E, skin-to-tongue distance at a maximum vertical distance from the dorsum of the tongue (STD_M), tongue thickness at maximum vertical distance from the dorsum of tongue (TT_M), DSE and the derived values of HMD_R, Delta_HMD were significantly associated with DL.

Hyomental Distance-related Parameters

Hyomental distance in extension (HMD_E) is an indirect estimate of submandibular space compliance.[1,20] Large submandibular compliance allows easy compression of the tongue's bulk, facilitating glottic vision during laryngoscopy. The USG measured HMD_E (5.10±0.53 cm for DL) was statistically significant in differentiating easy and DL groups in our study, and the results were consistent with Wojtczak[21] (<5.20±0.58 cm for DL) results. Lower HMD_E in Petrisor et al.[22] (<4.9±0.22 cm for DL) can be implicated in the high BMI (>40 kg m^{2-1}) of their study population.

Table 3. Comparison of Derived USG-Airway Parameters in Difficult and Easy Laryngoscopy Groups								
Parameters	**Difficult laryngoscopy (19) (95% CI)**	**Easy laryngoscopy (198) (95% CI)**	**Significance**	**Area under curve of ROC (95% CI)**	**Cut-off value**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Odds ratio (95% CI)**
HMD_R ($\frac{HMDE}{HMDN}$)	1.16 (1.11-1.20)	1.24 (1.22-1.25)	*P*=0.005[a]	0.73 (0.60-0.87)	<1.18	73.7% (51.2-88.2)	65.2% (61.4-71.3)	6.12 (2.07-17.29)
Delta_HMD ($\frac{HMDE-HMDN}{HMDN}$ X100)	16.11% (11.4-20.8)	24.06% (22.4-25.7)	*P*=0.005[a]	0.73 (0.60-0.87)	<18%	74.8% (55.2-88.2)	68.2% (62.4-74.3)	6.45 (2.40-22.42)
R1 ($\frac{STDM}{TTM}$)	0.71 (0.69-0.74)	0.71 (0.70-0.71)	*P*=0.628[a]	0.51 (0.38-0.65)	Insignificant *P* value			
R2 ($\frac{STDB}{TTB}$)	0.60 (0.55-0.63)	0.60 (0.59-0.61)	*P*=0.670[b]	0.47 (0.32-0.63)	Insignificant *P* value			

SD, standard deviation; CI, confidence interval; HMD_R, hyomental distance ratio; Delta_HMD, delta hyomental distance; HMD_E, hyomental distance in head extension position; HMD_N, hyomental distance in neutral head position; R1, ratio 1; STD_M, skin to tongue distance maximum; TT_M, tongue thickness maximum; R2, ratio 2; STD_B, skin to tongue distance at base of tongue; TT_B, tongue thickness at base.
a, Independent sample T test; b, Mann-Whitney U test.

Table 4. Comparison of HMD_E and DSE Parameters in CL 1, 2 and 3 Grade Groups				
Parameters	**CL1**	**CL2**	**CL3**	**Significance**
	Mean±SD (95% CI)	**Mean±SD (95% CI)**	**Mean±SD (95% CI)**	
HMD_E	5.90±0.54 (5.78-6.01)	5.68±0.51 (5.58-5.78)	5.10±0.53 (4.85-5.30)	*P*<0.001[a]
DSE	1.84±0.25 (1.79-1.88)	2.10±0.24 (2.05-2.14)	2.60±0.31 (2.46-2.76)	*P*<0.001[a]

SD, standard deviation; CI, confidence interval; HMD_E, hyomental distance in head extension position; DSE, distance from skin to epiglottis.
a, Dunnett's T test (multiple comparison of means).

Table 5. Diagnostic Profile of Difficult Laryngoscopy Prediction Score (DLP Score)		
Diagnostic profile	**Difficult Laryngoscopy Prediction Score (DLP Score) DLP Score= DSE+HMD_E+STD_M+ Delta_HMD**	
	DLP Score >2 (2 of 4 positive)	**DLP Score >3 (3 of 4 positive)**
Sensitivity (95% CI)	100% (83.2-100)	78.9% (56.7-91.5)
Specificity (95% CI)	79.6% (73.1-84.3)	98% (94.9-99.2)
PPV (95% CI)	31.7% (21.3-44.3)	78.9% (56.7-91.5)
NPV (95% CI)	100% (97.6-100)	98% (94.9-99.2)
LR+ (95% CI)	4.83 (4.60-5.01)	39.1 (23.1-66.1)
LR- (95% CI)	0.01 (0.008-0.012)	0.21 (0.13-0.35)
OR (95% CI)	483 (417-575)	182 (41.3-800)
Kappa (95% CI)	0.40 (0.30-0.50)	0.77 (0.63-0.90)
DA (95% CI)	81.1% (75.4-85.8)	96.3% (92.9-98.1)

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; OR, odds ratio; DA, diagnostic accuracy; DSE, Distance from skin to epiglottis; HMD_E, hyomental distance in head extension position; STD_M, skin to tongue distance maximum; Delta_HMD, delta Hyomental distance.

