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Implementation of ERAS Protocols: In Theory and Practice

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Abstract

The enhanced recovery after surgery (ERAS) pathway is a perioperative care pathway intended to facilitate early recovery and minimize hospital stays among patients undergoing major surgery. Critical factors for successful ERAS implementation, which may vary depending on care processes, include a multidisciplinary team, organizational commitment to change, and a real-time system for compliance and outcome audits. As most clinicians and health organizations can attest, incorporating and implementing new evidence-based practice changes almost always involves overcoming systemic challenges and obstacles. The same holds true for ERAS programs. The main barriers to ERAS protocol implementation have been resistance to change, lack of time and resources, and inadequate communication and coordination among departments. According to evidence-based ERAS guidelines, the best way to efficiently implement all recommendations into practice is to discover. Implementation science aims to identify and address care gaps, support change in practice, and enhance healthcare quality. Implementation research should also build a robust and generalizable evidence base to inform implementation practice. Most implementation investigations focus on one of two approaches to achieving change. Implementation can progress through top-down or bottom-up processes depending on factors such as national policies, organizational properties, or the implementation culture of society, especially for health issues. Although the ERAS guidelines are based on evidence-based knowledge, only a limited number of health centers around the world have officially been able to implement them. The purpose of this review is to analyze the implementation of the ERAS pathways in theory and practice in Turkey, considering the absence of an ERAS-qualified center in Turkey.

Keywords: Enhanced recovery after surgery, implementation science, practice guideline, surgery

Main Points

- Enhanced recovery after surgery (ERAS) is a patient-centered, evidence-based approach to improve perioperative care that involves collaboration among different healthcare disciplines.
- There has been a remarkable surge in the adoption of ERAS protocols worldwide.
- Implementation science involves integrating evidence-based practices, interventions, and policies into routine healthcare.
- Every healthcare system, hospital, and organization may require distinct implementation strategies.

Introduction

Enhanced recovery after surgery (ERAS) is a protocol-based pathway focusing on every step of perioperative care. The main fostering power of this concept was the realization that unimodal interventions did not address perioperative morbidity, which has a multifaceted genesis. Kehlet and Wilmore, the "father" of the ERAS concept, defined the essential mechanism of postoperative complications as the degree of pathophysiological stress response to surgery and subsequent organ dysfunction.[1] Accordingly, to decrease postoperative morbidity, the stress response to surgery should be reduced. Advances in this era have improved patient outcomes, including reduced postoperative length of stay, significant cost savings, and increased patient satisfaction for those undergoing both open and laparoscopic colorectal surgery.[2] In this context, multidimensional, multimodal, multidisciplinary, protocolized

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perioperative care bundles called ERAS protocols have been developed. Since the turn of the millennium, there has been a remarkable surge in the adoption and dissemination of protocols consisting of evidence-based interventions.

The ERAS pathways have been particularly pronounced in developed countries, indicating a significant shift in perioperative care practices. The concept has been accepted worldwide and continues to grow for almost every surgical specialty because of positive studies favoring ERAS protocols. However, despite such numerous clinical studies, there still needs to be more debate on whether ERAS implementation has the success it deserves. In this context, establishing the scientific and clinical benefits of ERAS protocols cannot guarantee their application in everyday clinical practice.

Advances in medical research have greatly extended human lifespans over the past century. A maximum of 50% of these medical research has been incorporated into routine use. Moreover, implementing an innovative approach into routine clinical practice usually takes 17-20 years.[3] Considering that the first ERAS recommendation paper was published for colon surgery in 2005, it was expected that ERAS protocols would take their place among routinely applied protocols between 2022 and 2025.[4] However, this differs from today's reality, especially in developing countries. The issue is why ERAS guidelines are still not used in routine practice, even though the time frame mentioned in implementation science has passed.

This review investigates the difficulties in implementing ERAS protocols and their implementation into routine daily practice in Turkey. This study also aimed to identify appropriate strategies to overcome the main problems by considering the rules of implementation science and explicitly focusing on the pioneering colorectal ERAS protocol.

Implementation Science Perspective

Implementation science is the scientific study of methods and strategies that help practitioners and policymakers incorporate evidence-based practices and research into their daily routines.[5] This field aims to bridge the gap between what we know and what we do by systematically identifying and addressing the barriers that impede the implementation of proven health interventions and evidence-based practices. The branch plays a crucial role in integrating concepts from various disciplines, such as organizational behavior, clinical epidemiology, intervention science, health economics, adult education, and marketing.[6] Additionally, healthcare researchers increasingly recognize the importance of implementation science. In the early 2000s, the United States established the quality enhancement research initiative (QUERI), and the United Kingdom established the National Institute for Health Research Service Delivery and Organization Program. These initiatives were created to promote the implementation of evidence-based practices and have been successful.

The lack of implementation of clinical advancements can be attributed to the rapid pace of modern biomedical research, which surpasses society's ability to absorb them. This explains why some developments or changes take a long time to be accepted by the societies interested in them.[7] The implementation process of ERAS protocols is likely relevant to the situation. ERAS protocols have been designed to meet the specific needs of medical fields and professionals within a required time frame, especially in countries with specific requirements for optimal perioperative care. However, in communities facing challenges beyond improving perioperative care, delays in implementing ERAS protocols are unavoidable. Interventions and evidence-based practices may not produce the expected outcome benefits if they are poorly implemented or not implemented at all. Even when effectively implemented, interventions and practice changes may still fail to deliver anticipated health benefits if their effectiveness is lost during implementation or if the intervention or practice was never effective in the first place.[8]

Several evidence-based initiatives with proven better patient outcomes, such as ERAS care bundles, have not been fully integrated into standard practice. The differences observed between the slow and rapid adoption of ERAS guidelines in clinical practice highlight the influential role of contextual factors in determining the speed and extent of their widespread use, in addition to their effectiveness. Ferlie et al.[9] claimed that the presence of complex organizations containing many different professional groups hinders the spread of what should be implemented. This theory helps us explain barriers to the spread of an initiative in large, multiprofessional organizations in both healthcare and other settings, such as in ERAS programs. Surgeons, anesthesiologists, nurses, physiotherapists, and nutritionists are employed within unprofessional communities in which the same language is spoken and who have common internal learning processes. Additionally, social and cognitive boundaries between different professions may impede the spread as individual professionals work within unidisciplinary communities of practice.[9] Hence, it is essential to address challenges like creating a unified and innovative language in a multidisciplinary working environment and aligning perspectives. This will facilitate the development of shared paths for the application of ERAS protocols.

The current evidence-based ERAS protocols face challenges in seamlessly integrating into clinical practice because of their scientific validity alone. The issue at hand is that each professional team aims to provide the highest level of evidence to patients. However, the reality is quite different. The effectiveness of ERAS protocols arises from the

combined application of good clinical practice to the same patient. This can be understood by observing that patient outcomes improve as the compliance rate with the protocol increases.[10] Implementation science should address this issue and provide a framework for this model.

More than just concise study results are necessary to ensure the regular adoption of a new clinical practice. The significance of training when integrating a new application into regular practice cannot be overstated. It is crucial that individuals who are expected to use this application receive proper training, are supervised, and receive feedback at the conclusion of training. However, a Cochrane meta-analysis showed that audit and feedback only increased target provider behaviors by 4.3%.[11] Therefore, education and monitoring are not sufficient to change provider behaviors. The longstanding and persistent problem of healthcare providers not adopting effective clinical initiatives is influenced by factors beyond the initiative itself. External factors, such as a different professional society or nationality, also play a significant role in determining whether or not the initiatives are properly utilized.

The ERAS guidelines are far from being implemented under the current leadership. Protocols are often complex and multifaceted, with many interacting components. Items can be conceptualized as having "core components" (the essential and indispensable elements of the protocol) and "peripheral components" (adaptable elements, structures, and systems related to the intervention and organization into which it is being implemented).[8] Due to its nature, a multifaceted strategy is needed to implement an ERAS protocol. It may include drawing baseline data, getting appropriate education regarding the whole process from a well-experienced group, establishing a registry of patients undergoing surgery using an ERAS protocol, and, last but not least, having both internal and external audits during and after completion of the implementation process. Therefore, the process should involve two main layers. The first layer identifies barriers to and facilitators of implementation across various levels of context, including patients, providers, organizations, and stakeholders such as policymakers. The next layer involves developing and implementing strategies to overcome these barriers and enhance facilitators to increase the adoption of evidence-based clinical initiatives.[12]

Barriers and Potential Solutions

• Healthcare System and Policy Level

ERAS is an evidence-based multidisciplinary perioperative care pathway. This concept of perioperative care brings together surgeons, anesthesiologists, nurses, physiotherapists, nutritionists, and even patients, all involved in the surgical care journey, to achieve favorable patient outcomes, as previously mentioned. This is best achieved by creating a multidisciplinary ERAS committee, which can be defined as a team that works well together and believes in the value of ERAS protocols.

In a hospital setting, the implementation of an ERAS program can be approached in two distinct ways from an organizational standpoint. The initial alternative can be executed by hospital management through top-down communication as a vertical structure. In this method, the hospital selects the individuals participating in the committee, regularly assesses the results, and devises corrective actions for any issues. Responsibility is assigned to one or a few individuals designated by hospital management. As a result, the support provided by other committee members may be limited, and the process may progress slowly. Nevertheless, the effectiveness of this approach lies in its strong enforcement ability. In the second method, the process progresses from bottom to top. This method involves team members forming an ERAS team and persuading hospital management to use data to emphasize increased service quality and patient satisfaction. In our country, the second option is more common to establish an ERAS program. However, it is easy to anticipate that the first option will become more prevalent in implementing ERAS protocols due to inevitable changes in national healthcare policies. For instance, the Ministry of Health has been developing a protocol for colorectal cancer, which has been in place nationwide since 2019 as part of a clinical quality improvement initiative.[13] However, the current protocol does not adequately cover the perioperative care of surgical patients. In the future, integrating the elements of the evidence-based ERAS guideline into this national protocol could significantly accelerate the adoption of ERAS practices throughout the country. In order to accomplish this goal, it would be advisable for the ERAS Turkey Society and the Ministry of Health to carry out a collaborative study.

Imagine that the outcomes of patients following surgical procedures are regularly provided as feedback to both institutions and the public. In this case, such information will at least push institutions to produce higher-quality service, on average, toward the country's average. It would even help to use a benchmarking approach that aims to achieve the "best in class".[14] Feedback on such information constitutes the most effective internal audit and regulation mechanism of the health system.[15] Therefore, it might be possible to foresee that ERAS protocols will become much more popular due to the increased quality of health services, and institutions will be encouraged to implement ERAS protocols in all types of surgery with top-down instructions, as previously mentioned. In addition, improvement in performance reimbursements for centers implementing ERAS, according to the performance-based payment system itself, may also be encouraging for centers planning ERAS implementation.

A 2021 study in Turkey on the health services system multidimensional trust scale found that public trust in health services was at a medium level, indicating a lack of strong trust.[16] Therefore, it is crucial to take measures to uphold public trust in healthcare systems when developing health policies. Becoming an ERAS center not only involves providing exceptional service but also building trust in the healthcare system using evidence-based data.

• Organizational Level

Healthcare professionals in the ERAS program must collaborate fully, prioritizing patient care. Common perspective and good communication are the minimum requirements for this harmony. Therefore, the greatest challenge in the implementation process is the requirement of an interdisciplinary effort.[17]

Communication is a cultural phenomenon that should be developed to advance an ERAS program. However, given the time constraints, thoroughly discussing and making a mutual decision with each patient is often challenging. This is where the designated ERAS coordinator plays a critical role. The coordinator provides ERAS education to patients before surgery, monitors ERAS patients after surgery, collects patient data on adherence to the ERAS protocol, and evaluates patient outcomes. Additionally, an ERAS coordinator should collaborate closely with frontline care teams and serve as the communication channel between frontline care members and executive and leadership members throughout the process. The coordinator should also consistently collaborate with team members, such as the anesthesiologist, nutritionist, patients, and data collector. This collaboration includes sharing information and data, highlighting successes and areas for improvement, and updating care plans as necessary. Conducting regular structured meetings, either weekly or monthly, depending on the need, to discuss all ERAS cases and ensure compliance with ERAS items is crucial for success. The discussions and updates revolve around modifying order sets, documenting issues, flow sheet issues, and complications. In these meetings, ERAS champions from all different surgical specialties can be identified, and other team members and hospital management can reward them in various ways.

Institutions implementing their ERAS programs can initially have a smaller team. However, it is essential to ensure that all group members are fully committed. Guidelines are crucial for process management. Each institution can decide by considering its capabilities, goals, and what is essential for success. Thus, each ERAS committee can create revised guidelines specific to the procedure and the institute.

• Patient Level

Different societies may have different attitudes toward health and disease. Supporting patients is a significant factor that influences barriers to and facilitators of care. In an ERAS program, patients play a major role in driving clinical care related to nutrition, mobilization, pain and symptom control, and hydration. Patients often desire to be actively involved in their care from diagnosis until recovery, although not always. In a study, patients who had face-to-face, semi-structured interviews with key stakeholders regarding their social support, satisfaction levels, preadmission information and education, pain management, and mobilization revealed that education level was considered an important barrier from the patient's perspective.[18] Therefore, the implementation process may involve various options regarding the level of education that can be delivered to the patient.

Patients may want to learn about ERAS and why it is important to follow the guidelines to support their surgical journey. Although patients may want to leave the hospital sooner, they are generally worried about the consequences after discharge. Patients who cannot advocate for themselves express interest in learning effective decision-making to advocate for themselves. The use of perioperative counseling and support, as well as yoga, meditation, mindfulness, and exercise, are potential strategies for managing stress. Almost 50% of patients should undergo colorectal surgery for cancer, and delays in test results and support for patients with earlier-stage cancers are barriers to treatment. Timely follow-up with the surgeon and postoperative communication with an ERAS coordinator can provide the patient with a sense of trust and well-being, along with valuable insight.

From the patient perspective, education strategies during the perioperative period might affect the implementation of ERAS. The mode of education (web-based, books, videos, face-to-face meetings) is a potential challenge. Strategies should be identified according to the features of the patients. Both patients and their families are involved in education planning. Options to support rural patients and address issues related to language, cognition, and elderly patients have been identified.

Sustainability of the ERAS Program

A systematic implementation model is essential to guarantee the sustainability of ERAS programs. Although implementing change in a single service line is challenging, implementing system-wide changes requires extensive collaboration, change management, and optimization strategies. These strategies are necessary to ensure that the healthcare system seamlessly embraces these programs. The real challenge often begins after implementation: maintaining consistent standardization of care and compliance across departments. An implementation practice should not only propose "what works," but also delve into what works where and why to make it sustainable. ERAS programs can be exciting at the start and initially successful, but they

require ongoing commitment to process mapping, problem-solving, and compliance with ERAS protocols, which may diminish over time.[19] To overcome such problems, hospital management can now appreciate and highlight the team and their successes. As is done in every quality process, the activities of the ERAS team can be conveyed to the entire hospital and perhaps even the university through advertising and promotional activities. An additional source of financial support can be created for the financial support that may be needed in the ERAS protocol, and additional financial support can even be provided to team members for their devoted efforts according to the rules of the performance system that already exists in the healthcare system.

