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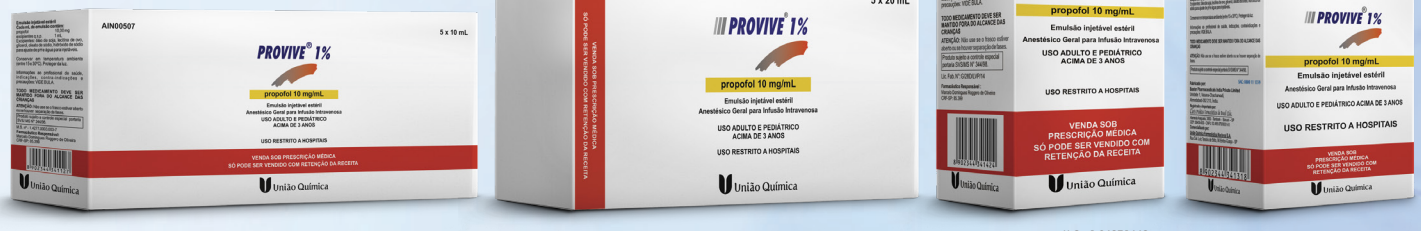

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Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

How to identify a high-risk surgical patient?



The number of surgical procedures continues to grow globally and there is a clear need to increase the availability of safe, timely, and affordable surgery, especially in constrained resources scenarios.[1] As overall life expectancy continues to increase, it is more common to offer complex procedures to patients displaying advanced age and serious comorbidities, with inevitable increases in morbidity and mortality after surgery despite the most recent technological advances in anesthetic care. Although both postoperative morbidity and mortality vary significantly among patients, it is particularly higher in a vulnerable group of high-risk patients. Therefore, accurate preoperative identification of high-risk patients is strongly recommended.

Risk stratification and early recognition of high-risk patients may improve outcomes since it facilitates surgical decision-making, preoperative optimization, and tailored intraoperative and postoperative management.[2] However, in order to enhance patient care, risk stratification tools should be validated to the target populations it will be applied, and should be easily applicable at the bedside. Ultimately, risk stratification needs to encompass the complex interaction between surgical and anesthetic procedures and patient specific features to be able to assess postoperative morbidity and mortality in different moments, including the preoperative, intra-operative, and postoperative periods.[3,4]

Plenty of surgical risk models have been developed and investigated. American Society of Anesthesiologists' Physical Status (ASA-PS) classification, Revised Cardiac Risk Index (RCRI), American College of Surgeons' National Surgical Quality Improvement Program Risk Calculators (ACS-NSQIP), and the Surgical Outcome Risk Tool (SORT) model are some of the most commonly used preoperative scoring systems. ASA-PS classification is the simplest scoring system and has been used since 1941.[5] Risk assignment is independent of the surgical procedure and is based solely on subjective assessment of a patients' overall health status, leading to significant inter-rater reliability. The RCRI was designed to focus on major cardiovascular mortality following noncardiac surgeries, consisting of six independent predictors: high-risk surgery, history of ischemic heart disease, congestive heart failure, cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine above 2 $mg.dL^{-1}$.[6] Unfortunately, it performs poorly when predicting cardiac events following vascular surgeries or all-cause mortality following noncardiac surgeries.[6] The ACS-NSQIP surgical risk calculator consists of 20 patient-specific variables including ASA-PS, patient-reported functional capacity, and the planned surgery with over 1500 current procedural terminology codes that allow procedure-specific estimation of postoperative risk.[7] However, the ACS-NSQIP also displays limitations, not capturing important cardiovascular complications, and it has not been extensively validated out of the United States, impairing its generalizability. Finally, the SORT model has been validated in a multicenter study in the United Kingdom that used a specific surgical severity classification, comprising six main variables: ASA-PS physical status, urgency of surgery (expedited, urgent, immediate), high-risk surgical specialty (gastrointestinal, thoracic, vascular), surgical severity (from minor to complex major), cancer, and aged 65 years or over.[8] The SORT model allows rapid and easy evaluation of mortality risk for individuals undergoing non-cardiac surgery. However, some recent studies have indicated that SORT performed poorly in other populations as compared to the original work[9] and may not be an accurate predictor of adverse outcomes in higher risk patients.[10]