During head extension at the OAA joint, the mandible moves away from the hyoid bone, whereas the stylohyoid ligament limits the movement at hyoid bone. Thus, the HMD_R was proportional to OAA extension.[23] Sonographic HMD_R cut-off observed in our study (<1.18, 73% sensitivity, 65% specificity for DL) was comparable with HMD_R values assessed ultrasonographically by Petrisor et al.[22] (<1.24, 86% sensitivity and 72% specificity) and clinically by Huh et al.[24] (<1.2, 88% sensitivity and 60% specificity). Since the measured distances are displayed in millimeters, sonographic HMD_R values confer good precision over clinical parameters, even in obese patients.[22,25]

Delta_HMD, defined as a percentage change in hyomental distance during OAA extension, is mathematically a better indicator than HMD_R for OAA extension. Delta_HMD < 18% indicates that at the end of complete OAA extension, the proportional change in hyomental distance is less than 18%, showing inadequate OAA extension, and DL may be anticipated.

Tongue Related Parameters

Anatomically, tongue is the largest structure in the oral cavity, obscuring the line of sight during laryngoscopy. Quantifying the tongue size or its volume for the oral cavity

can predict DL, as shown by Mallampati et al.[26]. Measuring the tongue and oral cavity volume using 2-dimentional USG was tried by Wojtczak et al.[21] and Andruszkiewicz et al.[27] using complex measurements and calculations, but failed to prove their significance in anticipating DL.

To circumvent these complex measurements and calculations, we hypothesized tongue thickness in the sagittal plane at its maximum thickness (TT_M) and its base (TT_B) as an indirect indicator of tongue volume. We also measured the distance from skin to dorsal surface of tongue at same points as skin-to-tongue distance maximum (STD_M) and skin-to-tongue distance at base (STD_B), respectively, representing the oral cavity volume. Their ratios, R1 (STDM/TTM) and R2 (STDB/TTB), were derived to quantify the tongue volume for oral cavity volume at maximum tongue thickness (R1) and at tongue base (R2). Despite good correlation of these tongue-related parameters with the MMP score, only TT_M and STD_M could anticipate the DL. However, their ratio R1 failed to express its significance. This failure can be attributed to the two-dimensional representation of tongue volume for the oral cavity.

Even though tongue and floor of the mouth are anatomically two distinct components of the oral cavity, USG measured tongue thickness at its maximum dimensions by Yao and Wang[28] (>6.2 cm±0.5 for DL) and Yadav et al.[29] (>6.1 cm IQR: 1.04 for DL) also included the floor of mouth thickness (equivalent to STD_M of our study). These results were comparable with STD_M of our study results (>5.75±0.32 cm for DL). The imperceptible difference in the results can be attributed to the of head positioning while performing sonography (extension position in their study vs. neutral position in our research). To extend the application of these tongue-related parameters in emergency and intensive care unit patients where the freedom for head extension is often limited, we preferred a head-neutral position over head-extended position.

Epiglottis Related Parameters

Laryngoscopy aims at lifting the epiglottis. With the increase in soft tissue in the anterior neck, the angle made by the epiglottis with the thyroid cartilage increases, making glottic visualization more difficult, corroborating with the DSE.

USG measurement of anterior neck soft tissue can be performed at the level of hyoid bone, epiglottis, vocal cords and suprasternal notch.[29-33] When measured at an epiglottic level as DSE, the advantage of indirect quantification of thyroid-epiglottic angle is added. As DSE gradually increases from thyroid to the hyoid bone, we preferred the hyoid bone as an anatomical landmark and measured DSE just below the hyoid bone, to maintain uniformity among measured values. DSE measured just below hyoid bone showed the highest individual sensitivity and specificity amongst all USG-measured parameters in our study.

Our results of DSE (>2.60±0.31 cm for DL) are comparable with Ni et al.[30] (>2.59±0.41 cm for DL) and Wu et al.[31] (>2.39±0.34 cm for DL), the indiscernible difference in the results can be due to East Asian ethnicity of their study population. Yadav et al.[29] (>1.84±0.39 cm for DL) measured DSE at the midpoint of the thyrohyoid membrane. They excluded the epiglottis in DSE measurement, thus explaining the lower DSE value in contrast to our study. Pinto et al.[32] depicted higher DSE value (>2.82±0.44 cm for DL), as they averaged the measured DSE values at the central axis, the right and left extremity of the epiglottis. The differences in the results can also be attributed to the European ethnicity and higher BMI of their study population.