Real-World Implementations

To establish the best ERAS practice, a center generally requires three items: an ERAS evidence-based surgery-specific guideline, an ERAS Implementation Program (EIP) for change management, and an ERAS interactive audit system (EIAS). The EIAS is a web-based data entry and analysis system that tracks compliance with evidence-based guidelines established by the site-based ERAS team. The EIP includes an implementation program for change management, coaching, and supervision of an implementation team in training-the-trainer sessions, with a surgeon, an anesthesiologist, and a nurse leader acting as the coordinator for a specific type of surgery. The latter two are provided by Encare, which is in close collaboration with the ERAS society and enables continuous data-driven improvement of patient outcomes based on best practices and current research.

Many theories and frameworks of behavioral change exist. However, only a small number of them have been tested in robust research in healthcare settings. Alberta health services used the theoretical domains framework (TDF) within the QUERI model at individual and organizational levels to identify barriers to and facilitators of spreading and scaling the implementation process. The TDF aims to identify the primary aspects of centers and their requirements. This is a systematic method for moving from target behaviors to theoretical domains, behavior change techniques, and finally to a full implementation intervention. Psychological theories can be used within this framework to identify barriers to changing practices. In Alberta, the implementation of the ERAS was guided by the following questions and their answers: 1. Who needs to do what differently? 2. What barriers to and facilitators of change practice? 3. What strategies were used to address barriers and enablers? 4. What strategies were used to measure behavioral change and its impact on outcomes? As a result, the implementation had a positive impact on patient and healthcare system outcomes and was effectively applied across multiple institutions. The median overall guideline compliance was 39 in pre-ERAS and 60% in post-ERAS patients. The median length of stay was six days for pre-ERAS and 4.5 days for post-ERAS patients. In addition, complications and readmission rates were reduced.[20]

Although utilizing the three items may seem sufficient for practical implementation, the costs associated with EIAS and EIP are significant, particularly in low- and middle-income countries. There are yet to be registered ERAS centers and ERAS centers of excellence from Turkey in the ERAS Society due to budget shortages. In many cases, determining costs accurately can be challenging, and the availability of resources may affect implementation more directly.

Finally, future ERAS strategies should shift away from the endpoints of early recovery and shortened length of stay and focus more on discharge problems, such as the risk of thromboembolic complications, postoperative orthostatic intolerance, late cognitive dysfunction, muscle function, and postoperative sleep disturbances.[21] Therefore, the new implementation strategies should focus on emerging trends to ensure the incorporation of more effective results into the guidelines.

Conclusion

As noted by famous Romanian sculptor, painter, and photographer Constantin Brancusi, "Seeing far is one thing, going there is another". ERAS protocols may have failed to be implemented for various reasons, although they are very efficient. Barriers to implementation may arise at the policy, organizational, provider, and patient levels. In addition to theory, in practice, the success of an ERAS implementation relies on motivated clinicians working together to engage stakeholders, understand workflow processes, and overcome barriers to the delivery of evidence-based care. We look forward to witnessing progress in the years to come and reaching a point where there is seamless integration of research into practice and policy.

Footnote

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Original Article
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Bispectral Index Guidance Reduced Target Plasma Propofol Concentration During ERCP in Patients with Liver Cirrhosis

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Abstract

Objective: The primary aim of this study was to investigate the guidance effect of the bispectral index (BIS) on the target plasma concentration (TPC) of propofol required for deep sedation during endoscopic retrograde cholangiopancreatography (ERCP). Second, to identify propofol consumption, recovery time, and adverse events.

Methods: A total of 42 consecutive patients with liver cirrhosis and 43 consecutive patients with healthy livers were enrolled. Propofol was administered via a target control infusion (TCI) syringe pump (Marsh Model) at BIS 60-70. Patients were not intubated, were placed in the prone position, and underwent spontaneous breathing. Propofol TPCs (μg mL^{-1}) and BIS values were recorded at T0 (baseline), T1 (5 min after induction), T2 (5 min into ERCP), T3 (15 min), T4 (30 min), and T5 (recovery).

Results: TPCs and propofol consumption were lower in patients with cirrhosis than in those without cirrhosis (T4: 2.7±0.5 vs. 3.3±0.4 μg mL^{-1}), *P*=0.001, and 270.4±6.9 mg vs. 390.8±13.4 mg, *P*=0.001), respectively. Patients with cirrhosis required more time to recover (8.5±2 vs. 6.2±0.9 min, *P*=0.001), despite comparable ERCP durations (31.1±11.1 vs. 34±12.5 min, *P*=0.28). A significant decline in TPC values among patients with cirrhosis with time (T1: 3.3±0.3, T2: 3.1±0.3, T3: 2.9±0.4, T4: 2.7±0.5 μg mL^{-1}, *P*=0.001), indicating a cumulative effect. One patient with cirrhosis required bag-mask ventilation, while three patients without cirrhosis were converted to general anaesthesia.

Conclusion: Combining the TCI Marsh pharmacokinetic model with BIS monitoring lowered the TPC levels required for deep sedation in patients with cirrhosis compared with healthy patients and allowed for individual variations. The prone position in deeply sedated and non-intubated spontaneous breathing patients is not without the risk of hypoxia.

Keywords: Cholangiopancreatography, endoscopic retrograde, liver cirrhosis, prone position, propofol, syringe pumps

Main Points

- Bispectral index-guided sedation toward optimal and lower target plasma propofol concentrations in liver cirrhotic patients compared to healthy counterparts.
- Prone position in patients undergoing spontaneous breathing is not without risk of hypoxia.
- Attention should be paid to the development of hypoxia and desaturation throughout the procedure, and the presence of a qualified anaesthesiologist at these remote endoscopy sites is essential.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has recently been performed with deep sedation more than with general anaesthesia (GA).[1] In 2021, ERCP under GA only ranged from 7% to 10% in the United Kingdom.[2] Deep propofol sedation for ERCP procedures is preferred to conscious sedation as patients often tolerate the procedure better.[2,3] However, deep sedation, as defined by the American Society of Anesthesiologists (ASA), can

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lead to airway compromise and inadequate spontaneous breathing. Propofol has a narrow therapeutic window, and patients can progress from deep sedation to GA. Individual variations and co-existing diseases, such as liver cirrhosis, should be taken into consideration.[4,5] The Royal College of Anaesthetists in the United Kingdom recommends that patients undergoing deep sedation should be monitored and an anaesthesiologist should be present.[6] Target control infusion (TCI) syringe pumps are designed to deliver propofol at a specific target plasma concentration (TPC) for sedation or anaesthesia, which can range from 2 to 5 μg mL^{-1}. However, the pharmacokinetic models incorporated in these TCI syringes were derived from pharmacological studies performed among patients without hepatic disorders, which might not be suitable for patients with hepatic cirrhosis.[7-11] Hepatic disease can affect drug pharmacokinetics and dynamics.[12-15] Inadequate sedative doses to hepatic patients can delay recovery and lead to drug accumulation.[13,16] The primary aim was to investigate the guidance effect of monitoring sedation depth with the bispectral index (BIS), an electroencephalogram (EEG)-processed monitor, on the required TPC of propofol required for deep sedating patients with and without hepatic cirrhosis during ERCP. Secondary to identify propofol consumption and recovery time, as well as reporting any adverse events associated with deep sedation.

Methods

The Institution Review Board of National Liver Institute, Menoufia University authorized (IRB NLI IRB 00003413 FWA0000227) this quasi-experimental study on the 1st of November 2019, with approval number 0177/2019. The study was conducted between 10th November 2019 and 1st November 2021 at National Liver Institute, Menoufia University, Egypt. All patients in the study provided informed consent to participate.

Inclusion Criteria

Patients aged 18-60 years who underwent elective ERCP. Patients were not intubated, were placed in a prone position, and underwent spontaneous breathing. Two groups of patients: the cirrhotic group that included forty-two consecutive hepatic cirrhotic patients with Child-Pugh classification (Child A or B) and with confirmed laboratory and ultrasound diagnosis for hepatic cirrhosis from chronic hepatitis C, which represent the main etiology of cirrhosis in this part of the world.[17] The non-cirrhotic group included 43 consecutive patients with healthy livers. Two patients were excluded from the cirrhotic group and three from the noncirrhotic group.

Exclusion Criteria

Participants with a history of severe chronic obstructive lung disease and a significant risk of aspiration. Patients were also excluded if they faced procedural or anatomical challenges not related to the sedation technique that could prolong the duration of the ERCP, when converted to GA with tracheal intubation, or if the procedure was aborted. In the study by Fanti et al.,[18] difficult ERCP affected the total dose of propofol consumed and the mean duration of ERCP. Both were related to the degree of procedural difficulty.[18] The exclusion criteria include patients with significant hepatic encephalopathy or coma, cardiovascular, respiratory, or renal diseases, drug abuse, and morbid obesity. Patients with significant encephalopathy have abnormal EEG results, which can affect the EEG and hence the BIS values, as stated by Mitra et al.[19]. The severity of hepatic encephalopathy was assessed using the West Haven criteria on a scale of 0-4. Stages 0-1 are minimal hepatic encephalopathy in which symptoms may not be noticeable clinically and were included in the study. Stage 2-4 is characterized by an increase in severity, and stage 4 is in coma.[20,21]

Target Control Infusion Technique

The TCI technique ensures that propofol reaches and maintains a desired concentration in the blood or at the effect site (Brain) via computerized syringe pumps, which constantly alter the propofol dosage. TCIp indicates that the blood plasma concentration for the drug is the principal target, whereas the target in TCIe is the effect site (Brain) concentration. In the current study, the TCIp was adopted, and doses were altered according to the changes in the BIS to keep it between 60 and 70. TCI models are based on pharmacokinetic studies embedded in the software of the smart syringe pump. For propofol, the Marsh and Schnider models are widely available; however, a newly developed model called the Eleveld model was recently introduced. The Marsh model was adopted in the current study.[22,23]

Deep Sedation Technique and Monitors

The ASA classified levels of sedation as minimal, moderate (conscious), or finally deep sedation, which can easily drift into GA. ERCP can be performed under moderate conscious sedation, with midazolam and opioid or under deep sedation with propofol.[24,25] In the current study, the anaesthesiologists provided deep sedation with monitored care to the patients, which was in line with Azimaraghi et al.[26] consensus for sedation. Azimaraghi et al.[26] favored monitoring deep sedation care over GA during ERCP, but with specific inclusion and exclusion criteria to reduce perioperative adverse events, and the criteria were respected in the current study. Patients with an increased risk of pulmonary aspiration and those undergoing prolonged high-complexity or difficult procedures were not considered for deep sedation and were excluded.[26]

The current study protocol does not allow premedication for any patient before induction. In the endoscopy suite, standard monitors [General Electric (Madison, USA)] were applied, including non-invasive blood pressure (NIBP), electrocardiogram (ECG), pulse oximetry with oxygen saturation (SaO_2), and end-tidal carbon dioxide percentage ($ETCO_2$) sampled from a modified nasal cannula capable of simultaneously delivering oxygen and sampling carbon dioxide (CO_2) at the same time. End-tidal carbon dioxide monitored the breathing rhythm and allowed early warning for any episodes of apnea, besides visual monitoring of chest movements. Qadeer et al.[27] demonstrated that hypoxia was reduced during ERCP by continuous monitoring of end-tidal CO_2 during the procedure. The wrist or forearm vein of the independent arm was cannulated for intravenous fluid and propofol infusion. Before sedation, each patient was independently positioned to avoid any possible nerve injury from passive positioning. Ringer's acetate (500 mL) was infused before commencing endoscopy. A 50 mL syringe containing 10 mg mL^{-1} propofol (Fresenius Kabi, Bad Homburg, Germany) was loaded into an automated, computer-controlled syringe pump (Agilia, Fresenius Kabi, Germany), and the Marsh pharmacokinetic model was selected. Age and weight were also added to the settings. The initial TPC was set at 4 μg mL^{-1}. After administration of 100% oxygen via the nasal cannula, the propofol TPC and doses were titrated to keep the patients deeply sedated at a BIS value (BIS, Aspect, MA, USA) between 60 and 70. BIS monitoring facilitates objective assessment of the sedation level during the procedure.[28] Recovery was defined as recovery after restoring consciousness or BIS values increase above 90. BIS monitoring is an EEG-processed method that guides the depth of anaesthesia using a complex algorithm to create an index score. BIS objectively measures the level of consciousness as mentioned above and titrates the propofol dosage toward the desired effect. Any increase in BIS readings >70 indicates the inadequacy of sedation and the need to increase the targeted plasma concentration in steps of 0.5 μg mL^{-1} every 20 seconds and vice versa until BIS falls back to values between 60 and 70.[29]

Precautions During Deep Propofol Sedation

Propofol is a short-acting intravenous anaesthetic agent with better sedation and recovery outcome compared to conscious sedation.[30] However, Propofol has a narrow therapeutic window, and it can easily progress from deep sedation to GA, which can affect airway patency and spontaneous breathing. The presence of an anaesthesiologist and continuous monitoring of breathing, SaO_2, and $ETCO_2$ are mandatory to allow for early air way obstruction warning.[31] The Royal College of Anaesthetists in the United Kingdom recommends that the presence of an airway supporter to immediately interfere when in need.[32] Oxygenation is maintained during spontaneous breathing with 100% oxygen at 4-8 L min. Airway opening skills, such as jaw thrust and head tilt and chin lift, should be applied initially to relieve obstruction whenever SaO_2 falls below 90% or the capnography waves become interrupted. However, if this approach is insufficient, the patient should be moved to the prone position for manual ventilation and endotracheal intubation if necessary.

Maintenance of Hemodynamics

Hypotension is defined as a reduction of >20% of the baseline mean NIBP. Hypotension should be initially assessed for hypovolemia, and fluids should be replaced when required. Otherwise, treatment with intravenous boluses of ephedrine (5 mg). Bradycardia [heart rate (HR) <45 beats min] should be treated with Atropine (0.25 mg). Any increase in HR (beat min) or mean MAP mm Hg by more than 20% of baseline within a BIS value between 60 and 70 indicates the need for fentanyl. Adverse events, such as hypoxia, hypotension, and bradycardia were all recorded.

Data and Measured Times

HR (beat min), mean NIBP (mmHg), SaO_2 (%), TPC (μg L^{-1}), BIS values at T0 (baseline), T1 (5 minutes after induction), T2 (5 min ERCP), T3 (15 min ERCP), T4 (30 min ERCP), and T5 (end ERCP).

Power of the Study

The power was achieved by a sample size of 40 patients per group (number of groups is 2) for the t-test means: difference between to independent means (two groups) based on a comparison of total anaesthetic consumption (primary outcome), resulting in a two-tails standardized effect size (d) of 1.160 and a power of 99.92%. A sample size of 40 patients per group is sufficient to conduct this study with a power of >80%. The post-hoc computation for the achieved power was performed using G*Power version 3.1.9.2.[33]

Statistical Analysis

Demographics, monitor parameters and TPC data were expressed as mean and standard deviation for analysis. Data were loaded into the Statistical Package for Social Science (SPSS) software package (version 21) (SPSS, Inc., Chicago, IL, USA). Repeated measures ANOVA (chi-square) was applied between the measured times. Propofol TPC and SaO_2 in the studied groups are shown as clustered bar charts with a 95% confidence interval (Dunn-Sidek technique). T-test for comparisons performed between the two groups.

Results

Eighty-five patients were enrolled in this study. Only five participants were excluded, as demonstrated in the

CONSORT flow chart in Figure 1. Forty-two consecutive patients were allocated to the cirrhotic group, and 43 consecutive patients with healthy livers were allocated to the noncirrhotic group. Two patients were excluded from the cirrhotic group and three from the. Table 1 presents the demographic characteristics of the included patients in each group. Age 47.93±11.62 vs. 47.43±10.62-years, P=0.84, and body mass index 26.89±2.58 vs. 27.15±2.91 kg m^{2-1}, P=0.67 in cirrhotic versus non-cirrhotic patients, respectively. None of the included patients had significant neurological disorders. Hypertension was the most frequent cardiovascular comorbidity (30%), and 10% had a previous history of biliopancreatic surgery.