Of note, prediction of postoperative complications is quite difficult. Predictors of perioperative outcomes are usually categorized into two groups: patient-related and surgery-related factors. Patient age, comorbidities such as cardiovascular and pulmonary diseases, functional status, frailty, and perioperative biomarkers may predict outcomes. Emergency or urgent surgeries significantly increase the risk of postoperative complications. Other surgery-related predictors include length of surgery, blood loss, and major surgery.[11] Nevertheless, so far, most complication prediction scores display moderate accuracy in predicting postoperative complications, especially in some surgical subpopulations.[12] It is important to emphasize that these tools predict outcomes in a "typical patient", but are limited in

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accurately predicting risk for an individual patient as specific factors related to the patient and the surgery must be considered. Alternatively, subspecialty prediction models may be more accurate for high-risk patients and new risk models addressing individual high-risk groups are in constant development and validation. At the end of the day, the ultimate goal of any prediction tool is providing adequate and clear information to patients and clinicians in order to preemptively discuss management options, rescue strategies, and, in a more extreme scenario, end-of-life decisions.

As demonstrated, several assessment tools have been implemented to identify high-risk surgical patients. However, most of these models have been developed and validated in high income countries. The feasibility of reliable risk assessment is particularly important when resources are limited, especially in low- and middle-income countries (LMICs) where primary care is insufficient and advanced conditions of diseases compound the surgical scenario. Therefore, prospective validation is warranted across different geopolitical sectors to test the external validity of those scores. Brazil, as well as most countries in Latin America, present huge disparities in terms of healthcare access and medical available resources to assist surgical patients, factors that may significantly impact in poorer outcomes for individual patients undergoing surgery.[13]

In this context, Gutierrez et al.,[14] using a large Brazilian surgical cohort, have developed and investigated a multivariable logistic regression model, which predicts in-hospital mortality (the Ex-Care risk model). In this risk model, patient and perioperative predictors were considered, and its performance was compared to well-known surgical risk tools, namely the Charlson comorbidity index (CCI), the RCRI, and the SORT risk model. The Ex-Care risk model was very efficient at identifying high-risk surgical patients, displaying superior accuracy than the RCRI and similar performance as compared to the CCI and SORT models. Although these findings are promising, the new surgical risk model needs to be further investigated in multicenter studies, requiring an assessment of its accuracy in other national and international institutions.

For all the reasons above, in this issue of the Brazilian Journal of Anesthesiology we invite readers to access several interesting studies providing new insights into the stratification and management of high-risk surgical patients. These studies have addressed a myriad of topics related to high-risk surgery, from measures to detect patients at higher risk for complications to strategies focused on providing enhanced perioperative care in high-risk surgical patients.[15-22]

Among these studies, it is tempting to highlight the multicenter study protocol described by Passos et al.,[15] proposing a large national investigation of the Ex-Care model as a new and valid risk tool for the Brazilian surgical population. This is a retrospective, multicenter, cohort study which aims to build a national preoperative risk model based on Ex-Care model of probability of death within 30 days after surgery. In-hospital mortality within 30 days after surgery will be the primary outcome. Importantly, to date, there is no surgical risk model developed for the Brazilian population. Therefore, the Ex-Care model may be a helpful tool to accurately stratify the risk of death after surgery in Brazil, supporting professionals involved in perioperative care to identify high-risk surgical patients and to better plan therapeutic strategies.