Difficult Laryngoscopy Prediction Score

Since DL is influenced by complex airway anatomy involving both static and dynamic components of the upper airway, the diagnostic accuracy of a test could be improved by investigating multiple factors affecting DL. The composite DLP score combines 4 crucial anatomical aspects of DL-DSE for anterior neck soft tissue thickness and thyroid-epiglottic angle, HMD_E for submandibular compliance, STD_M for tongue and floor of mouth thickness and Delta_HMD for OAA joint extension.

With a 100% sensitivity, 100% NPV, LR- 0.01 and 81% DA, the DLP score ≥2 can be employed as a screening test for DL, thus warning the intubating team about the possibility of DL. DLP score ≥3 had a 98% specificity, 79% PPV, LR+ 39 and 96% DA for DLP and can be employed as a diagnostic test in anticipating DL.

Strengths and Limitations

The main strength of our study is the simplified three-step Airway-USG assessment method, which may be used in future studies to decrease heterogeneity in the sonographic airway parameters assessed. It systematically examines both static and dynamic components of airway anatomy responsible for DL with good precision. Second, we have highlighted the diagnostic accuracy of the composite DLP score derived for the first time in our study, which encompasses four independent anatomical factors responsible for DL.

Our study has many limitations.

- It is a single center study with limited patients.

- Due to the low incidence of DL, the two study groups had an unequal sample size, which may have impacted the diagnostic profile of the USG parameters.

- We excluded patients with known anticipated DL, like pregnant, morbidly obese, and patients with airway anatomical abnormalities to avoid confounding factors.

- In our study, we never encountered someone with MMP4 score (large tongue to oral cavity ratio); this might

have underscored the tongue related USG parameters in anticipating DL.

- We did not have a USG parameter to measure mouth opening, hence lacking complete independence of protocolized step-wise Airway-USG examination in anticipating DL.

Conclusion

Direct laryngoscopy predictor score derived from a three-step sonographic airway assessment may be utilized as a screening and diagnostic tool for DLP in patients undergoing elective surgery to avoid unanticipated difficult airway. We recommend further studies in different populations to validate the DLP score derived in our study.

Ethics Committee Approval: Ethical clearance was given by the Institutional Ethics Committee (IHEC-LOP/2019/MD0049).

Informed Consent: All study participants gave written informed consent.

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Author Contributions: Concept - S.P.; Design - S.P., S.T.K.; Supervision - S.T.K.; Materials - S.P.; Data Collection and/or Processing - V.W.; Analysis and/or Interpretation - S.P., P.S., H.K.; Literature Review - P.S., H.K.; Writing - P.S., S.S.; Critical Review - S.T.K., V.W., S.S.

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Original Article

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Comparison of the Analgesic Efficacy of Ultrasound-Guided Quadratus Lumborum Block and Ilioinguinal-Iliohypogastric Nerve Block in Paediatric Patients After Inguinal Hernia Surgery: A Prospective Randomized Controlled Trial

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Abstract

Objective: To compare the postoperative analgesic efficacy of quadratus lumborum block (QLB) and ilioinguinal-iliohypogastric nerve block (IIIHB) in paediatric patients who have undergone unilateral inguinal hernia surgery.

Methods: This prospective randomized controlled study was designed in a single center and included 60 paediatric patients aged 2-7 years who had undergone inguinal hernia repair surgery and received an American Society of Anesthesiologists score of 1-2. Patients were randomized into two groups: those receiving ultrasound-guided QLB and those receiving IIIHB. The primary outcomes of the study were patients' face, legs, activity, cry, and consolability (FLACC) scores at 1, 2, 6, 12, and 24 hours post-surgery.

Results: The mean heart rate 15 and 30 minutes post-surgery in the QLB group was lower than that of the IIIHB group, and the difference at both times was statistically significant ($P < 0.001$). The mean FLACC score of the QLB group was lower than that of the IIIHB group at 6, 12, and 24 hours post-surgery, and the differences were statistically significant ($P=0.004$, $P=0.006$, and $P < 0.001$, respectively). Between the groups, there was no statistically significant difference in the number of patients who were administered rescue analgesics or oral ibuprofen, the time of first ibuprofen administration, or the frequency of complications ($P=1.000$, $P=0.145$, $P=0.195$, and $P=1.000$, respectively).

Conclusion: Compared with IIIHB, QLB achieves superior postoperative analgesic effects in paediatric patients who have undergone inguinal hernia surgery, as evidenced by longer analgesic periods, lower pain scores, and lower analgesic consumption.

Keywords: Inguinal hernia, nerve block, paediatric anaesthesia, pain, regional anaesthesia

Main Points

- Quadratus lumborum block (QLB) achieves longer analgesic duration, lower pain scores, and lower analgesic consumption than ilioinguinal-iliohypogastric nerve block (IIIHB) in paediatric patients who have undergone inguinal hernia surgery.
- Both QLB and IIIHB are effective and safe block methods.
- A significant decrease in heart rate at 15 and 30 minutes post-surgery in patients receiving QLB compared with IIIHB may be associated with the former's greater analgesic effect.