Hepatic patients (Child-Pugh classification: A 50% and B 50%) consumed less total propofol for sedation during ERCP (270.48±6.91 mg vs.390.88±13.44 mg, P=0.001), (Table 1). A lower propofol TPC was required to sedate patients with cirrhosis compared with patients without cirrhosis (T4: 2.7±0.5 vs. 3.3±0.4 µg mL^{-1}) (P=0.001). Total propofol consumption and TPC were significantly reduced among patients with cirrhosis compared with those without cirrhosis when guided by BIS. The mean recovery times (minute) were longer among cirrhotic vs. non-cirrhotic patients (8.53±2.09 vs. 6.25±0.90; P< 0.001, respectively), despite similar ERCP durations (Table 1 and Figure 2). The mean BIS values for patients with cirrhosis tend to drift to lower values (BIS<60) compared with those with healthy livers (T1: 59.40±7.30 vs 70.95±5.13; P < 0.001, T2: 56.13±5.76 Vs 58.50±4.67; P=0.05, T3: 56.58±7.32 vs 60.98±6.50; P=0.006, T4: 56.08±6.42 vs 63.08±6.30; P < 0.001, T5: 58.00±6.61 vs 63.63±6.92; P=0.001, respectively), as shown in Table 2 and Figure 3.

Another significant finding was the gradual decrease in the BIS-guided propofol TPC (µg mL^{-1}) required to deeply sedate patients with cirrhosis as time proceeds with ERCP, suggesting a cumulative effect: T1: 3.3±0.3, T2: 3.1±0.3, T3: 2.9±0.4, T4: 2.7±0.5, repeated-measures ANOVA, P=0.001. Figure 2. The systemic hemodynamics were not different between the two study groups (P > 0.05) (Table 3). No intraoperative awareness was reported for any of the study patients.

In the cirrhotic group, only one patient required temporary bag-mask ventilation to support his breathing, and ERCP was resumed immediately. Three non-cirrhotic patients required endotracheal intubation to treat desaturation and avoid aspiration during prolonged ERCP and were excluded from the study (Figure 1).

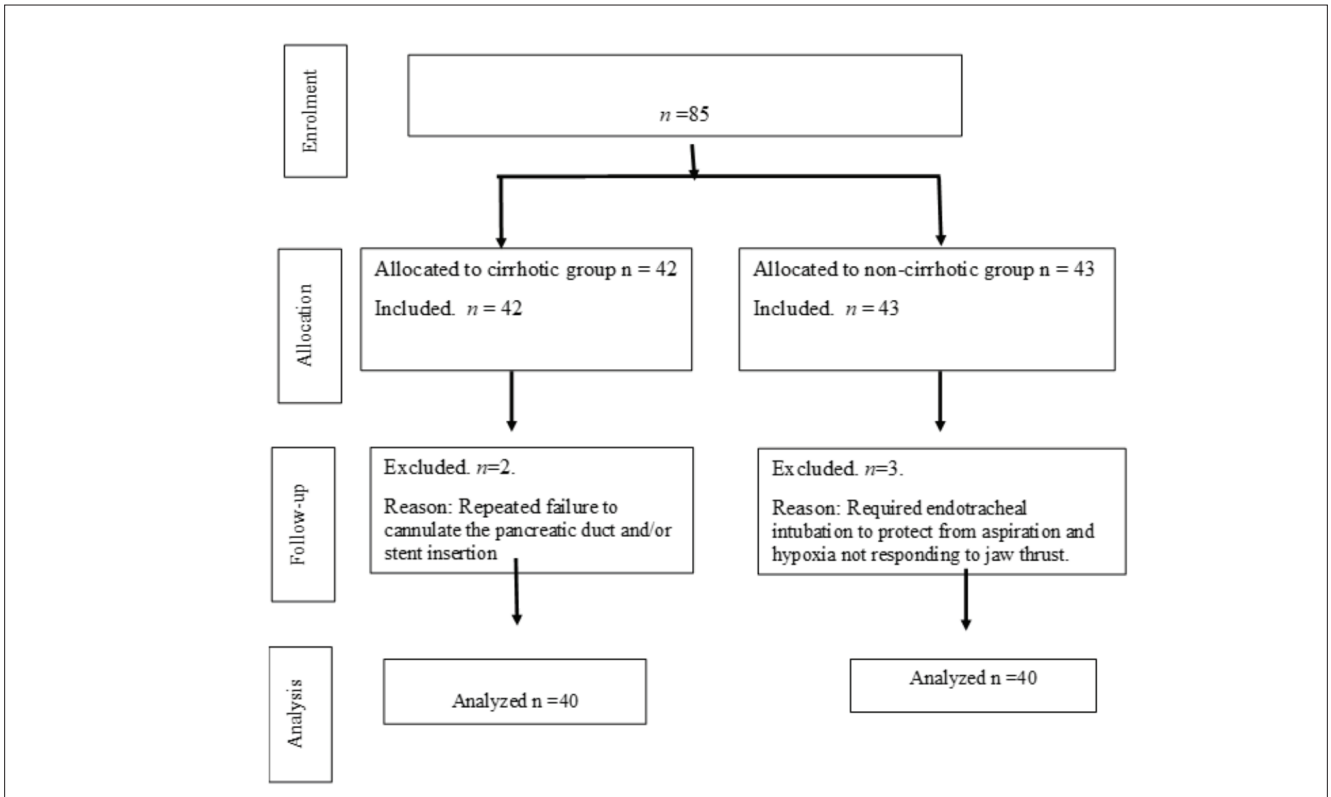

Figure 1. Consort flow graph

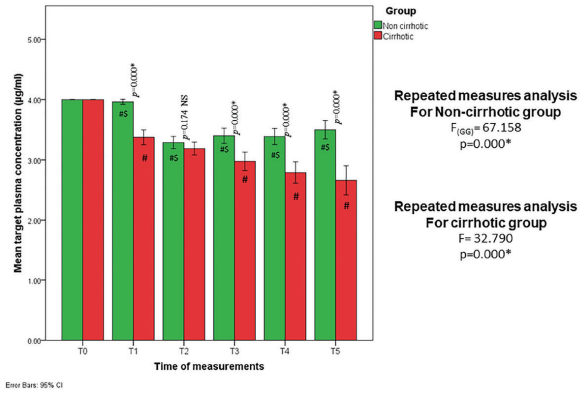

Figure 2. Target plasma concentration in the studied groups, shown as a clustered bar chart with a 95% confidence interval (Dunn-Sidek technique). T0 (baseline), T1 (5 min after induction), T2 (5 min ERCP), T3 (15 min ERCP), T4 (30 min ERCP), and T5 (End ERCP)

ERCP, endoscopic retrograde cholangiopancreatography; #means statistical significance with measurement time T0, $means statistical significance with previous time of measurement.

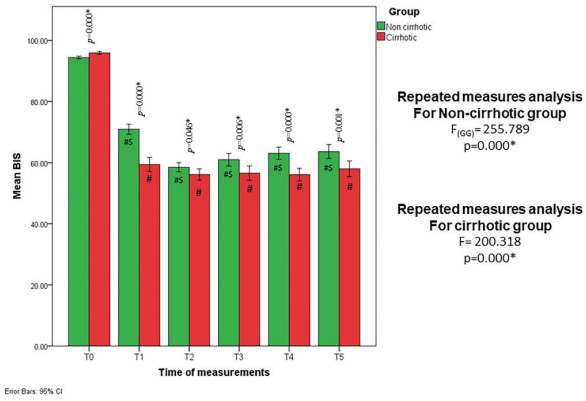

Figure 3. Mean BIS in the studied groups, shown as a clustered bar chart with a 95% confidence interval (Dunn-Sidek technique). T0 (baseline), T1 (5 min after induction), T2 (5 min ERCP), T3 (15 min ERCP), T4 (30 min ERCP), and T5 (End ERCP)

BIS, bispectral index; ERCP, endoscopic retrograde cholangiopancreatography; #means statistical significance with measurement time T0, $means statistical significance with previous time of measurement.

Table 1. Demographics and Perioperative Study Findings

	Group		Test of significance *P* value
	Non-cirrhotic	**Cirrhotics**	
Age (year)			
n	40	40	$t_{(df=78)} = 1.09$
Mean ± SD	47.43±10.67	47.93±11.62	*P*=0.28, NS
BMI (kg m²)			
n	40	40	$t_{(df=78)} = 0.43$
Mean ± SD	27.15±2.91	26.89±2.58	*P*=0.67, NS
Total procedure time (min)			
n	40	40	$t_{(df=78)} = 1.09$
Mean ± SD	47.43±10.67	31.15±11.15	*P*=0.28, NS
Total propofol (200 mg/20 mL) consumption (mg)			
n	40	40	$t_{(df=78)} = 5.19$
Mean ± SD	390.88±13.44	270.48±6.91	*P*=0.000*
Recovery time (min)			
n	40	40	$t_{(df=78)} = 6.33$
Mean ± SD	6.25±0.90	8.53±2.09	*P*=0.000*

Age expressed as years and body mass index (BMI) expressed as kg m².
*Denotes statistical significance (p<0.05), while NS denotes statistical non-significance (*P* > 0.05).
SD, standard deviation; t, independent Student's t-test; df, degree of freedom; n, number of patients.

Table 2. Bispectral Index (BIS) Trend Changes in the Two Studied Groups

BIS	Group		Test of significance *P* value
	Non-cirrhotic	Cirrhotics	
T0			
n	40	40	$t_{(df=78)} = 4.76$
Mean ± SD	94.40±1.35	95.90±1.46	*P*=0.000*
T1			
n	40	40	$t_{(df=69.98)} = 8.18$
Mean ± SD	70.95±5.13	59.40#±7.30	*P*=0.000*
T2			
n	40	40	$t_{(df=78)} = 2.03$,
Mean ± SD	58.50±4.67	56.13#±5.76	*P*=0.05*
T3			
n	40	40	$t_{(df=78)} = 2.84$,
Mean ± SD	60.98±6.50	56.58#±7.32	*P*=0.006*
T4			
n	40	38	$t_{(df=76)} = 4.855$
Mean ± SD	63.08#$±6.30	56.08#±6.42	*P*=0.000*
T5			
n	38	28	$t_{(df=64)} = 3.3$,
Mean ± SD	63.63#$±6.92	58.00#±6.61	*P*=0.001*
Repeated measures ANOVA			
Chi-square	$F_{(GG)}$= 255.789	F= 200.318	
p	*P*=0.000*	*P*=0.000*	

T0 (baseline), T1 (5 minutes after induction), T2 (5 min ERCP), T3 (15 min ERCP), T4 (30 min ERCP), and T5 (End ERCP).
*Denotes statistical significance ($P < 0.05$), while NS denotes statistical non-significance ($P > 0.05$). #Means statistical significance with measurement time T0, $means statistical significance with previous time of measurement.
SD, standard deviation; t, independent Student's t-test; df, degree of freedom; n, number of patients.

Table 3. Systemic Hemodynamics of Patients

Variables	Mean ± SD		Test of significance *P* value
	Non-cirrhotic	Cirrhotics	
Heart rate (beat min) T0	80.53±9.64	90.00±14.21	$t_{(df=78)}$=3.49 *P*=0.001*
T1	77.53#±10.43	89.18±13.76	$t_{(df=78)}$=4.27 *P*=0.000*
T2	79.93#±9.82	88.20±14.25	$t_{(df=69.232)}$=3.03, *P*=0.003*
T3	82.55#±9.37	89.35#±12.50	$t_{(df=72.33)}$=2.75 *P*=0.007*
T4	85.92#±10.13	88.54#±12.76	$t_{(df=76)}$=1.00, *P*=0.319 NS
T5	85.37#±9.18	88.73#±12.31	$t_{(df=69)}$=1.31 *P*=0.19 NS
Repeated measures ANOVA (chi-square) *P*	$f_{(GG)}$=12.364 P=0.000*	$f_{(GG)}$ = 0.559, *P*=0.662 NS	
Mean blood pressure (mmHg) T0	93.7±13.8	94.5±10.9	$t_{(df=78)}$=0.16 *P*=0.795 NS

Table 3. Continued

Variables	Mean ± SD		Test of significance *P* value
	Non-cirrhotic	Cirrhotics	
T1	85.6#±14.0	81.9#±10.5	$t_{(df=78)}$ =1.34 *P*=0.183 NS
T2	85.1#±14.5	85.0±10.2	$t_{(df=78)}$ =0.05, *P*=0.965 NS
T3	84.6±14.0	87.1±9.2	$t_{(df=78)}$ =0.93, *P*=0.354 NS
T4	85.9±11.3	89.0±9.7	$t_{(df=76)}$ =1.12 *P*=0.267 NS
T5	87.1±11.2	86.4±9.6	$t_{(df=64)}$ =0.006 *P*=0.995 NS
Repeated measures ANOVA (chi-square) *P*	$F_{(GG)}$=10.043, *P*=0.000*	F=8.084 *P*=0.000*	

T0 (baseline), T1 (5 minutes after induction), T2 (5 min ERCP), T3 (15 min ERCP), T4 (30 min ERCP), and T5 (end ERCP).
*Denotes statistical significance ($P < 0.05$), while NS denotes statistical non-significance ($P > 0.05$). #Statistical significance with measurement time T0
SD, standard deviation; t, independent Student's t-test; df, degree of freedom; ERCP, endoscopic retrograde cholangiopancreatography.

Discussion

The optimal propofol TPC for deep sedation when guided by BIS was found to be lower for patients with cirrhotic livers compared with those with healthy livers, as shown in the results. Liver cirrhosis leads to a reduction in liver mass and hepatic blood flow, which can affect propofol pharmacokinetics, dynamics, and clearance.

Pros of Processed ECG Monitoring

One of the lessons learned from the current study is the ability of the BIS to identify individual variations. The TPC of propofol for deep sedation was gradually and progressively reduced among patients with cirrhosis, specifically as the ERCP progressed from one measurement time to another, indicating a cumulative effect. These findings support the beneficial role of the BIS as a processed EEG monitor for sedation depth and as a guide for the optimal propofol TPC. These findings agree with the recommendations and guidelines for safe practice published by the Association of Anesthetists and the Society for Intravenous Anesthesia in 2019,[34] as well as those extracted from the work by Castellanos Peñaranda et al.[35].

Few publications have investigated the impact of monitoring the depth of sedation on the consumption of hypnotic medications in this specific group of patients with liver cirrhosis. Deep sedation can easily drift into GA (<BIS 60), particularly among hepatic patients, as evident from the mean BIS values compared with the controls (Table 2), which warrant the need for continuous monitoring of the BIS values and frequent adjustment of the propofol infusion rates to prevent any further increase in sedation depth. However, few patients in both groups required assisted breathing and endotracheal intubation. This study demonstrated the importance of combining BIS monitoring with TCI. Manual propofol injection or continuous infusion without EEG monitoring or TCI software is not recommended. There is a need to train anaesthesiology staff on TCI protocols for sedation and explain the beneficial role of monitoring sedation depth using processed EEG monitors on a wider scale, as recommended by the Total Intravenous Association.