Morbidity and mortality for high-risk surgical patients are often high, especially in low-resource settings. The development of several risk calculators has enhanced our ability to comprehensively quantify the risk of adverse postoperative events, especially surgery-related mortality. The association of these tools with new perioperative biomarkers, frailty scores, and a more comprehensive assessment of functional status may further refine our ability to detect high-risk surgical patients. As knowledge continues to grow in this area, new research should focus on the implementation of mitigation strategies to reduce adverse events after surgery. For those patients who are identified as having increased surgical risk, perioperative strategies to mitigate risk may need a whole new surgical model associated with an enhanced perioperative care with the potential to reduce preventable deaths and the risk of postoperative major adverse cardiac events. These strategies might include timing of surgery after cardiac events or interventions, an improved perioperative management of ischemic or valvular heart disease, hypertension, arrhythmia, and heart failure.[23] Additionally, postoperative comprehensive monitoring should be performed at least in the first 48 hours after surgery in order to detect adverse events and implement early rescue strategies. This postoperative enhanced care pathway for high-risk surgical patients, or in other words, a "high-risk surgical bundle" with a patient-centered decision-making, may significantly improve the patient's experience and outcomes through the surgical process for patients at higher risk of adverse events.[24] In this context, a recent before-and-after cohort study with a clinical pathway based on enhanced surveillance for high-risk surgical patients has demonstrated a significant reduction of in-hospital mortality.[24] Particularly in this study, the "high-risk surgical bundle" has included six main elements, such as risk identification and communication, adoption of a high-risk post anesthesia care unit discharge checklist, prompt nursing admission to ward, intensification of vital signs monitoring, perioperative troponin measurement, and prompt access to medical support if required.[24] New research is still warranted to further evaluate which strategies designed to enhance perioperative care can actually reduce morbidity and mortality in high-risk surgical subpopulations.

In summary, the high-risk surgical patient is a growing challenge to the modern anesthetic care. Perioperative risk stratification is currently a fundamental principle of an adequate care for surgical patients. The surgical risk should be predicted for every patient in the preoperative period, and risk models are valuable clinical tools for shared decision-making and the development of individualized care plans. Methods for stratifying individual risk include assessment tools, measures of functional capacity and biomarker assays. They have the potential to contribute to the delivery of a high quality and up-to-date anesthetic and perioperative care. Notably, the development and application of robust tools to properly identify high-risk patients is essential to ground future intervention studies toward improved outcomes for all surgical patients.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Derivation and validation of a national multicenter mortality risk stratification model – the ExCare model: a study protocol

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KEYWORDS
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Risk assessment;
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Validation studies;
Mobile health application

Abstract
Introduction: Surgical care is essential for proper management of various diseases. However, it can result in unfavorable outcomes. In order to identify patients at higher risk of complications, several risk stratification models have been developed. Ideally, these tools should be simple, reproducible, accurate, and externally validated. Unfortunately, none of the best-known risk stratification instruments have been validated in Brazil. In this sense, the Ex-Care model was developed by retrospective data analysis of surgical patients in a major Brazilian university hospital. It consists of four independent predictors easily collected in the preoperative evaluation, showing high accuracy in predicting death within 30 days after surgery.
Objectives: To update and validate a Brazilian national-based model of postoperative death probability within 30 days based on the Ex-Care model. Also, to develop an application for smartphones that allows preoperative risk stratification by Ex-Care model.
Methods: Ten participating centers will collect retrospective data from digital databases. Variables age, American Society of Anesthesiologists (ASA) physical status, surgical severity (major or non-major) and nature (elective or urgent) will be evaluated as predictors for in-hospital mortality within 30 postoperative days, considered the primary outcome.