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Introduction

Perioperative and postoperative pain management has often been neglected in paediatric patients.[1] Effective perioperative and postoperative analgesic techniques reduce surgical stress and contribute to a physiologically and psychologically more comfortable postoperative experience, shorter recovery and hospitalization times, and positive long-term personality development in children.

Children's physiological, pharmacokinetic, and pharmacodynamic differences from adults delay the metabolization and elimination of systemic analgesics, which can result in prolonged analgesic effects and an increased risk of apnea.[2] Regional anaesthesia and central block procedures minimize systemic opioid consumption, reduce adverse drug events, and ensure efficient and safe analgesia; however, some central block procedures (e.g., caudal block) have disadvantages, including motor block and urinary retention.[3]

Inguinal hernia surgery is one of the most common paediatric surgical procedures. Peripheral block techniques, such as transversus abdominis plane (TAP) block and ilioinguinal-iliohypogastric nerve block (IIIHB), have been proven to safely and effectively manage perioperative and postoperative pain in paediatric patients and have replaced central block techniques.[4,5] In recent years, quadratus lumborum block (QLB) has emerged as a regional anaesthetic technique and been proven to promote analgesia in children as effectively as the caudal block procedure and more effectively than the TAP block.[6] Nevertheless, the literature contains only one study comparing the effectiveness of IIIHB and QLB in paediatric patients.[7]

This study aims to compare the postoperative analgesic efficacies of QLB and IIIHB in paediatric patients who have undergone unilateral inguinal hernia surgery.

Materials and Methods

Approval for this prospective randomized controlled study was obtained from the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (approval no: 3445, date: March 08, 2022) and from the Turkish Medicines and Medical Devices Agency on October 13, 2022 (approval no: 22-AKD-177). Clinical trials were initiated on October 28, 2022 upon registration with NCT05610943. Written and verbal consent was obtained from the parents of the children. All procedures were carried out in accordance with the ethical standards of the Declaration of Helsinki (2008), and the study was conducted according to Consolidated Standards of Reporting Trials guidelines.

Inclusion Criteria

The study included 60 patients aged 2-7 years who received American Society of Anesthesiologists (ASA) physical scores of 1-2 and who were scheduled to undergo unilateral inguinal hernia surgery. Patients with coagulopathy, skin infection at the surgical site, a bupivacaine allergy, or a neuropsychiatric disease were excluded from the study.

Sample Size and Randomization

Considering previous studies, the effect size [calculated as 1 according to the face, legs, activity, cry, and consolability (FLACC) score] taken as one unit of difference between the two groups after 24 hours (2 vs. 1) and the standard deviation of each group as 1, and the two-tailed t-test was calculated at a significance level of 0.05 and 95% power among independent groups and was determined to be 27 patients per group and 54 patients in total.[8] A total of 60 patients were included, considering the margin of error.

Patients were randomized into two groups by the closed-envelope method using opaque envelopes prepared and sealed by study clinicians. The intervention group each patient would join was determined in the following manner: as patients were brought to the operating room, an envelope was selected in the preoperative admission area by a nurse blind to the entire study. All blocks were performed by the same anaesthesiologist. Patients' FLACC scores were evaluated by a different anaesthesiologist who was blind to the blocks.

Procedure

Premedication (midazolam) was administered orally at 0.5 mg kg^{-1} 30 minutes before surgery. Patients were then taken to the operating room, and their noninvasive arterial blood pressure, end-tidal carbon dioxide (CO_2), peripheral oxygen saturation, and electrocardiogram readings were monitored continuously. Intravenous vascular access was opened with a 22-24-gauge cannula. After preoxygenation with a face mask, propofol (3 mg kg^{-1}) and fentanyl (1 µg kg^{-1}) were administered to induce anaesthesia. A ProSeal laryngeal mask of appropriate size based on each patient's weight was deployed. Anaesthesia was maintained with a mixture of sevoflurane (2%), oxygen (50%), and air (50%).

The patients undergoing the QLB procedure was referred to as Group QLB, and the patients undergoing IIIHB were referred to as Group IIIHB. Block procedures were performed using an Esaote MyLab Five ultrasonography (USG) device (Florence, Italy) with a multifrequency linear probe (6-19 MHz) and a 22 g and 50 mm peripheral nerve block needle (Braun Sonoplex, Melsungen, Germany).