Entropy, another processed EEG monitor, also revealed similar findings to GA in surgery when applied to hepatic patients, as in Yassen et al.[36], Vakkuri et al.[37], and Wang et al.[38] studies. Schumann et al.[39] Yassen et al.[40] and Refaat and Yassein[41] believe that anaesthesia depth monitors should be implemented and encouraged. This will help identify variations in individual responses to different anaesthetic agents. Processed EEG monitors should be combined with other standard monitors to enable a multimodal monitoring approach. In the current trial, the dual monitoring of the BIS and other hemodynamic parameters helped reduce drug delivery and hemodynamic instability. Sessler et al.[42] their study showed that low BIS levels were correlated with both low mean blood pressure and minimum alveolar concentrations. They linked this to increased hospitalization and mortality. Leslie et al.[43] reported a relationship between low BIS values and survival.

Limitations of Processed EEG Monitoring

Processed EEG monitors are not without limitations and practical challenges. Hajat et al.[44] review in 2017 discussed the limitations raised by the National Institute for Clinical Excellence (NICE) in 2013. The NICE report supports their use, particularly in patients at higher risk. However, evidence of their impact on reducing awareness is not enough.[45] Ibrahim et al.[46] noted that BIS scores can vary significantly between patients, making it difficult to predict ED depth without considering individual variations. In the current study, the results support these allegations. BIS values not only varied from one patient to another but also from a measured time to another in the same patient. One of the arguments that limit the spread of processed EEG monitoring among anaesthesiologists is the belief that monitoring end-tidal concentrations of inhaled anaesthetics can represent an accurate reflection of the drug's effect on the brain. However, these end-tidal concentrations will never reflect individual variations. The cost and availability of EEG depth monitors worldwide remain challenges. Most processed EEG devices derive their results from sampling the frontal area, not the rest of the brain.

Recently during the Euroanesthesia 2024 Meeting; May 25-27; 2024; in Munich, Germany, Matthias Kreuzer, from the Technische Universität München, Germany, discussed how hypotension, hypoxia, hypercarbia, and the combination of more than one anaesthetic drug could affect EEG interpretation.[47] In our study, no hypotensive events were reported, and only propofol was infused. Recently, in 2020, Kaiser et al.[48] conducted a narrative review discussing the pros and cons of the available EEG monitors and the need to respect individual variations, particularly among the elderly.

Marsh Target Control Infusion Model

The Marsh pharmacokinetic parameters incorporated into the TCI smart syringes, as previously mentioned, were designed for patients without organ dysfunction and might not be optimal for patients with hepatic disease. Wu et al.[49] measured propofol plasma concentrations and discovered significant changes during the three stages of liver transplantation. The preset TCI model does not take into consideration these significant changes in propofol plasma concentrations, and a method is required to guide propofol doses. Tremelot et al.,[50] later in 2008 confirmed these propofol pharmacokinetic changes during the anhepatic phase of liver transplantation. Tremelot et al. [50] had to decrease the propofol TPC during the anhepatic phase to 2.0 μg mL^{-1} ±0.8 compared to 3.0 μg mL^{-1} ±0.9, ($P < 0.0001$) in the other phases of the transplant procedure. The above two studies indicate that liver patients should not be subjected to the same TCI Marsh pharmacokinetic settings as for other patients with healthy livers and that a method to monitor the effect of the drug should be introduced to guide the TCI settings. Joosten et al. [51] in 2020 developed a multiple closed-loop system that included a TCI syringe pump and a BIS monitor together with a carbon monoxide monitor (Flotrac, Edwards Life sciences, USA). This system was able to provide promising results but needed to be evaluated in large populations. Kamel et al. [52] studied a group of patients with cirrhosis undergoing liver resection using the Marsh model and found that an adequate TPC for propofol with fentanyl was 3.00 μg dL^{-1}.

Accuracy of Target Control Infusion Models

TCI models were created from studies performed on a limited group of patients, and thus, they might not accurately represent the vast variety of patients encountered in daily practice. A pharmacokinetic model based on a wider population is still needed to reflect and describe adequate plasma concentration changes and predicted plasma concentrations. The effect site brain concentration might not improve the performance of the current pharmacokinetic (PK) models, but adopting more improved PK models will. The Eleveld propofol model is one of these recently developed models, which is considered to be more accurate in predicting plasma concentrations and more applicable to a wider range of patients than the Marsh and Schnider models. However, the Eleveld model needs to be installed on a wider scale, and more PK models need to be designed to target specific patient populations, such as patients with liver dysfunction and cirrhosis.[53]

Hypoxia and Desaturation

The main challenge in the current study was the remote position of the endoscopy suite, which should be equipped with the same standard facilities, such as those prescribed by the ASA in 2018, for operating rooms. The procedures include the presence of a qualified anaesthesiologist and anaesthesia machines with electrocardiogram, NIBP, SaO_2, and capnography. The American Society for Gastrointestinal Endoscopy also published guidelines for procedural sedation, which are similar to the ASA recommendations; but unfortunately, the capnography monitoring was not considered mandatory.[54-57]

Sedation-related complications prescribed by Azimaraghi et al. [26] and Hormati et al.[58] include desaturation and pulmonary aspiration, as well as hemodynamic instability and apnoea.

Hypoxia can develop with deep sedation Metzner et al.[59] and Goudra et al.[60] reported that desaturation can double that of operating rooms. Goudra et al.[61] in a retrospective analysis showed that 72% of the adverse events in the endoscopic setting were related to desaturation.

One of the lessons learned from the current study was the need to monitor the capnography rhythm and chest movements continuously and interfere when needed. Four

of the enrolled patients required interference to protect them from desaturation, as mentioned in the results section. The availability of an anaesthesiologist to manage airway obstruction was recommended by the European Society of Anesthesiology and in the European Board of Anesthesiology guidelines for procedural sedation and analgesia in adults.[62]

Hypoxia in patients with prone-positioned spontaneous breathing represents a serious adverse event. Melis et al.[63] study a significant portion of their patients suffered from desaturation (35%); they were non-intubated healthy persons prone to undergoing ERCP with TCI propofol. In the current study, the results indicated that three patients developed hypoxia (3/85, 3.5%) and were intubated and excluded from the study. One patient required temporary supportive facemask ventilation during ERCP, and the procedure was not aborted. Smith et al.[30] conducted a randomized control trial and reported a 10% conversion rate to GA in high-risk patients, but this rate was significantly reduced with lower ASA grades (1 or 2) to 3.7%, which is similar to the 3.5% in our current study.[64]

The recovery time was statistically prolonged among patients with cirrhosis compared with the controls, but without noticeable clinical significance; however, in a high-turn flow endoscopy unit, this could have an impact on the ready-to-discharge time, which unfortunately was not studied and can be considered one of the limitations in the study. However, given the cumulative effect observed with TPC among the cirrhotic patient group only, one would expect a significant delay in hepatic recovery would be expected if TPC were not monitored and guided with BIS.

Finally, Hormati et al.[58], Althoff et al.[2] and Khoi et al.[65] and reported an increase in hypotensive events with GA during ERCP compared with deep sedated with propofol. Fortunately, hypotension was not observed in the current study. This could be due to the careful selection of the included patients or the combination of TCI with BIS monitoring, which helped to avoid overdosing and to respect individual variations.

Conclusion

In conclusion, combining the Marsh TCI pharmacokinetic model with BIS monitoring reduced the TPC required for deeply sedating patients with cirrhosis undergoing ERCP and identified individual variations. This study demonstrated the importance of shifting to TCI during deep sedation and avoiding manually injecting propofol or continuously infusing propofol with ordinary syringe pumps without a mean of sedation depth monitoring, particularly among patients with hepatic cirrhosis. The prone position in patients without intubated spontaneous breathing is not without risk. Attention should be paid to hypoxia and desaturation development throughout the procedure. Adhering to the exclusion criteria, monitoring of breathing and the presence of a qualified anaesthesiologist at these remote endoscopy sites are essential.

Footnote

Ethics Committee Approval: Ethical approval was obtained from the Institution Review Board of Menoufia University, Shebeen Elkom City, Egypt (approval no.: 0177/2019, date: November 01, 2019).

Informed Consent: All patients in the study provided informed consent to participate.

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

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Dexmedetomidine Versus Fentanyl in Intraoperative Neuromuscular Monitoring Using A Propofol-based Total Intravenous Anaesthesia Regimen in Spine Surgeries

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Abstract

Objective: This prospective, double-blind, randomized study aimed to compare the effects of dexmedetomidine and fentanyl on the latency and amplitude of transcranial motor evoked potentials (TcMEPs) under propofol-based total intravenous anaesthesia (TIVA) in spine surgery. Secondarily, intraoperative hemodynamics, total propofol consumption, recovery profile, and surgical field quality were compared.

Methods: TcMEP amplitude and latency recordings of bilateral abductor pollicis brevis and abductor hallucis muscles posted for elective lumbar spine surgery under TcMEP monitoring randomly divided into two study groups. Throughout the surgery, TIVA was administered using intravenous propofol (100-150 μg kg^{-1} min^{-1}) and dexmedetomidine (0.5-0.7 μg kg^{-1} h^{-1}) in group D and intravenous propofol (100-150 μg kg^{-1} min^{-1}) and fentanyl (1 μg kg^{-1} h^{-1}) in group F. TcMEPs were recorded at various time points during the surgery. Immediately after extubation recovery from anaesthesia was noted. Additionally, hemodynamic parameters, total propofol consumption, and surgical field quality were assessed.

Results: Latency and amplitude were comparable between the groups. Time to extubation was significantly longer in group D, but the mean (standard deviation) duration of stay in recovery was shorter in group D [47.55 (7.51) 95% confidence interval (CI) (44.863-50.237)] (*P*=0.046). Total propofol consumption was reduced in group D [220 (38) 95% CI (206.402-233.598)] (*P*=0.025) and surgical field condition was better in group D.

Conclusions: Dexmedetomidine and fentanyl do not have any effect on TcMEP amplitude and latency. However, dexmedetomidine provides the additional advantage of reduced total propofol consumption, shorter stay in recovery, and better surgical field quality.

Keywords: Dexmedetomidine, evoked potentials, fentanyl, hemodynamics, propofol

Main Points

- Dexmedetomidine and fentanyl had no effect on the transcranial motor evoked potential amplitude and latency.
- Dexmedetomidine reduces total propofol consumption, provides a better quality of surgical field.
- Dexmedetomidine provides a shorter stay in recovery.

***This study has been presented in any APNCC 2024 conference held at Kuching, Sarawak Malaysia on 29th June, 2024.**

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Introduction

Currently, monitoring of transcranial motor evoked potential (TcMEP) intraoperatively is routinely performed and is regarded as a vital tool available to the surgical team that guides them in avoiding any motor tract injury during certain surgeries of the spine and cranium.[1]

The motor cortex is stimulated through the skull to produce compound muscle action potentials (CMAP), which are produced from peripheral muscles to maintain the motor pyramidal pathway intact. TcMEP has 91% sensitivity and 96% specificity, making it a gold standard modality.[2]

Intraoperatively, several factors influence CMAP apart from surgical manipulation like blood pressure, temperature, expired carbon dioxide partial pressure, and oxygen, so for optimal TcMEP recording, all the aforementioned factors should be optimized.[3] Anaesthetic agents like muscle relaxants, are known to block signal transmission over the neuromuscular junction. Inhalational agents should be used at a low minimum alveolar concentration to suppress CMAP. Opioids have a minimal influence on CMAP.[3,4] Intravenous (IV) anaesthetics are known to suppress the TcMEPs less in comparison to inhalational agents.[5]

Most commonly, propofol-based total IV anaesthesia (TIVA) along with opioid is used during TcMEP monitoring, which is recommended as an ideal regime by the American Society of Neurophysiological Monitoring. Propofol is metabolized rapidly so its effect on motor evoked potential (MEPs) and sedation can be titrated quickly. However, higher doses are required for maintaining the surgical depth then it may depress the TcMEP readings.[3,6] Therefore adjuvants like an opioid or dexmedetomidine can be employed for maintaining the anaesthetic depth without affecting the MEP.[7]

Modified Delphi consensus recommendations support using the standard regime of TIVA along with an adjuvant like dexmedetomidine, ketamine, or lignocaine without any effect on TcMEP signals.[8]

Therefore, we aimed to evaluate and compare the effects of dexmedetomidine and fentanyl in intraoperative neurophysiological monitoring using a propofol-based TIVA regimen in spine surgery.

Methods

Study Design

Prospective, randomized, double-blind study was conducted in strict compliance with the principles of the Declaration of Helsinki. Informed written consent from the patients and institutional Ethics Committee of Mahatma Gandhi Medical College & Hospital, Mahatma Gandhi University of Medical Sciences & Technology, Jaipur (approval no.: MGMC&H/IEC/JPR/2022/1148, date: 22.09.2022) were obtained before the conduct of this study. Registration with the Clinical Trials Registry - India (CTRI/2022/12/048497) was also performed. The study was conducted over a span of 1 year in which all patients of either sex, aged 18 to 65 years, posted for elective spine surgery under transcranial MEP monitoring with a Medical Research Council Scale motor power ≥4/5 were included. Patients who refused to participate, were allergic to the study drugs, had impaired renal and hepatic function, or had any contraindications to TcMEP monitoring like pacemaker, vascular clips, epilepsy, intracranial electrodes, or cortical lesions with raised intracranial pressure were excluded.

Sample Size Determination

Sample size determination was based on the efficacy of dexmedetomidine and fentanyl in terms of the ratio of complete response (defined as no change in amplitude or latency of TcMEP potentials). We selected a baseline ratio of 40% for complete responses based on a previous study.[1] Sample size of 32 patients in each group was derived, where 80% power was present at an alpha 0.05 to detect a difference of 30% between the two groups in terms of the ratio of complete response. Considering a dropout rate of approximately 5%, we calculated that 30 patients would be appropriate.

Randomization, Allocation, Blinding

Sixty patients who fulfilled the inclusion criteria were distributed into two study groups with the help of a computer-generated random number table written in an opaque sealed envelope (Figure 1). For group D n = 30 patients, we administered infusion propofol [Neorof 10 mg mL^{-1} (20 mL), Neon laboratories limited, Mumbai, India] with infusion dexmedetomidine hydrochloride [Dexem 200 µg (2 mL), Themis medicare limited, Uttarakhand, India] prepared in a 50 ml syringe by adding normal saline (48 mL) making 4 µg mL^{-1} drug concentration.

Group F n = 30 patients received infusion propofol [Neorof 10 mg mL^{-1} (20 mL), Neon laboratories limited, Mumbai, India] along with infusion fentanyl citrate [Themifent 500 µg (10 mL), Themis medicare limited, Uttarakhand, India] prepared in a 50 mL syringe by adding normal saline (40 mL) making 10 µg mL^{-1} drug concentration.

An anaesthesiologist who is not associated with the study prepared all infusions. The patient and the anaesthesiologist administering the medications were unaware of the contents of the syringe.