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Expected results: We believe that the Ex-Care model will present discriminative capacity similar to other classically used scores validated for surgical mortality prediction. Furthermore, the mobile application to be developed will provide a practical and easy-to-use tool to the professionals enrolled in perioperative care.
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Introduction

Surgical care is essential for proper management of several clinical conditions and the number of procedures performed over the years has been increasing in Brazil and worldwide.[1,2] However, it can lead to relevant negative outcomes. The global perioperative risk is multifactorial, depending on the interaction between anesthesia, patient's clinical status, surgical trauma, and hospital care. In high income countries, the risk of complications and postoperative morbidity is estimated at 3% to 17%.[3,4]

In this sense, perioperative risk stratification as part of safety and quality of care policies facilitates informed consent and assists professionals involved in the perioperative care to plan assistance.[5] Therefore, different assessment tools have been implemented to identify patients at high surgical risk. Most of these models, however, have been developed and validated in high income countries.[6,7]

In this scenario, our research group developed the SAMPE model. Derived from the analysis of 13,524 surgical patients at Hospital de Clínicas de Porto Alegre (HCPA), it incorporates 4 variables easily collected in the preoperative period: age, American Society of Anesthesiologists physical status (ASA-PS) classification, nature of the procedure (urgency or elective) and surgical severity (major, intermediate, or minor). The resulting model showed good discriminative capacity for 30-day in-hospital mortality, but it still had some inconsistencies.[8] To correct these instabilities, we developed the Ex-Care model, evaluating a different sample of 17,791 patients at our institution. After statistical refinement, the Ex-Care model performed better than its predecessor[9] using the same predictors. Nevertheless, this result is validated for HCPA population, requiring an assessment of its accuracy in other national institutions.

Thus, considering the recent recommendations in perioperative care, which guide the creation of a national system to identify patients with a higher risk of post-surgical morbidity and mortality,[10] we aim to build a robust model based on data from patients operated in Brazil. Information regarding surgeries performed in hospitals in different regions of the country will be collected. The Ex-Care model will have its performance evaluated based on the data collected at participating centers. Thereafter, an update of the Ex-Care model will be built and validated. Finally, as previously done for Ex-Care (available on iOS platforms, https://apps.apple.com/br/app/excare/id1515296910?l=en, and Android, https://play.google.com/store/apps/details?id=excare.model), a mobile application for smartphones contemplating the data of the updated model will be developed.

Methods

Study design

Retrospective, multicenter, cohort study which aims to build a national preoperative risk model based on Ex-Care model of probability of postoperative death within 30 days, with hospital as a random effect. The updated Ex-Care model will be validated in a different sample from that of the derivation. The study will be conducted and reported according to Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[11]

Source of data and participants

The study will be carried out in ten national reference hospitals located in different Brazilian regions and will be coordinated by the Anesthesia and Perioperative Medicine Service of HCPA – called the Executive Committee (EC). To analyze the performance of the Ex-Care model and to update it, all consecutive hospitalized patients who underwent procedures from January 1st, 2017 to April 30th, 2018 in the participating centers that meet the inclusion criteria will be enrolled. For its validation, another sample containing data from patients who underwent surgery from May 1st to December 31st, 2018 will be evaluated. All subjects above 16 years of age who are candidates for elective or emergency surgery will be considered eligible. Diagnostic procedures and those under sedation or local anesthesia will be excluded; in addition, if a patient was submitted to more than one surgical intervention during hospitalization, only the major one will be considered for outcome analysis. Liver, lung, and heart transplantation and patients diagnosed with brain death who were candidates for organ donation will be excluded.

Outcome

In-hospital mortality within 30 days after surgery will be the primary outcome. Every patient included in both derivation and validation cohort will be followed until this period. Those who remain hospitalized after 30 days of surgery, or who are discharged before that period, will not be followed-up from that point on. All participating centers must have a digital database capable of determining the status of patients (hospital discharge, hospitalization, or death) on the 30th postoperative day.

Model Development

Selection of predictors for derivation cohort

When building surgical risk stratification instruments, variables related to patient's clinical condition and procedure to be performed must be considered. These variables can be measured at different times of perioperative care.[12] Ideally, a risk score should be simple, reproducible, objective, accurate, applicable to most surgeries (including emergency ones), and validated for all populations.[7] In the construction of the original SAMPE model, four variables with proven accuracy in existing perioperative risk models were considered: ASA-PS classification, age, surgical severity (minor, intermediate, and major), and nature (urgent or elective). The classification of surgical severity in three categories was carried out through the opinion of specialists and literature review, taking into account surgical time, magnitude of the trauma and predicted bleeding.[13] For its development, urgent surgical procedures were considered those in which there is risk of death and/or limb loss within 24 hours.