Group QLB (n = 30)

A Type 2 (posterior) QLB was applied to patients in Group QLB. The patients were placed in a lateral position, with

the side to be blocked in the superior position. To prevent airway complications during block application (e.g. when the patient's position changed), an anaesthesiologist or senior assistant continuously monitored the patient's head and laryngeal mask position. A sterile cover was placed at the injection site after skin antisepsis was ensured with 5% povidone-iodine. The USG probe was covered with a sterile sheath, and the probe was placed between the iliac crest and the costal margin. The external-internal oblique and transversus abdominis muscles were screened, and the probe was advanced through the posterior. The quadratus lumborum, psoas major, and erector spinae muscles were screened. The needle was advanced to the middle thoracolumbar fascia between the quadratus lumborum muscle and the erector spinae muscle by the in-plane technique, and the needle's location was confirmed by injecting 1 mL of 0.9% saline solution. Following negative aspiration, 0.25% bupivacaine was injected at a dose of 0.5 mL kg^{-1}.

Group IIIHB (n = 30)

Patients in Group IIIHB were placed in a supine position. A sterile cover was placed after skin antisepsis was ensured with 5% povidone-iodine. The USG probe was covered with a sterile sheath and placed on the anterior abdominal wall parallel to the imaginary line between the umbilicus and the anterior superior iliac crest. After screening the external-internal oblique and transversus abdominis muscles, the IIIHB was screened as two small hypoechoic areas between the internal oblique muscle and the transversus abdominis muscle. The needle's location was confirmed by injecting 1 mL 0.9% saline solution and advancing the needle toward the nerve structures using the in-plane technique. Following negative aspiration, 0.25% bupivacaine was injected at a dose of 0.2 mL kg^{-1}.

Postoperative Pain Management and Data Collection

Demographic data such as age, gender, and weight were recorded for all patients. Heart rate (HR) was recorded in both groups 15 and 30 minutes after block application. The time from induction of anaesthesia to awakening was recorded as the anaesthesia period; the time from cessation of sevoflurane administration to patient recovery was recorded as the recovery period; and the time from surgical incision to the final suture was recorded as the surgery period.

Data on the block technique used was collected by an anaesthesiologist blind to block procedure. Pain assessment was performed and FLACC scores were recorded 1, 2, 6, 12, and 24 hours after surgery, and patients were followed up for two hours in the recovery room. Fifteen mg kg^{-1} paracetamol rescue analgesia was administered intravenously to patients with FLACC scores ≥4 in the first two hours following surgery, and this was recorded. Two hours after surgery, patients were transferred to the ward, their oral intake was opened, and their FLACC scores were evaluated at 2nd, 6th, 12th, and 24th hours post-surgery by an anaesthesiologist. Patients with FLACC scores ≥4 were administered 7 mg kg^{-1} of oral ibuprofen. The time of initial ibuprofen administration within the first 24 hours post-surgery was recorded. Complications such as nausea, vomiting, desaturation, bradycardia, tachycardia, hypotension, hematoma, and visceral damage from the procedure (e.g., intravascular puncture) were monitored and recorded.

Primary Outcomes

The primary outcomes of the study were the FLACC scores of each group of patients 1, 2, 6, 12, and 24 hours post-surgery.

Secondary Outcomes

The secondary outcomes of the study were perioperative HRs, the number of patients administered postoperative rescue analgesics, the number of patients administered postoperative oral ibuprofen, the time of the first postoperative administration of oral ibuprofen, and any complications that arose due to the block procedures used and/or postoperative use of systemic analgesics.

Statistical Analysis

Statistical analysis was conducted using SPSS 15.0 (Armonk, New York, USA). The descriptive statistics captured were numbers and percentages (for categorical variables) and mean, standard deviation, minimum, maximum, and median (for numerical variables). The rates in the groups were compared with the chi-squared (χ^2) test. Comparisons of numerical variables between the two groups were made with the Student's t-test (when the normal distribution condition was met) and the Mann-Whitney U test (when the normal distribution condition was not met). Dependent group analyses were performed with repeated measurement analysis of variance (when the normal distribution condition was met) and the Friedman test (when the normal distribution condition was not met). Subgroup analyses were performed with the Wilcoxon test and interpreted with the Bonferroni correction. Alpha significance level was accepted at $P < 0.05$.

Results

Inguinal hernia surgery was performed on a total of 71 patients aged 2-7 years between November 2022 and March 2023. One patient was not included in the study due to an ASA score >3, two patients were not included due to the presence of neuropsychiatric disease, and eight patients who did not provide consent were not included in the study (Figure 1). The study ultimately included 60 patients. There was no statistically significant difference