A thorough pre-anaesthesia check-up was conducted where neuromonitoring was explained to the patients and consent was obtained. Any neurological deficit, including sphincter disturbance, was noted. Instructions were given to patients

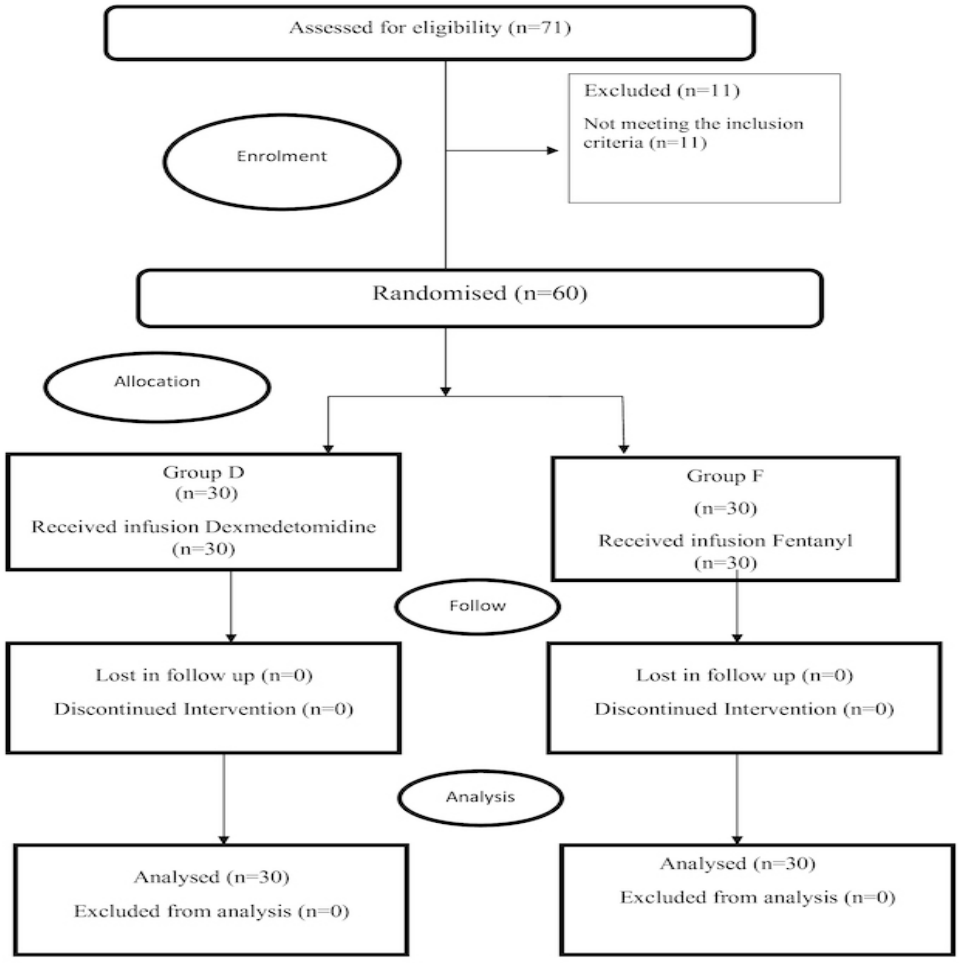

Figure 1. Consolidated standards of reporting trials (CONSORT) flow diagram of participants. D, dexmedetomidine; F, fentanyl; n, number of cases.

to remain nil oral for at least 6 hours (solid food) and 2 hours (clear liquids) before surgery. In operating theater, multipara monitor (MX-550 Philips Medizin Systeme, Germany) showing electrocardiogram, non-invasive BP monitoring, pulse oximetry, and temperature was attached. An IV access with a wide-bore cannula was secured. The anaesthesia regimen was standardized. Preoxygenation with 100% oxygen for at least 3 min, premedication with IV glycopyrrolate 4 µg kg^{-1} and IV fentanyl 2 µg kg^{-1}. Induction was performed with IV propofol 2 mg kg^{-1}, and once ventilation was confirmed, IV succinylcholine 2 mg kg^{-1} was administered to facilitate intubation. A bite block was placed to prevent tongue laceration. An arterial cannula was secured in the radial artery for monitoring beat-to-beat blood pressure. Neuromuscular blockade was monitored using a train-of-four (TOF) ratios in which electrodes were placed at the wrist for the ulnar nerve. Once the TOF ratio was >90%, baseline MEP readings were noted in supine position. Paracetamol 15-20 mg kg^{-1} IV was administered as an analgesic agent in both groups.

NIM-Eclipse (Medtronic, Minneapolis, MN, USA) was used to obtain MEP. Bispectral index (BIS) (Covidien Digital, MN, USA) monitoring was also used to guide the depth of anaesthesia. Using a skin probe, the temperature was recorded and maintained at 35-36 degrees Celsius using warming devices. Surgery was performed in the prone position. Hemodynamic variables like mean arterial pressure (MAP) and heart rate (HR), were documented every 30 min. For assessment of surgical field quality Former's score was used, where 1- stands for only mild bleeding, with no surgical nuisance; 2- moderate bleeding, no surgical interference; 3- moderate bleeding, compromising field of surgery moderately; 4- heavy but controllable bleeding, significant interference with the surgery; and 5- for massive uncontrollable bleeding. scores of 1 and 2 were considered acceptable, whereas the rest were unacceptable.

Throughout the surgery, TIVA was administered using IV propofol (100-150 µg kg^{-1} min^{-1}) with dexmedetomidine (0.5-0.7 µg kg^{-1} h^{-1}) in group D whereas IV propofol (100-150

μg kg^{-1} min^{-1}) with fentanyl (1 μg kg^{-1} h^{-1}) in group F. The propofol and dexmedetomidine infusions were titrated to maintain BIS values between 40 and 60. Ventilator settings were adjusted to maintain end-tidal carbon dioxide within 35-45 mmHg. None of the neuromuscular blocking agents were used during surgery.

TcMEP Recording

International 10-20 electrode placement system was used to place cork screws at C3 and C4. Six consecutive pulses with a duration of 0.5 ms were used for stimulation. A constant current with 70-200 mA strength at a time interval of 2-5 msec in between the two stimuli was applied. These settings were kept the same in all cases. Recordings from the upper limb were obtained from the abductor pollicis brevis muscle (C8, T1 median nerve innervation) that serves as the control, whereas the abductor hallucis muscle (L4, L5 medial plantar nerve) was used for the lower limbs. TcMEP were noted first in the supine position (Ts) as baseline, then after positioning the patient in prone (Tp), before any surgical manipulation (Tm), followed by subsequently as per the surgeon's demand (Tm1, Tm2) and finally at completion of the surgery (Te).

All infusions were stopped prior to completion. The total requirement of propofol was also noted. The patient was turned to Ts and extubated. Immediately after extubation, the time to verbal response/eye opening (T1), time to extubation (T2), and duration of stay in recovery (T3) was noted.

Any untoward events, such as bradycardia, hypotension, tongue laceration, injury at the electrode insertion site, and any unwanted limb movements or respiratory efforts, were also recorded.

The MAP was maintained within 20% of the baseline in all cases. In case of a fall of MAP >20% of the baseline value, first, an IV fluid bolus was given with 200 mL but if there was persistent hypotension, then a mephenteramine 6 mg bolus IV was given. Any episode of hypertension (MAP>20% of baseline) was managed with IV Labetalol (5 mg) incrementally.

Statistical Analysis

SPSS Statistics (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 23.0. The IBM Corp. (Armonk, NY: IBM Corp.) software was used for the analysis. All continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range, depending on the normal condition of the data. The normalcy condition was checked using the Kolmogorov-Smirnov test before applying the parametric or non-parametric tests. Categorical data are presented as frequencies (percentage). The comparison of continuous variables like current mA, Latency, Amplitude, duration, age, height, weight, BIS, between the Dexmedetomidine and Fentanyl was done by using Independent Student's t-test or Mann-Whitney U test depending upon the data distribution. Furthermore, the comparison of continuous variables within the groups at different time points was carried out using repeated measures ANOVA (RMANOVA) or Friedman's test. All statistical tests were performed at a 5% significance level, and a *P* value of less than 0.05 was considered statistically significant.

Results

1. Demographics

Demographic data were comparable between the two groups (Table 1).

2. TcMEP

No significant difference was found over time in latency and amplitude between the groups (Tables 2, 3).

Table 1. Demographic Data of Patients in Groups D and F

	Group D (n = 30)	Group F (n = 30)	*P* value
Age (years)	43.30 (10.36)	41.73 (9.83)	0.551
Weight (kg)	61.27 (8.17)	62.23 (8.32)	0.652
Height (cm)	164.97 (7.79)	165 (7.80)	0.882
Gender (Male/Female)	20/10	21/9	0.677
ASA physical status (I/II)	24/6	25/5	0.334
The type of lumbar surgery			
Tumor (intradural extramedullary)	18	17	
Canal stenosis	05	03	0.819
Listhesis	05	09	
Pott's spine	02	01	
Duration of surgery (min)	192 (21.71)	191.88 (20.14)	0.422

Data expressed as mean (standard deviation) or numbers.
ASA, American Society of Anesthesiologists; n, number of patients; D, dexmedetomidine; F, fentanyl; n, number of cases.

Table 2. Comparison of Latency Between and Within Groups D and F

Time	Group D (n = 30)	Group F (n = 30)		Group D (n = 30)	Group F (n = 30)		Group D (n = 30)	Group F (n = 30)		Group D (n = 30)	Group F (n = 30)	
	RUL	RUL	*P* value	RLL	RLL	*P* value	LUL	LUL	*P* value	LLL	LLL	*P* value
Ts	29.40 (12.16)	29.31 (12.26)	0.97	26.23 (9.19)	27.94 (4.53)	0.38	31.31 (13.06)	25.86 (12.21)	0.51	25.79 (9.17)	27.26 (9.63)	0.54
Tp	27.82 (10.62)	26.98 (10.11)	0.75	26.93 (9.52)	28.61 (4.24)	0.38	27.79 (9.84)	30.23 (13.58)	0.42	25.27 (8.83)	26.14 (8.72)	0.70
Tm	26.82 (9.86)	26.55 (9.14)	0.91	26.29 (8.98)	27.78 (4.13)	0.41	28.37 (14.07)	26.14 (10.39)	0.48	25.11 (7.85)	26.90 (8.97)	0.41
Tm1	29.20 (11.62)	26.87 (10.19)	0.41	26.32 (9.01)	27.31 (4.35)	0.59	29.75 (10.02)	26.85 (9.59)	0.25	25.53 (8.44)	26.98 (8.42)	0.50
Tm2	27.71 (8.78)	27.48 (8.09)	0.92	26.32 (8.97)	26.92 (4.24)	0.74	29.45 (10.75)	27.65 (11.91)	0.54	25.74 (8.64)	27.19 (8.73)	0.52
Te	29.29 (11.21)	25.79 (9.19)	0.19	26.66 (4.80)	27.10 (4.09)	0.70	31.63 (11.10)	29.50 (12.73)	0.50	25.25 (8.78)	27.17 (8.79)	0.40
P value	0.635	0.335		0.718	0.432		0.662	0.442		0.487	0.053	

Data expressed as mean (standard deviation) or numbers. D, dexmedetomidine; F, fentanyl; n, number of cases; RUL, right upper limb; RLL, right lower limb; LUL, left upper limb; LLL, left lower limb; Ts, baseline latency in the supine position; Tp, latency in the prone position; Tm, latency before any manipulation; Tm1, latency as per the surgeon's demand; Tm2, latency as per the surgeon's demand; Te, latency at the end of surgery (Te).

Table 3. Comparison of Amplitude Between and Within Groups D and F

Time	Group D (n = 30)	Group F (n = 30)		Group D (n = 30)	Group F (n = 30)		Group D (n = 30)	Group F (n = 30)		Group D (n = 30)	Group F (n = 30)	
	RUL	RUL	*P* value	RLL	RLL	*P* value	LUL	LUL	*P* value	LLL	LLL	*P* value
Ts	172.40 (130.75,248.20)	180 (139.50,234.25)	0.900	194.50 (137,302)	152 (108,240.25)	0.204	203.05 (123.75,245.35)	139.95 (107.50,236.50)	0.438	224 (109,265.75)	223 (105.05,278.25)	0.767
Tp	170 (139.75,251)	186 (140.47,236)	0.988	222.50 (136.10,275.25)	157.50 (110.87,235.25)	0.143	210.50 (125,245)	141.50 (107.50,235.25)	0.371	174.50 (125.15,288.20)	163 (115.75,269.75)	0.446
Tm	166.45 (143.75,242.25)	184 (145.25,235.75)	0.751	187.30 (121.07,247.05)	176 (112.62,234.25)	0.773	207.50 (132.20,252.25)	138 (109.25,235.25)	0.274	246 (171.30,299.80)	193.50 (135.65,259)	0.133
Tm1	167.50 (129.87,251.75)	183.95 (137.87,251.75)	0.589	213.25 (85.75,272.50)	164.10 (90,236.50)	0.433	200 (129.12,245)	138.50 (108.25,236.50)	0.297	216 (153.87,303.82)	202.60 (114.20,290.50)	0.355
Tm2	180 (128.25,265.25)	178.75 (120,251.75)	0.819	229 (127.50,328.50)	211 (111.95,302.75)	0.473	211 (127.75,256)	141 (106.75,235)	0.246	238.50 (121,289.52)	227.50 (123.50,282.40)	0.679
Te	181 (129,260)	182.95 (127.82,255)	0.959	230.50 (128.75,336)	216 (110.25,294.50)	0.539	202 (127.82,252.72)	138.45 (106.22,231)	0.308	219.50 (112.87,330)	221.50 (113.75,322.75)	0.756
P value	0.907	0.006		0.850	0.528		0.982	0.294		0.864	0.991	

Data expressed as median (Q1,Q3) or numbers. D, dexmedetomidine; F, fentanyl; n, number of cases; RUL, right upper limb; RLL, right lower limb; LUL, left upper limb; LLL, left lower limb; Ts, baseline latency in the supine position; Tp, latency in the prone position; Tm, latency before any manipulation; Tm1, latency as per the surgeon's demand; Tm2, latency as per the surgeon's demand; Te, latency at the end of surgery (Te)

Table 4. Comparison of Recovery Data, Complications, and Total Propofol Consumption Between the Groups

Time (min)	Group D (n = 30)	Group F (n = 30)	*P* value
T1	2.04 (1.27)	1.70 (0.81)	0.322
T2	2.08 (1.56)	1.46 (0.67)	0.062
T3	47.55 (7.51) 95% CI (44.863-50.237)	51.10 (8.73) 95% CI (47.976-54.224)	0.046*
Bradycardia	4 (13.33%)	2	0.117
Hypotension	7 (23.33%)	3 (10%)	1.00
Total consumption of propofol (mg)	220 (38) 95% CI (206.402-233.598)	282 (140) 95% CI (231.903-332.097)	0.025*

Data expressed as mean (standard deviation) or numbers, *P value<0.001

D, dexmedetomidine; F, fentanyl; n, number of cases; T1, time for response/eye opening; T2, time to extubation; T3, duration of stay in recovery; CI, confidence interval.

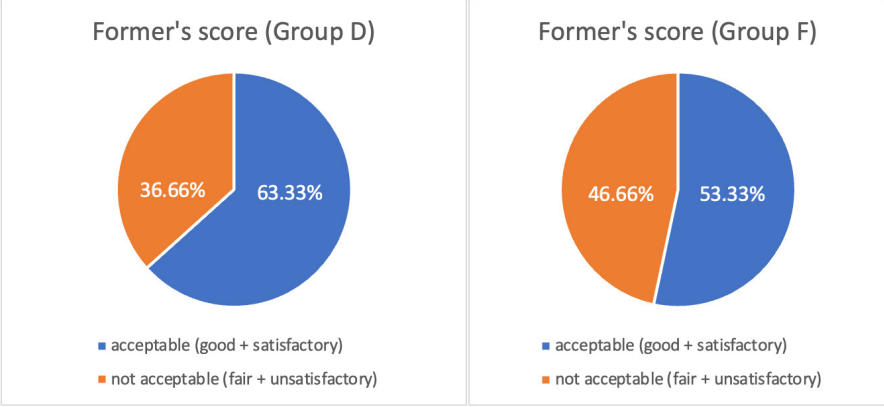

Figure 2. Former's score in both the groups. D, dexmedetomidine; F, fentanyl.