While building the SAMPE model, 13,524 patients were evaluated, a logistic regression model was adjusted for the four variables analyzed and all correlated significantly with in-hospital death within 30 days. C-statistic demonstrated excellent predictive capacity for probability of death within 30 days with area under receiver operating characteristic (AUROC) of 0.9137, a high-performance value. The Hosmer-Lemeshow statistic of 13.28 (p = 0.125) in the derivation data set proved to be an acceptable calibration model. Subsequently, the model was validated with a new sample of 7254 patients, with a sensitivity of 86.4% and specificity of 81.4%. The c-statistic of the validation sample was 0.922.[8]

When evaluating SAMPE model statistics, however, there was no difference in the odds ratio (OR) of the variable surgical size for small and medium-sized procedures (OR 0.691; CI 0.467–1.022). Thus, this variable was adjusted unifying small and medium-sized surgeries into a single group, ''non-major procedures''. This adjustment did not show a good fit by the Hosmer-Lemeshow test and, from a later verification, it was noticed that the variable age did not meet the assumption of linearity, showing that the risk of death did not increase steadily throughout life. In order to deal with this lack of linearity, a new logistic regression model was adjusted using polynomial regression splines technique for the independent variable age. It consists of the inclusion of continuous exposure coded by using splines functions. The junction between two intervals is called ''knot''.[15] We have modeled age using splines with five knots to allow for non-linearity. The final tool developed was given the name Ex-Care model. It presented an AUROC of 0.926 (CI 0.91–0.93) for the derivation sample, with goodness-of-fit by the Hosmer-Lemeshow Test of 9.26 (p = 0.41), indicating good calibration.[9] The update of the Ex-Care model at the national level will maintain the adopted statistical refinements and will have patients operated at hospitals in different country regions as a sample.

Sample size

A robust derivation model requires at least 100 events per candidate variable and a validation study requires at least 10 events.[14,15] Therefore, a minimum of 440 events were needed to achieve stable estimates from the regression model. Although there are regional differences, the mean mortality rate across all surgical procedures in Brazil was 1,6% in the period of 2008 to 2016,[16] requiring a minimum sample size of 27,500.

We aim to recruit as many hospitals as possible. Considering data from previous studies at HCPA that involved similar profile of participants and the same time interval, we believe that approximately 6500 patients/year will be enrolled at HCPA.[8] Furthermore, based on a survey carried out with the coordinating researchers from the other centers, we estimate to collect data from 77,000 patients (Table 1).

Table 1 Estimated sample size per participating center per year.

Participating centers	Estimated subjects (per center/ annually)
Hospital de Clínicas de Porto Alegre City: Porto Alegre - RS	6500
Hospital Ernesto Dornelles City: Porto Alegre - RS	4000
Hospital Tacchini City: Bento Gonçalves - RS	3500
Hospital Moinhos de Vento City: Porto Alegre – RS	3500
Hospital São Paulo City: São Paulo - SP	4000
Hospital São Carlos City: Fortaleza - CE	3500
Hospital Brasília City: Brasília - DF	3000
Campus de Botucatu Faculdade de Medicina UNESP – SP City: São Paulo - SP	4000
Instituto do Câncer do Estado de São Paulo City: São Paulo - SP	3500
Hospital Universitário Prof. João Cardoso Nascimento City: Aracajú - SE	3000

Data management

Participating centers will be asked to send a *query* to the EC reporting the following characteristics of each eligible patient: age, sex, medical record number, ASA-PS classification, surgery performed, nature of the procedure (elective or urgency/ emergency), date of surgery, date of discharge or death (if it occurs until before the 30th day), origin of the patient (public health system or private sector). *Queries* will be built by the Information Technology (IT) Services of each participating center. IT, using Structured Query Language (SQL), creates programs that interact with the relational database and generate information organized in rows and columns – for our purpose, a spreadsheet will be developed in Microsoft Excel. In order to ensure data confidentiality, patients name will not be recorded. Additionally, the database will be shared on a drive exclusively available

Table 2 Color-coded risk classification based on the probability of death within 30 days.