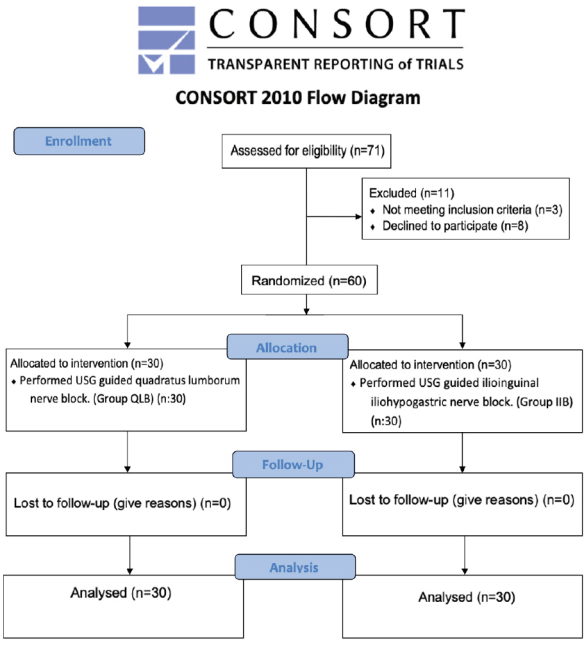

Figure 1. Consolidated Standards of Reporting Trials diagram comparing the postoperative analgesic efficacy of USG-guided quadratus lumborum block (QLB) and ilioinguinal-iliohypogastric nerve block (IIIHB) in infants undergoing inguinal hernia surgery.

USG, ultrasonography.

in the demographic findings ($P > 0.05$; Table 1) or in the anaesthesia administration, surgical process, or recovery periods ($P > 0.05$; Table 1) between the two groups.

There was no statistically significant difference between the mean HR values of the two groups at the beginning or after anaesthetization (P=0.082 and P=0.428, respectively; Table 2). The mean HR values of Group QLB after 15 and 30 minutes were lower compared with those of Group IIIHB, and the differences were statistically significant ($P < 0.001$ for each time mark; Table 2).

The mean FLACC score of Group QLB was found to be lower than that of Group IIIHB at 6, 12, and 24 hours post-surgery, and these differences were statistically significant (P=0.004, P=0.006, and $P < 0.001$, respectively; Table 3).

There was no statistically significant difference between the groups in the number of patients administered rescue analgesics and oral ibuprofen, the time of first administration of oral ibuprofen, or the frequency of complications (P=1.000, P=0.145, P=0.195, and P=1.000, respectively; Table 4).

Table 1. Demographic Data and Time Period Comparisons Between Group QLB and Group IIIHB

Characteristics	Group IIIHB (n = 30)	Group QLB (n = 30)	*P* value
Age (years)			
Min.-max. (median)	2-6 (4)	2-6 (4)	0.952[b]
Mean ± SD	3.8±1.2	3.8±1.5	
Gender			
Male	19 (63.3%)	18 (60.0%)	0.791[c]
Female	11 (36.7%)	12 (40.0%)	
Weight (kg)			
Min.-max. (median)	10-23 (15)	10-21 (15)	0.508[b]
Mean ± SD	15.1±3.1	15.6±2.7	
Duration of anaesthesia (min)			
Min.-max. (median)	45-90 (62.5)	30-90 (65.5)	0.431[b]
Mean ± SD	63.7±10.9	63.9±11.5	
Duration of surgery (min)			
Min.-max. (median)	22-70 (43)	25-70 (44)	0.744[a]
Mean ± SD	45.0±10.1	45.0±11.7	
Duration of recovery (min)			
Min.-max. (median)	3-10 (7)	5-10 (6)	0.394[b]
Mean ± SD	6.5±1.8	6.4±1.5	

[a]Student's t-test
[b]Mann-Whitney U test
[c]Chi-squared (χ^2) test
Min.-max., minimum-maximum; SD, standard deviation; QLB, quadratus lumborum block; IIIHB, ilioinguinal-iliohypogastric nerve block.

Table 2. Comparison of Heart Rates (beats min^{-1}) Between Group QLB and Group IIIHB

Characteristics	Group IIIHB (n = 30)	Group QLB (n = 30)	*P* value
Basal HR			
Min.-max. (median)	105-135 (119)	89-136 (125)	0.082[a]
Mean ± SD	118.8±7.6	121.5±11.5	
Post-anaesthesia HR			
Min.-max. (median)	105-135 (119)	84-139 (110)	0.428[b]
Mean ± SD	111.8±9.0	109.7±12.0	
HR 15 minutes post-block			
Min.-max. (median)	92-125 (109)	71-126 (95.5)	<0.001[a]
Mean ± SD	108.4±8.8	96.7±13.1	
HR 30 minutes post-block			
Min.-max. (median)	90-120 (104)	70-115 (90)	<0.001[a]
Mean ± SD	103.9±8.3	92.0±12.6	

[a]Student's t-test
[b]Mann-Whitney U test
[c]Chi-squared (χ^2) test
Min.-max., minimum-maximum; SD, standard deviation; QLB, quadratus lumborum block; IIIHB, ilioinguinal-iliohypogastric nerve block.