Within dexmedetomidine, there was a decrease in the amplitude value in right upper limb (RUL) compared with baseline at Tp, Tm, and Tm1, and subsequent increase at Tm2 and Te was statistically as well as clinically insignificant (Table 3). In group D, latency decreased compared with baseline at all time intervals in RUL, which was clinically and statistically non-significant (Table 2).

Within the fentanyl group, latency was well preserved within the baseline value throughout the surgery in all four limbs, whereas there was an increase in the amplitude as compared with baseline in RUL at Tp, Tm, Tm1, and Te, which was statistically significant (Tables 2, 3).

3. Hemodynamics and BIS

MAP and HR were found to be comparable between both the groups. Although statistically non-significant, lower values were obtained in Group D than in Group F. Also lower BIS scores were recorded in group D compared with group F.

4. Recovery profile, complications, total propofol consumption, and former score

The time to response or eye opening was comparable. The time to extubation was significantly more in group D though statistically not significant but the mean (SD) duration of stay in recovery was 47.55 (7.51) [95% confidence interval (CI) (44.863-50.237)] in group D and 51.10 (8.73) [95% CI (47.976-54.224)] in group F, which was statistically significant (*P*=0.046) (Table 4).

Bradycardia was seen in 4 and 2 patients in groups D and F, respectively, which was statistically non-significant. Hypotension noted in 7 patients as compared to 3 in D group and F, respectively, which is statistically non-significant. None of the patients experienced tongue laceration or injury at the electrode site insertion (Table 4).

A statistically significant difference was noted in total propofol consumption, which was 220 (38) [95% CI (206.402-233.598)] in group D and 282 (140) [95% CI (231.903-332.097)] in F group (*P*=0.025) (Table 4).

Surgical field condition as determined using the Former's score was better in group D than in group F, although statistically non-significant (*P*=0.436) (Figure 2).

Discussion

While monitoring TcMEP, any interruption in the motor tract pathway is determined by either all or none phenomena

(means whether there is generation of CMAP or not), or if there is >50% reduction in amplitude or an increase in latency by >10%.[9] Recording of TcMEP might sound simple just like any other monitoring, but when it comes to practicality it requires expertise and advanced skills as a number of factors including anaesthetic agent affect both latency and amplitude.

We were able to successfully record TcMEP in all patients. Our primary objective was to note any change in latency and amplitude in both the upper and lower limb values between the dexmedetomidine and fentanyl groups at any given point in time, and we found no significant change in latency and amplitude in either group. This finding is consistent with previous studies in literature.[10-12] However, there was a decrease in RUL amplitude compared with baseline at Tp, Tm, and Tm1 and a subsequent increase at Tm2 and Te, but these changes were statistically as well as clinically insignificant. This result could be attributed to the cumulative effect of loading doses of dexmedetomidine and propofol after induction.

Identical to our findings, various studies by Tobias et al.[12], Tsaousi et al.[13], Li et al.[14], and Anschel et al.[15] have reported no significant change in MEP latency or amplitude when using dexmedetomidine with propofol. Bala et al.[11] found that dexmedetomidine until a plasma concentration of 0.6 ng mL^{-1} does not affect the MEP threshold current intensity and amplitude. All of these studies used the same dose of dexmedetomidine as used in our study.

We observed that there was a reduced consumption of propofol in group D, which is in agreement with a study on spinal surgeries by Tsaousi et al.[13].

Our study showed that in group D, there was a significantly prolonged time to extubation compared with group F. This finding is contrary to most studies that showed no alteration in the recovery parameters whether dexmedetomidine was used alone or in combination with propofol.[14-18] However, this can be explained by the fact that the elimination half-life of dexmedetomidine is 2-3 hours but the context-sensitive half-life is increased from 4 min after a 10 min continuous infusion to 250 min after an 8 h infusion.[19] Hence, it may prolong recovery owing to analgesic and sedative actions and also a longer context-sensitive half-life in long-duration surgeries. However, there was a faster discharge from recovery in group D patients, which indicates overall better recovery.

Throughout the surgery at all points, the HR was lower in group D, although not statistically significant, which is in agreement with previous literature.[14,15,20-24] We also report a statistically significant reduction in the total consumption of propofol as well as deepened plane of anaesthesia, as suggested by the lower BIS value in patients receiving dexmedetomidine. This finding is in agreement with the findings of a study by Panse et al.[1] as well as in literature.[25]

To the best of our knowledge, no previous study has compared the surgical field quality during MEP recordings in spine surgeries, which makes our study unique. We found that dexmedetomidine provides better surgical field conditions, meaning that it helps maintain better hypotensive anaesthesia than fentanyl. This further provides an additional advantage of reduced bleeding from the surgical field. Our findings are consistent with those of Panse et al.[1] where they used Former score to assess surgical field quality in surgeries for kyphoscoliosis correction but monitored only somatosensory-evoked potentials intraoperatively.

Study Limitations

A few limitations are present in our study. Our sample size is relatively small. Plasma concentrations of the study drugs were not measured, so plasma concentrations can vary despite a fixed dose regime. Postoperative analgesic requirement was not studied. Further studies with larger sample sizes are needed to validate the findings of our study.

Conclusion

Our findings revealed that better surgical field quality can be achieved using dexmedetomidine infusion with propofol-based TIVA. Both fentanyl and dexmedetomidine facilitate MEP recordings without any effect on amplitude or latency. Dexmedetomidine provides an additional advantage of reducing total propofol consumption and maintaining the depth of anaesthesia.

Footnote

Ethics Committee Approval: Ethics committee approval was received from the Institutional Ethics Committee of Mahatma Gandhi Medical College & Hospital, Mahatma Gandhi University of Medical Sciences & Technology, Jaipur (approval no.: MGMC&H/IEC/JPR/2022/1148, date: 22.09.2022).

Informed Consent: Informed written consent from the patients were obtained before the conduct of this study.

Author Contributions: Surgical and Medical Practices - R.S.S.; Concept - V.M., S.S.; Design - S.S.; Data Collection and/or/Processing - M.B., R.S.S.; Analysis and/or/Interpretation - A.M.; Literature Search - M.B., V.M.; Writing - M.B., V.M., A.M.

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

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A Comparative Study of Magnesium Sulfate, Lignocaine, and Propofol for Attenuating Hemodynamic Response During Functional Endoscopic Sinus Surgery Under General Anaesthesia: A Prospective Randomized Trial

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Abstract

Objective: This study functional endoscopic sinus surgery (FESS) is a surgical procedure requiring minimal bleeding to optimize the surgical field. This study aimed to evaluate the effectiveness of magnesium sulfate, lignocaine, and propofol in attenuating hemodynamic response. The primary objective of this study was to compare the efficacy of these agents in reducing hemodynamic response. The secondary objectives included assessing the quality of the surgical field, recovery time, and total neuromuscular dose.

Methods: We randomly allocated 105 patients scheduled for FESS into three groups: lignocaine, propofol, and magnesium sulfate. Heart rate and mean arterial pressure were recorded every 5 min for the first 30 min, followed by measurements every 10 min at the end of the procedure. Moreover, recovery time, total neuromuscular blocking dose, and surgical field score were noted upon completion of the procedure. Statistical analysis was conducted using the number cruncher statistical systems version 9.0.8 software.

Results: All three groups showed comparable hemodynamic response and surgical field scores. The recovery time was notably longer in the magnesium sulfate group [10.94 min (2.45)] than in the lignocaine [4.37 min (1.03)] [95% confidence interval (CI) -7.32, -5.83; *P*=0.000] and propofol groups [4.60 min (0.60)] (95% CI 5.60, 7.095; *P*=0.000). Moreover, the total neuromuscular blocking agent used was significantly lower in the magnesium sulfate group [5.89 mg (0.47)] than in the lignocaine [6.26 mg (0.56)] (95% CI 0.66, 0.03; *P*=0.035).

Conclusion: Propofol, magnesium sulfate, and lignocaine exerted equal efficacy in attenuating hemodynamic responses during surgery and ensuring a satisfactory surgical field. However, magnesium sulfate led to significantly longer recovery times compared with propofol and lignocaine. In addition, magnesium sulfate required a significantly lower total dose of neuromuscular blocking agents than lignocaine.

Keywords: Propofol, lignocaine, hypotension, hemodynamic response, magnesium sulfate

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Main Points

- In our study we aimed to compare the effects of MgSO4, lignocaine, and propofol on attenuating hemodynamic response during functional endoscopic sinus surgery.
- Our primary aim was to compare the hemodynamic attenuation response among the study drugs.
- Our secondary aims were to compare the quality of the surgical field, recovery time, and total neuromuscular dose requirement.
- We concluded that propofol, MgSO4, and lignocaine were equally effective in attenuating the hemodynamic response to surgery and achieving a satisfactory surgical field.
- However, the recovery time was significantly longer with MgSO4 than with propofol and lignocaine.
- The total neuromuscular blocking agent dose was significantly lower with MgSO4 than with lignocaine.

Introduction

Functional endoscopic sinus surgery (FESS) is a minimally invasive technique aimed at enlarging the nasal drainage pathways of the paranasal sinuses and improving sinus ventilation. This procedure is generally used to treat chronic rhinosinusitis that is unresponsive to drugs, nasal polyps, and certain cancers and to decompress the optic nerve in Graves' ophthalmopathy. The sinonasal mucosa is highly sensitive and vascular; even minor bleeding can impair surgical field visibility, prolong the procedure, and reduce the quality of the intervention.[1] This may necessitate blood transfusion and increase the risk of complications like optic nerve injury, orbital cellulitis, meningitis, and rhino-oral fistulas.

An important modality for minimizing this bleeding is the attenuation of the hemodynamic response associated with endoscopic maneuvering. This can be achieved with topical vasoconstrictors, local anaesthesia, or controlled hypotension with drugs like propofol, magnesium sulfate, nitroglycerin, lignocaine, dexmedetomidine, and esmolol.[2-4] However, these methods present significant challenges, including drug resistance, tachyphylaxis, cyanide toxicity, and delayed recovery.[3] Specifically, magnesium sulfate, lignocaine, and propofol are easily available, cost-effective, and have a high safety margin. Although these drugs have been evaluated in previous studies, they have not been compared for their efficacy in reducing hemodynamic responses to FESS. In our study, we aimed to compare magnesium sulfate, lignocaine, and propofol for their ability to attenuate hemodynamic response, improve the quality of the surgical field, reduce recovery time, and decrease the total neuromuscular dose requirement during FESS.

Methods

After receiving approval from the Institutional Ethics Committee of Employees' State Insurance Corporation Medical College Hospital & Super Speciality Hospital (approval no.: ESICMC/SNR/IEC-DNB/S002/08/2019, date: 29.08.2019) and registration with the Clinical Trial Registry India (CTRI/2020/06/025648, www.ctri.nic.in), this prospective randomized trial was conducted over a period of one year, from September 1, 2020, to August 31, 2021, in compliance with the Declaration of Helsinki of 1975, as revised in 2013. All eligible participants were informed about the study, and written informed consent was obtained for their participation and use of their data for research and educational purposes. A total of 105 patients aged between 18 and 60 years, classified as American Society of Anesthesiologists Physical Status grades I and II and scheduled to undergo FESS under general anaesthesia, were randomly allocated into three groups using a computer-generated random table. Allocation concealment was achieved using the sequentially numbered and sealed opaque envelope method. Patients allergic to the studied drugs, hypertension, diabetes mellitus, and coagulopathies, those on medications influencing coagulation, coronary artery disease, renal, hepatic, or cerebral insufficiency, and pregnant patients were excluded from the study.

All patients were orally administered 0.25 mg alprazolam and 40 mg pantoprazole before surgery. On the day of surgery, peripheral venous access was secured, and basic standard monitors were used. Premedication on the day of surgery included 0.004 mg kg^{-1} glycopyrrolate, 2 μg kg^{-1} fentanyl, followed by propofol induction (2 mg kg^{-1}) titrated to loss of verbal contact. This was further followed by administration of 0.1 mg kg^{-1} vecuronium for endotracheal intubation and throat packing. General anaesthesia was maintained using sevoflurane adjusted to 1 minimum alveolar concentration, with maintenance doses of IV vecuronium (0.05 mg kg^{-1}) administered if required based on clinical assessment of increased peak airway pressures, spontaneous movements in the reservoir bag, and sudden increases in pulse rate and blood pressure. Patients received mechanical ventilation using the volume-controlled mode with a tidal volume of 6-7 mL kg^{-1} and respiratory rate adjustment to maintain an end-tidal carbon dioxide level of 35-40 mmHg, supplemented with positive end-expiratory pressure set at 5 cmH_2O using an oxygen/air mixture. Prior to initiating drug infusion, the nasal mucosa of all patients was infiltrated with 5 mL

of a solution containing 1 mg adrenaline in 200 mL of normal saline by the surgeon. In the investigation, patients were allocated into three groups: Group magnesium sulfate n = 35 received a loading dose of monosodium glutamate at 25 mg kg^{-1} followed by an infusion of 15 mg kg^{-1} h^{-1}; Group propofol n = 35 received a propofol infusion of 10 µg kg^{-1} min^{-1}; Group lignocaine n = 35 received a lignocaine infusion of 2 mg kg^{-1} h^{-1}. Infusions began after securing the throat pack. Additionally, all patients received an injection of 15 mg kg^{-1} paracetamol. In the event of bradycardia [heart rate (HR) less than 45 bpm], 0.6 mg atropine was intravenously administered. In cases of hypotension [mean arterial pressure (MAP) <60 mmHg], the study drug infusions were stopped, and vasoconstrictors like mephentermine or phenylephrine were administered, along with the titration of the inhalational agent. These patients were subsequently excluded from the study. HR, MAP, systolic blood pressure, and diastolic blood pressure were recorded every 5 min for the first 30 min, followed by every 10 min until the end of the procedure. Drug infusions were discontinued at the end of the procedure, and patients were extubated after the reversal of residual neuromuscular blockade using neostigmine at 0.05 mg kg^{-1} and glycopyrrolate at 0.01 mg/kg based on predefined criteria. The primary outcome was the comparison of the attenuation of hemodynamic responses among the groups. Secondary outcomes included the quality of the surgical field, recovery time, and the total neuromuscular dose requirement during FESS. The attenuation of hemodynamic response was defined as a reduction or moderation of changes in hemodynamics, specifically HR and MAP by 15%. Recovery time was defined as the interval between discontinuation of anesthesia and eye-opening to verbal commands. The surgical field was assessed using the Fromme-Boezaart grading scale, which categorizes the surgical field as follows: 0 = No bleeding; 1 = Slight bleeding, no suctioning of blood required; 2 = Slight bleeding, occasional suctioning required, surgical field not threatened; 3 = Slight bleeding, frequent suctioning required, bleeding threatens the surgical field a few seconds after suction is removed; 4 = Moderate bleeding, frequent suctioning required, bleeding threatens the surgical field immediately after suction is removed; 5 = Severe bleeding, constant suctioning required, bleeding appears faster than can be removed by suction, surgical field severely threatened, and surgery not possible.[5,6] A surgical field score of 0-2 was deemed satisfactory. Furthermore, the total dose of muscle relaxant was standardized using vecuronium, administered at an initial loading dose of 0.1 mg kg^{-1}, followed by a maintenance dose of 0.05 mg kg^{-1} whenever the patient showed signs of spontaneous effort. The total dose utilized by each patient was recorded.