Risk class	Predicted mortality within 30 days
Class I	< 2%
Class II	≥ 2 to < 5%
Class III	≥ 5 to < 10%
Class IV	≥ 10%

for the project researchers. Each participating center has a coordinator responsible for adequate data collection at the institution. EC will be responsible for calculating the risk of death in 30 days based on the Ex-Care model. Following stratification, patients will be divided into 4 classes of probability of death within 30 days (Table 2).

This risk stratification will be compared with the clinical evolution of the patients, with mortality within 30 days after surgery as primary outcome to be analyzed. The full data collection and record linkage strategy are depicted in Figure 1.

Missing data

Most prediction models, including those based on logistic regression, are not able to deal with missing data, requiring care when developing, validating, and implementing.[11] In order to reduce this inconvenience, we chose to only select centers that have electronic medical records and in which all the predictors necessary for the calculation of surgical risk by the Ex-Care model are routinely registered in clinical practice. Missing data will be handled in complete-case analysis.

Statistical analysis methods

Categorical data will be summarized in absolute and relative frequencies. Continuous data will be presented as mean and confidence interval (95%). Each patient will have their probability of death quantified using the Ex-Care model for temporal validation. Logistic regression model adjusted for the independent predictors of Ex-Care model (age, ASA-PS score, surgical severity, and nature of the procedure) will assess the association with primary endpoint mortality within 30 days; the magnitude with which each variable is related to the outcome will be demonstrated with *odds ratios* and 95% confidence intervals. In this model, the linearity assessment of the age predictor will be performed using splines.[17]

Model calibration will be evaluated by plotting the proportion of expected events and the predicted probabilities for the defined risk groups. The Hosmer-Lemeshow test will be used to establish this calibration, comparing the expected and observed number of deaths by group risk and performing the AUROC measurement for discrimination. AUROC represents the overall accuracy or performance of the test, as it takes into account all sensitivity and specificity values for each variable value.

For Ex-Care model update, a mixed logistic regression model with random effect for hospitals will be adjusted, aiming to control the heterogeneity among different centers. This will consist of the same independent predictors previously mentioned and will be validated in another sample (patients operated from May to December, 2018), using the methods above described. All analysis will be performed using the R-3.5.1 and SAS, version 9.4 programs.

Discussion

Perioperative risk stratification is a fundamental principle of care for surgical patients. Adopting an easy-to-use tool in the preoperative period for different specialties and capable of identifying patients most likely to have complications is part of the risk management strategy to be implemented by hospitals worldwide. In theory, the concept that high-risk patients need more care seems clear and easy to understand; in daily practice, however, there is a systematic failure in the individual clinical judgment of physicians to identify and manage these patients.[18]

In an ideal scenario, every patient who undergoes a procedure should have their surgical risk predicted in the preoperative period. The use of surgical risk models, in addition to assisting decision-making by health professionals, facilitates dialogue with patients and family members, as well as allows monitoring and comparison of outcomes between centers.

Finally, in view of the great heterogeneity between surgical mortality rates among countries, it is not viable to generalize parameters validated for specific populations to all centers. Furthermore, when assessing the socioeconomic, cultural, and health service structure between developed and developing countries, the difference in outcomes becomes evident.[1,18,19] In a cohort published in 2016 for elective surgeries, similar mortality rates were evidenced when comparing high-income to middle- and low-income countries. However, patients operated in high-income countries were older, had more comorbidities and, once developed complications, were better treated, as determined by a minor failure to rescue rate.[20] When evaluating non-elective surgeries, outcome differences become more evident.[21] Hence, creating a risk model developed and validated for the Brazilian reality must take priority.