Table 3. Comparison of Face, Legs, Activity, Cry, and Consolability Scores Between Group QLB and Group IIIHB					
	Group IIIHB (n = 30)		Group QLB (n = 30)		
	Mean ± SD	Min.-max. (median)	Mean ± SD	Min.-max. (median)	*P* value
1 hour	0.80±1.06	0-4 (0)	0.53±1.01	0-4 (0)	0.218[b]
2 hours	0.87±1.22	0-4 (0)	0.70±0.99	0-3 (0)	0.607[b]
6 hours	1.30±1.37	0-5 (1)	0.47±0.94	0-3 (0)	0.004[b]
12 hours	1.37±1.43	0-5 (1)	0.60±1.16	0-4 (0)	0.006[b]
24 hours	1.20±1.10	0-4 (1)	0.17±0.46	0-2 (0)	<0.001[b]

[b]Mann-Whitney U test
Min.-max., minimum-maximum; SD, standard deviation; QLB, quadratus lumborum block; IIIHB, ilioinguinal-iliohypogastric nerve block.

Table 4. Comparison of Oral Ibuprofen Need, Time of First Analgesic Requirement, Rescue Analgesic Requirement, and Complications Between Group QLB and Group IIIHB			
	Group IIIHB (n = 30)	Group QLB (n = 30)	*P* value
Rescue analgesic n (%)	2 (6.7%)	1 (3.3%)	1.000[b]
Oral ibuprofen n (%)	7 (23.3%)	2 (6.7%)	0.145[b]
Time of first ibuprofen requirement (min)			
Mean ± SD	7.4±4.6	12±0	0.195[c]
Min.-max. (median)	2-12 (6)	12-12 (12)	
Complications n (%)	2 (6.7%)	1 (3.3%)	1.000[b]

[b]Mann-Whitney U test
[c]Chi-squared (χ^2) test
Min.-max., minimum-maximum; SD, standard deviation; QLB, quadratus lumborum block; IIIHB, ilioinguinal-iliohypogastric nerve block.

Discussion

The authors of this prospective randomized controlled study found that, in paediatric patients undergoing inguinal hernia surgery, the use of QLB achieved longer analgesic duration, lower pain scores, and less analgesic consumption than the use of IIIHB.

There was less need for oral ibuprofen in the first 24 hours post-surgery in Group QLB (6.7%) than in Group IIIHB (23.3%). The need for rescue analgesics occurred in two patients in Group IIIHB and one patient in Group QLB in the first two hours after surgery. Samerchua et al.[9] compared the use of posterior QLB and IIIHB in paediatric patients who had undergone inguinal hernia surgery and similarly found the consumption of analgesics to be lower in the QLB group (the need for rescue analgesics was observed in one patient in the QLB group, versus five patients in the IIIHB group). Priyadarshini et al.[7] evaluated the efficacy of lateral QLB against TAP block and IIIHB in paediatric patients who had undergone inguinal hernia surgery, using paracetamol for postoperative analgesia, and found no difference in total paracetamol consumption between groups. The same study used tramadol in patients who experienced pain despite the administration of paracetamol. Finding that 55% of the TAP block group, 35% of the IIIHB group, and 15% of the QLB group required additional tramadol, Priyadarshini et al.[7] concluded that, compared with TAP block or IIIHB, the use of QLB leads to a decrease in opioid consumption in children undergoing inguinal hernia surgery. Data on total analgesic agent dosage were not included in the aforementioned study.

In this study, a postoperative analgesic was first required 12 hours after surgery in Group QLB and 7.4 hours after surgery in Group IIIHB. Comparatively, the mean time of first analgesic need post-surgery was 8.4 hours in the QLB group and 4.8 hours in the IIIHB group in the study by Samerchua et al.[9], and the analgesia period was shorter. Priyadarshini et al.[7] found that first analgesic need emerged 6 hours, 8 hours, and 12 hours after surgery in the TAP block, IIIHB, and QLB groups, respectively, a finding that corroborates the present study. As in this study, posterior QLB was performed in the study by Samerchua et al.[9], whereas lateral QLB was performed in the study by Priyadarshini et al.[7].

The analgesic efficacy of QLB has been associated with the spread of local anaesthesia through the middle thoracolumbar fascia. Due to the complex structure of the thoracolumbar fascia, local anaesthesia administered at the L4 level spreads to the endothoracic fascia through the medial-lateral arcuate and aortic hiatus. Although magnetic resonance imaging and cadaver studies have yielded different results, it is generally accepted that posterior QLB administration affords dermatomal spread between T11 and L1 and ensures somatic and visceral analgesia through paravertebral distribution and involvement of the ventral rami of the spinal nerves.[10,11] The extent of dermatomal spread and visceral analgesia may explain QLB's greater efficacy as an analgesic compared with IIIHB.