Sample size calculations were performed using G*Power software. A repeated measures analysis of variance (ANOVA) with a within-between interaction was chosen as the statistical test. The parameters used for the calculation were as follows: effect size (f) = 0.1, significance level (α) = 0.05, desired power (1-β) = 0.80, number of groups = 3, number of measurements within each group = 10, correlation among repeated measures = 0.5, and non-sphericity correction (ε) = 1. The sample size calculation yielded a total sample size of 105.

The data were analyzed using number cruncher statistical systems version 9.0.8 software (Utah, USA). Continuous data were represented as means, ordinal data as medians with interquartile ranges, and categorical data as ratios or percentages. ANOVA was employed to compare continuous data among the three groups and hemodynamic parameters, whereas the chi-square test was performed for categorical data. A significance level of $P < 0.05$ was considered statistically significant.

Results

In this study, a total of 120 patients underwent eligibility screening. Of these, 15 were excluded and 105 were enrolled in the trial (Figure 1). All eligible participants were monitored throughout the trial period and were included in the analysis. The three groups were comparable in terms of demographic characteristics, baseline variables, and drug infusion time (Table 1). Each group exhibited a significant decrease in HR and MAP from baseline; however, no statistically significant differences were observed among the groups (Table 2, Figures 2 and 3). A significant difference in the MAP was noted from 1.2 to 1.5 h, whereas the other parameters showed no variation, and no clear rationale was provided for this statistically significant disparity.

Furthermore, the surgical field scores were comparable among the three groups (Table 1). Nonetheless, the recovery time was significantly longer in the magnesium sulfate group [10.94 min (2.45)] than in the lignocaine [4.37 min (1.03)] (95% confidence interval (CI) -7.32, -5.83; *P*=0.000] and propofol groups [4.60 min (0.60)] (95% CI 5.60, 7.095; *P*=0.000). Notably, the difference in recovery time between the lignocaine and propofol groups was not statistically significant (95% CI -0.97, 0.52, *P*=0.545).

The total neuromuscular blocking agent used was significantly lower in the magnesium sulfate group [5.89 mg (0.47)] than in the lignocaine group [6.26 mg (0.56)] (95% CI 0.66, 0.03; *P*=0.035). However, it was comparable to the propofol group [6.20 mg (1.02)] (95% CI 0.29, 0.40; *P*=0.073). Conversely, no significant difference in the total neuromuscular blocking agent dose was observed between the propofol and lignocaine groups (95% CI -0.29, -0.40; *P*=0.743).

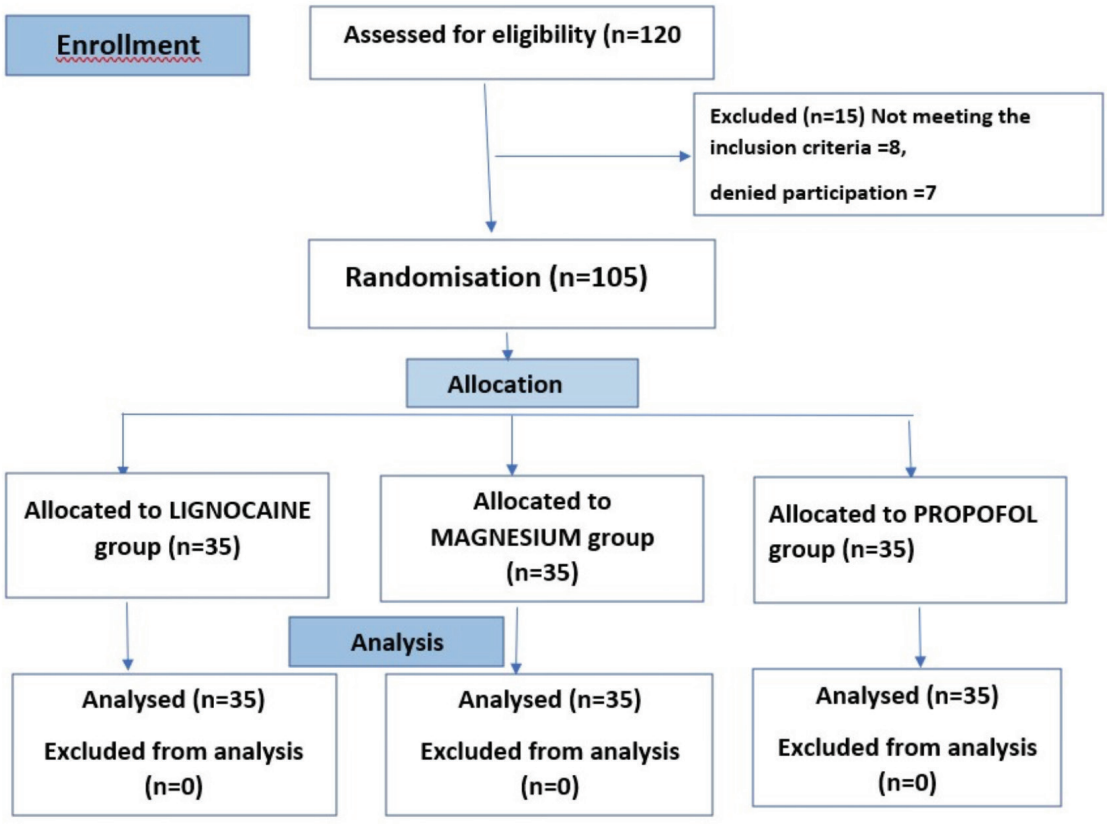

Figure 1. Consolidated standards of reporting trials (CONSORTs) flow of participants.

Table 1. Demographic Characteristics and Baseline Variables

	Lignocaine Mean (SD)	Magnesium sulfate Mean (SD)	Propofol Mean (SD)	*P* value
Age (years)	34.11 (8.79)	34.97 (8.24)	37.71 (10.41)	0.123
Gender (Male/Female)	18/17	14/21	19/16	0.449
Weight (kg)	64.69 (6.35)	65.17 (6.10)	64.11 (4.90)	0.749
Baseline HR (min-1)	88.4 (13.079)	89.03 (12.965)	92.26 (14.084)	0.436
Baseline mean arterial pressure (mmHg)	93.51 (16.136)	99.11 (18.149)	97.26 (13.05)	0.329
Drug infusion time (min)	62.57 (22.79)	60.85 (26.71)	61.42 (26.36)	0.959
Recovery time (min)	4.37 (1.03)	10.94 (2.45)	4.60 (0.60)	<0.001
Total NMBA (mg)	6.26 (0.56)	5.89 (0.47)	6.20 (1.02)	0.075
Surgical field score	1.83 (0.62)	1.91 (0.74)	2.06 (0.34)	0.267

Values are expressed as mean (SD) or proportion
SD, standard deviation; HR, heart rate; MAP, mean arterial pressure; NMBA, neuromuscular blocking agent.

Table 2. Variation of Mean Arterial Pressure and Heart Rate Among the Three Groups

Time	Mean arterial pressure Mean (SD) [mmHg]			*P* value	Heart rate Mean (SD) [min^{-1}]			*P* value
	Lignocaine	Magnesium sulfate	Propofol		Lignocaine	Magnesium sulfate	Propofol	
Pre-op	93.51 (16.136)	99.11 (18.14)	97.26 (13.05)	0.329	88.4 (13.079)	89.03 (12.96)	92.26 (14.08)	0.436
0 min	81.6 (14.72)	86.94 (17.57)	84.63 (13.46)	0.348	86.06 (12.286)	86.57 (10.13)	85.91 (13.45)	0.972
5 min	76.09 (12.31)	75.49 (10.38)	77.29 (7.482)	0.757	83.09 (12.356)	84.89 (7.24)	86.37 (12.76)	0.465
10 min	70.54 (9.19)	72.91 (6.90)	72.51 (8.552)	0.442	81.4 (11.413)	81.03 (8.29)	82.43 (10.64)	0.838
15 min	71.2 (7.31)	73.74 (8.84)	70.54 (7.052)	0.196	80.2 (13.807)	79.31 (9.62)	81.74 (9.754)	0.659
20 min	72.83 (7.30)	70.66 (5.567)	68.4 (7.453)	0.029	80.06 (13.104)	80 (8.647)	79.2 (8.881)	0.929
25 min	69.77 (7.04)	70.4 (6.549)	66.26 (4.967)	0.014	78.34 (12.105)	79 (7.742)	79.03 (8.631)	0.945
30 min	71.09 (6.59)	70.17 (6.675)	68.34 (5.861)	0.193	76.14 (12.666)	79.37 (7.923)	79.06 (10.29)	0.367
40 min	71.31 (7.62)	70.23 (6.916)	69.74 (6.771)	0.64	76.74 (12.816)	78.34 (8.349)	76.51 (9.577)	0.727
50 min	70.6 (5.36)	69.13 (7.182)	67.84 (10.82)	0.52	77.08 (14.192)	74.88 (9.695)	76.79 (11.48)	0.843
60 min	68.64 (4.71)	71.57 (7.377)	69 (6.738)	0.354	77.18 (14.789)	77.86 (12.90)	79.27 (15.46)	0.926
1.1 h	70.28 (6.22)	70 (8.571)	64.6 (4.949)	0.091	75.22 (14.926)	74.33 (8.239)	74.3 (8.932)	0.972
1.2 h	71 (7.69)	65 (2)	66.2 (4.756)	0.047	76.4 (15.231)	71.5 (10.268)	74.2 (7.7)	0.66
1.3 h	71.62 (6.09)	64.67 (1.862)	65.67 (3.122)	0.005	79.31 (15.091)	73 (12.992)	76.56 (7.435)	0.601
1.4 h	79.33 (12.67)	66.67 (1.366)	69 (3.098)	0.025	73.5 (17.05)	72.67 (13.09)	80 (4.472)	0.561
1.5 h	78.75 (7.08)	61.5 (9.815)	72.5 (1.732)	0.021	82.75 (24.047)	66.5 (10.97)	85.5 (1.732)	0.219

Values are expressed as mean (SD)
Pre-op, Preoperative; SD, standard deviation.

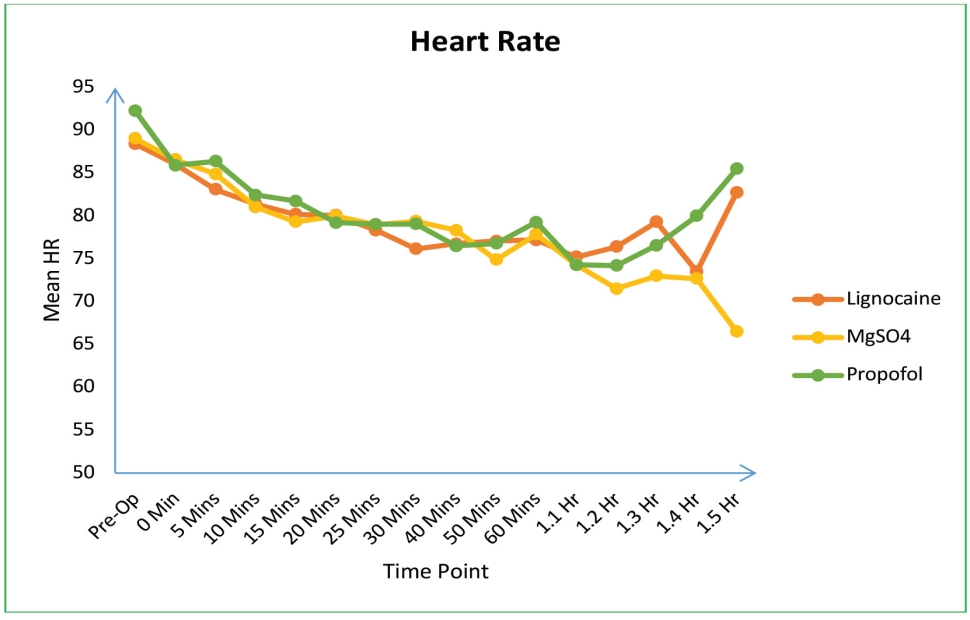

Figure 2. Heart rate variability among the groups.

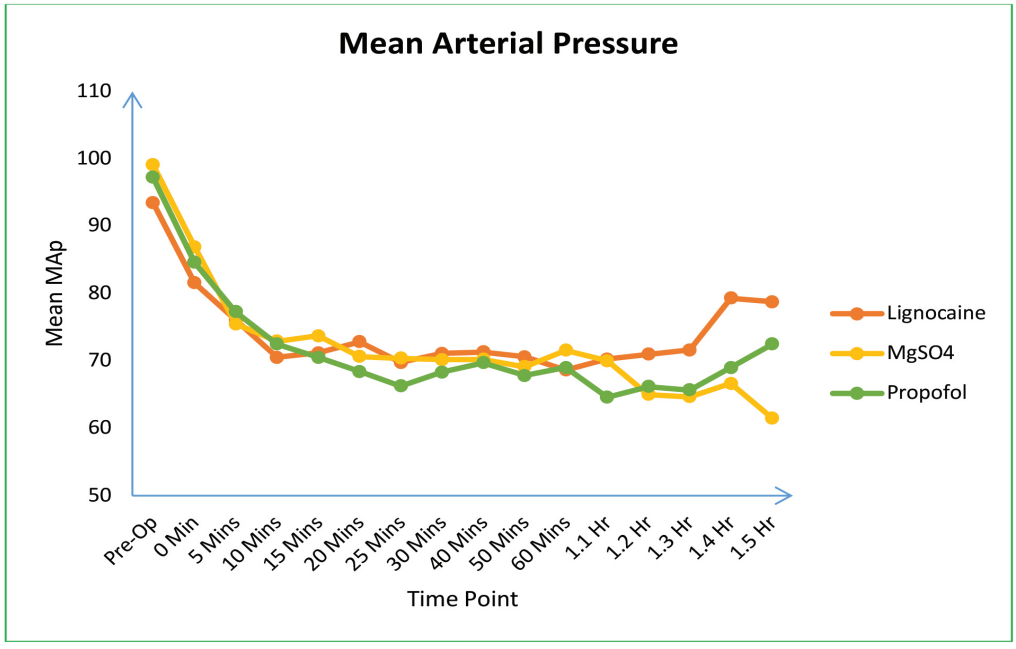

Figure 3. Variation in mean arterial pressure among the groups.

Discussion

FESS is one of the most commonly performed procedures for rhinosinusitis. This technique involves the use of an endoscope and forceps within the nasal cavity, which may lead to bleeding from the highly vascular nasal mucosa. Minimizing this bleeding improves the quality of the surgical field, shortens the operative time, and lowers the risk of major complications.[1,7,8] Attenuating the hemodynamic response is crucial for reducing surgical-site bleeding. This involves reducing blood pressure by 30-40% below the baseline and maintaining this level throughout the surgery while ensuring adequate perfusion to vital organs.[9] Notably, attenuation of hemodynamic responses can be achieved using a variety of drugs like sodium nitroprusside, nitroglycerin, inhaled anaesthetics, beta-blockers, propofol, dexmedetomidine, lignocaine, and magnesium sulfate.[10] The ideal agent should be a well-known drug that is easy to use, has rapid onset and remission, and has minimal side effects. In our study, we compared the hypotensive properties of three drugs-propofol, lignocaine, and magnesium sulfate. Although the efficacy of these drugs in blunting hemodynamic responses has been previously investigated, a direct comparison among these drugs has not been conducted.[11-13]

We observed a favorable hemodynamic attenuation response with all three drugs, although there was no statistically significant difference among the groups. In a double-blind randomized controlled study, Omar[11] found that intravenous lignocaine infusion (1.5 mg kg^{-1} h^{-1}) resulted in controlled hypotension, stable hemodynamics, and improved surgical conditions at all time points in patients undergoing FESS. Similarly, our study demonstrated stable hemodynamics, controlled hypotension at all time points, and satisfactory surgical field scores with intravenous lignocaine infusion. This hypotensive effect of lignocaine can be attributed to its negative inotropic effect and ability to blunt airway reflexes to the endotracheal tube.[11,14,15] The reductions in MAP and good surgical field scores in the lignocaine group were comparable to those in the magnesium sulfate and propofol groups. Moreover, propofol infusion was equally effective in attenuating hemodynamic response. The proposed mechanisms include vasodilation, a decrease in systemic vascular resistance, and a negative inotropic effect.[16] In this regard, Gupta et al.[13] also observed hemodynamic control and satisfactory surgical field scores with propofol during FESS.

Similar to our findings, Elsharnouby and Elsharnouby[17] observed a significant reduction in MAP and HR with the use of magnesium sulfate for controlled hypotension in patients undergoing FESS. We found that the reductions in MAP and HR in the magnesium sulphate group was comparable to those in the propofol and lignocaine groups. Additionally, we noted a statistically significant decrease in MAP from 1.2 to 1.5 h in the magnesium sulfate group compared with the lignocaine and propofol groups. However, this difference was not clinically significant, and none of the patients in the magnesium sulfate group required vasopressor therapy or discontinuation of drug infusion.

Furthermore, we observed that the recovery time was notably longer when using magnesium sulfate than when using lignocaine and propofol. Chhabra et al.[12] similarly found an extended recovery time of 10.78 min (3.44) with magnesium sulfate, which was similar to our finding of 10.94 min (2.45) in the same group. In another study, Soliman and Fouad[18] reported a significantly prolonged extubation time of 13.2 min (1.75) with magnesium sulfate. Additionally, Abu-sinna and Abdelrahman[19] documented an extended recovery time of 5.2 min (1.8) with propofol infusion in patients undergoing FESS, a finding comparable to our observation of 4.60 min (0.60) with propofol infusion.

Furthermore, the requirement for a total neuromuscular blocking drug was significantly lower with magnesium sulfate than with propofol, although it was similar to lignocaine. The reduced dosage of neuromuscular blocking agents in these patients may be due to the enhancement of nondepolarizing muscle relaxants by magnesium sulfate.[20]

In addition, we noted satisfactory surgical field scores across all three groups, with no significant difference among them. Notably, Elsharnouby and Elsharnouby's[17] study demonstrated significantly improved surgical field scores with magnesium sulfate compared with the control group. Similarly, Bharathwaj and Kamath[21] reported surgical field scores of 2-3 when using propofol in FESS patients, a finding consistent with our own results.

Study Limitations

The limitations of our study included the lack of comparisons regarding the time required to attain the target MAP and the subjectivity inherent in evaluating the surgical field score. Additionally, train-of-four monitoring was not conducted during the procedures. Double blinding was not feasible because an additional bolus dose was administered alongside the infusion in the magnesium sulfate group, which compromised the blinding process. Furthermore, propofol, with its milky white appearance, was visually detectable within the infusion line.

Conclusion

Propofol, magnesium sulfate, and lignocaine had comparable efficacy in attenuating hemodynamic response during surgery and achieving a satisfactory surgical field. However, recovery time was notably prolonged with magnesium sulphate compared to propofol and lignocaine. Furthermore, magnesium sulfate resulted in a significantly lower total dose requirement of neuromuscular blocking agents compared with lignocaine.

Footnote

Ethics Committee Approval: After receiving approval from the Institutional Ethics Committee of Employees' State Insurance Corporation Medical College Hospital & Super Speciality Hospital (approval no.: ESICMC/SNR/IEC-DNB/S002/08/2019, date: 29.08.2019) and registration with the Clinical Trial Registry India (CTRI/2020/06/025648, www.ctri.nic.in).

Informed Consent: All eligible participants were informed about the study, and written informed consent was obtained for their participation and use of their data for research and educational purposes.

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

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

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Case Report
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Anaesthesia Management of A Patient with Airway Obstruction Caused by Prosthetic Vascular Graft Invasion into the Tracheal Lumen

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Abstract

Primary intratracheal masses causing luminal obstruction are relatively rare, posing a challenge for anaesthesiologists in airway management. This case report describes a distinctive airway management approach in a 71-year-old female patient with an aorta-carotid artery bypass graft that significantly obstructed the trachea.

The patient presented with worsening shortness of breath, and a thoracic computed tomography scan revealed a 19.2 mm×9.9 mm×19.3 contrast-enhancing mass penetrating the right anterolateral tracheal wall, resulting in 80% occlusion of the tracheal lumen. Awake fiberoptic bronchoscopy (FOB)-guided nasotracheal intubation was performed following topical upper airway anaesthesia, with the patient positioned at a 30° head-up angle and slight right-up tilt to minimize discomfort. A 6.0 mm ID cuffed endotracheal tube was successfully placed under fiberoptic guidance distal to the intratracheal vascular graft but proximal to the carina. Intratracheal masses can lead to severe tracheal obstruction followed by progressive airway obstruction, which can be life-threatening when effective ventilation cannot be established after the induction of general anaesthesia. We recommend the use of awake FOB-guided intubation in such cases. Additionally, contingency plans should be prepared and meticulously prepared in the event of intubation or ventilation failure.

Keywords: Anaesthetic management, bronchoscopy, difficult airway, prosthetic vascular graft, tracheal obstruction

Introduction

Tracheal masses are extremely rare; however, they can result in various complications, depending on their growth rate, duration, and degree of obstruction.[1] Severe airway obstruction is generally defined as occlusion of >70% of the tracheal lumen.[2] Obstruction can occur due to external compression or the presence of masses within the trachea. Both conditions can pose challenges for airway management, especially during the perioperative period.[3] Anaesthesiologists face particular difficulties in the perioperative management of patients with tracheal masses.[3] The anaesthetic approach requires careful planning, especially when preoperative assessment indicates difficulty. We present a unique case of safe and successful airway management via awake fiberoptic bronchoscopy (FOB)-guided nasotracheal intubation in a patient with an aortic-carotid artery bypass graft that was invading and significantly obstructing the trachea.

Case Report

Medical History

The patient provided consent for the clinical information pertaining to the case to be published in a medical journal. The patient was a 71-year-old with no history of smoking and was taking a calcium channel blocker

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for hypertension and an inhaler beta-agonist for asthma. In 2018, she underwent surgery for type 2 aortic dissection according to the DeBakey classification. In 2022, the patient was admitted due to a pulsatile mass extending to the skin at the site of the sternum defect. Further examination revealed saccular aneurysmatic dilation at the arcus aorta. As a result, the patient underwent ascending aortic replacement, hemiarch replacement, and right-left debranching bypass. Subsequently, she returned to our hospital due to increasing respiratory distress during the 21-month postoperative period. Thorax computed tomography of the patient revealed a 19.2 mm×9.9 mm×19.3 contrast-enhancing mass perforating the right anterolateral wall of the trachea, occluding the tracheal lumen by 80% (Figure 1A-C). Preoperative FOB showing a hole in the anterolateral tracheal wall with invasion of the tracheal lumen by the prosthetic vascular graft (Figure 1D). The patient was scheduled for a revision of the aorta-carotid artery bypass graft and tracheal resection with primary anastomosis.

Anaesthesia Management

Standard endotracheal intubation was considered unfeasible and extremely risky. The primary aim was to perform fiberoptic intubation of the patient's trachea. Plan B involved performing airway rescue using an extraglottic airway device. The patient was categorized as American Society of Anesthesiologists IV. Her body mass index was approximately 21 kg m^{-2} (height 155 cm, weight 50.3 kg). The patient's airway was evaluated as Mallampati class II. The preoperative hemoglobin level was 10 g dL^{-1}, and the hematocrit value was 31. Other laboratory tests exhibited normal results.

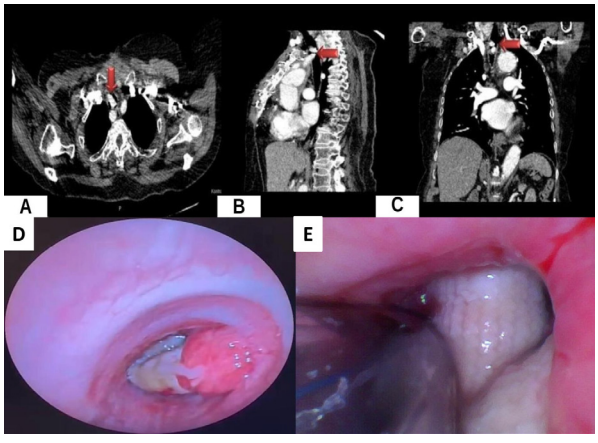

Figure 1. A-C) Contrast-enhanced computed tomography of the chest shows an aorta-carotid bypass graft perforating the right anterolateral wall of the trachea, occluding the tracheal lumen, D) Preoperative video-bronchoscopy showing intratracheal aorta-carotid bypass graft significantly obstructing the tracheal lumen, E) Standard tracheal tube (6.0 mm ID) passing over the prosthetic vascular graft in the trachea.

After the patient entered the operating room, standard non-invasive monitoring was initiated. Invasive arterial pressure was monitored using left radial artery catheterization. The nasotracheal route was prepared by applying 4% lidocaine for anaesthesia, and "conscious sedation" was achieved using midazolam (3 mg intravenous) and infusion of remifentanil (0.05-0.1 μg kg^{-1} min^{-1}). Awake FOB-guided nasotracheal intubation was performed. Under fiberoptic guidance, a 6.0 mm ID cuffed endotracheal tube was placed distal to the intratracheal vascular graft but proximal to the carina (Figure 1E). The patient was then anaesthetized and paralyzed with an injection of propofol (1 mg kg^{-1}, fentanyl 2 μg kg^{-1}, and rocuronium (0.6 mg kg^{-1}).

The patient underwent tracheal resection and reconstruction, as well as aorto-carotid artery re-interposition. Anaesthesia was maintained with FiO_2 0.5, sevoflurane 1-2%, and remifentanil infusion at 0.05-2 μg kg^{-1} min^{-1}. The procedure lasted for 374 minutes. During the perioperative period, patients with a blood loss of 2,000 cc received 4 units of packed red blood cells and 1 unit of fresh frozen plasma transfusion. The patient also received a crystalloid infusion of 3,000 cc and an 800 cc urine output.

Postoperative Management

Extubation was not performed at the end of the operation due to the patient's initial partial carbon dioxide pressure of 75 mmHg, indicating hypercapnia. In addition, persistent hypoxemia was observed during surgery. The patient was then transferred to the intensive care unit (ICU) in an intubated state. On postoperative day 7, the patient's mechanical ventilation parameters and clinical conditions improved. Her oxygen saturation improved to 97% with an FiO_2 of 50% and a positive end-expiratory pressure of 5 cm H_2O. She had stable vital signs. She was extubated on postoperative day 7 and discharged from the ICU on postoperative day 12. The preoperatively positioned 6.0 mm ID cuffed endotracheal tube facilitated continued mechanical ventilation during surgery and until extubation. The patient experienced an uncomplicated recovery and was discharged from the hospital 39 days later.

Discussion

Primary intratracheal masses causing luminal obstruction are relatively uncommon, and they pose a therapeutic challenge for anaesthesiologists during airway management.[4] Several processes are responsible for tracheal obstruction. These etiologies include benign and malignant primary tracheal tumors, extrinsic compression of the airway, postintubation or posttracheostomy tracheal stenosis, stenosis related to airway stents, inflammatory diseases (e.g., sarcoidosis, granulomatosis with polyangiitis, relapsing polychondritis), and dynamic airway narrowing (tracheobronchomalacia).[2] Tracheal obstruction due to

the thyroid and parathyroid glands has been reported.[5,6] However, tracheal stenosis resulting from a prosthetic vascular graft within the trachea has not been previously described. This unique case involved erosion of the anterolateral tracheal wall over time by the aorta-carotid artery bypass graft, resulting in its entry into the tracheal lumen. The possible etiology of this condition is that the prosthetic vascular graft is longer than it should be, and chronic irritation and erosion occur as a result of the graft's contact with the tracheal wall.

Patients with tracheal stenosis may present with dyspnea on exertion, shortness of breath, stridor, or wheezing, with symptoms lasting several years.[7] Often, they remain asymptomatic until approximately two-thirds of the tracheal diameter is occluded, potentially leading to a life-threatening condition.[8] In our case, 80% occlusion of the tracheal lumen aggravated dyspnea, prompting a surgical decision to remove the intratracheal mass. Patients experiencing respiratory distress due to an intratracheal mass are frequently initially misdiagnosed. In our case, the patient's pre-existing asthma diagnosis delayed the identification of a tracheal mass. The patient's unresponsiveness to bronchodilator treatment was key to diagnosis. Similarly, a case of intratracheal schwannoma misdiagnosed as asthma has been reported in the literature.[9] Failure to respond to standard treatment should prompt consideration of alternative diagnoses.

Intratracheal masses can lead to severe tracheal obstruction followed by progressive airway obstruction, which can be life-threatening when effective ventilation cannot be established after the induction of general anaesthesia.[3] Consequently, intraoperative airway management in patients with endotracheal mass or severe airway stenosis poses a significant challenge for anaesthesiologists. In our case, conventional tracheal intubation was found to pose a significant risk to the patient. The most perilous scenario was the misplacement of the tracheal tube into the mediastinum during intubation performed without FOB guidance, in which the tube exited the tracheal defect. Another significant risk was the potential for the tracheal tube to displace the prosthetic vascular graft into the lower trachea, leading to complete airway obstruction. Both scenarios posed substantial risks to the patient's life; hence, awake FOB-guided intubation was performed. Additionally, various perioperative airway management strategies were devised to address expected and unexpected conditions, such as intubation and ventilation failure. Instruments for cardiopulmonary bypass and extraglottic airway devices were made available. On the other hand, in cases of upper tracheal masses, preoperative tracheostomy under local anaesthesia can be an alternative to FOB-guided endotracheal intubation.[1] However, for masses in the middle and lower tracheal regions, FOB-guided intubation appears to be the only alternative.

In the present case, we preferred a standard 6.0 mm ID cuffed endotracheal tube for tracheal intubation. The micro laryngeal surgery tube, an alternative to the conventional tube for cases in which the tracheal tube cannot bypass the mass, is longer and softer than the standard tracheal tube, enabling it to reach the carina while minimizing trauma to the endotracheal mass.[4] However, unlike tracheal tumors, the prosthetic vascular graft embedded in the trachea was neither rigid nor posed a risk of bleeding during tube passage. Therefore, we selected the largest tracheal tube that we thought would not cause a serious decrease in blood flow past the graft. The preoperatively positioned tracheal tube facilitated continued mechanical ventilation during surgery and until extubation on postoperative day 7.

Early extubation is recommended to prevent tension on the suture line caused by the tracheal tube cuff and the potential adverse effects of mechanical ventilation.[10] Although early extubation was not achieved due to persistent postoperative hypoxemia, the patient was successfully extubated without complications on postoperative day 7. The patient experienced an uncomplicated recovery and was discharged from the hospital 39 days later.

In summary, before the procedure, the risks associated with airway management techniques and the anaesthetic approach must be evaluated due to severe airway obstruction caused by intraluminal tracheal masses. We recommend the use of awake FOB-guided intubation in such cases. Furthermore, alternative plans should be formulated and meticulously prepared in case of intubation or ventilator failure. Effective communication and collaboration between healthcare providers are also crucial for ensuring successful outcomes.

Footnote

Informed Consent: The patient provided consent for the clinical information pertaining to the case to be published in a medical journal.

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