In a meta-analysis of seven randomized controlled studies comparing QLB with different analgesic techniques in paediatric patients who had undergone lower abdominal

surgery, pain scores 2, 4, and 12 hours after surgery were found to be lower in the QLB group. Based on limited data, QLB achieved more efficient postoperative analgesia in lower abdominal surgery in paediatric patients.[12] Additionally, a new meta-analysis of 69 randomized controlled studies comparing different regional anaesthesia techniques in paediatric patients who had undergone inguinal surgery found that QLB had the longest analgesia period.[13]

In the present study, postoperative pain was assessed by FLACC score, and FLACC scores at 0, 6, 12, and 24 hours postoperation were lower in Group QLB than in Group IIIHB. The mean FLACC score was <4 in both groups, indicating that IIIHB, too, is an effective regional anaesthetic technique after inguinal hernia surgery. No difference was found between the pain scores of the groups in the studies by Samerchua et al.[9] or Priyadarshini et al.[7], a fact that may be attributable to the smaller sample sizes of these studies compared with that of this study. Edwards et al.[14] compared the analgesic efficacy of transmuscular QLB and IIIHB in adult inguinal hernia surgery patients[9] and found that pain scores during activity and at rest were similar 24 hours after surgery and that analgesic duration and the time of first opioid consumption post-surgery was similar in both groups, a result that deviates from the findings of paediatric studies. Edwards et al.[14] used a similar dose and volume of local anaesthesia in both groups, and adjuvant clonidine was added.

With the increasing use of USG in regional anaesthesia application, the search for minimum dosages and volumes that are still effective and safe has emerged. In the present study, 0.25% of bupivacaine was administered at 0.5 mL kg^{-1} in Group QLB and 0.2 mL kg^{-1} in Group IIIHB. Unfortunately, there are insufficient data on the pharmacodynamic efficacy and systemic toxicity of local anaesthetic agents in children.[15] Willschke et al.[16] conducted a study to determine the optimal volume for IIIHH administration under ultrasound guidance in paediatric patients and showed that, for IIIHH, ultrasound-guided local anaesthetic volume could be reduced to 0.075 mL kg^{-1} in children. These different doses and volumes were selected according to studies on effective dose in paediatric patients.[15-19] Samerchua et al.[9] employed similar doses of bupivacaine. Priyadarshini et al.[7], by contrast, administered 0.25% ropivacaine at 0.2 mL kg^{-1} in the IIIHB group and 0.4 mL kg^{-1} in the QLB group. Using similar dosages and volumes for both blocks, Edwards et al.[14] found the analgesic efficacy of QLB and IIIHB to be similar in adult patients. Alternatively, Mostafa et al.[20] used similar doses and volumes to compare the analgesic efficacy of QLB and IIIHB in children who had undergone inguinal hernia surgery and found lower postoperative pain scores and less analgesic consumption in the QLB group. Mostafa et al.[20] attributed this outcome to the wide dermatomal dissemination and visceral-somatic analgesic activity of QLB.

In the present study, HRs at 15 and 30 minutes after block procedures were lower in Group QLB than in Group IIIHB. Both groups had a decrease in HR at all times compared with baseline and after anaesthesia. It is known that effective anaesthetic techniques provide perioperative hemodynamic control; thus, a greater decrease in HR at 15 and 30 minutes in Group QLB may be associated with greater analgesic effect. It has been suggested that local anaesthetic spread to the paravertebral area in QLB and dermatomal involvement in the wider area may be associated with hypotension.[21,22] Arterial blood pressure monitoring data were not evaluated in this study.

No complications related to regional anaesthesia procedures were observed in this study. Postoperative vomiting was observed in two patients in Group IIIHB and one patient in Group QLB. Samerchua et al.[9] observed vascular intervention in the IIIHB group in only one patient. No complications were observed in the study by Priyadarshini et al.[7]. In both studies, only procedure-associated complications were evaluated.

Study Limitations

A limitation of this study is absence of block performance times, such that sensory block levels could not be evaluated and total analgesic consumption could not be recorded. Another limitation of the study is its exclusion of hemodynamic parameters such as blood pressure, end-tidal CO_2, and oxygen saturation, as it is not sufficient to comment on hemodynamic changes based on HR alone.

Conclusion

In paediatric patients undergoing inguinal hernia surgery, QLB provides longer analgesic duration, lower pain scores, and lower analgesic consumption than IIIHB. More randomized controlled studies and meta-analyses are needed to determine the greater analgesic effect of QLB in paediatric patients.

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (approval no: 3445, date: March 08, 2022).

Informed Consent: Written and verbal consent was obtained from the parents of the children.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Concept - M.A., H.Ş.T.; Design - M.A., H.Ş.T.; Supervision - M.A., H.Ş.T.; Materials - M.A., H.Ş.T.; Data Collection &/or Processing - M.A., H.Ş.T.; Analysis and/or Interpretation - M.A., H.Ş.T.; Literature Search - M.A.; Writing - M.A., H.Ş.T.; Critical Review - M.A., H.Ş.T.

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