In order to fill this gap, based on the Ex-Care model, the update proposed by this protocol, through the use of an application to be developed, will provide an easy-to-use digital tool, with the possibility of interactive improvements, capable of incorporate a robust surgical risk prediction score, validated in a Brazilian surgical sample. It is important to highlight that when using the application to calculate the risk by the Ex-Care model the professional will have, in addition to stratification in the classes described (Table 2), the percentage value of the individual probability of in-hospital death within 30 days.

Limitations

Although the Ex-Care model has been validated with good accuracy in the population assisted by Hospital de Clínicas de Porto Alegre, we cannot assertively guarantee that it will have the same performance at national level. Brazil is a country of continental dimensions with great socioeconomic disparity and availability of resources among its regions.[16,22] This feature may make it difficult to create a single model representative of the assistance provided throughout its territory. In fact, before applying it more widely in Brazil, we

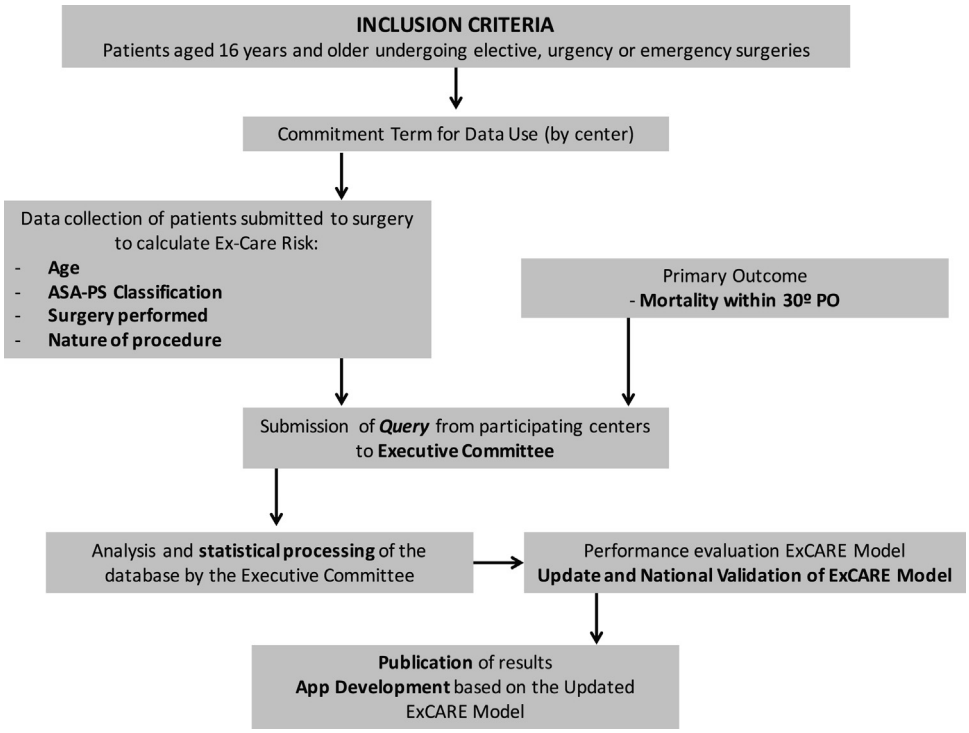

Figure 1 Model development methodology.

must test its performance in different scenarios and populations. In the literature, there are examples of risk prediction models that, when used without adjustments in samples other than the one originally used for their construction, did not show good calibration capacity, requiring corrections in the original model.[23,24] Perhaps different models will be necessary for distinct groups of hospitals (for example, regional models). That being said, it is important to note that the external validation of the Ex-Care model is the next step in the strategy of consolidating and disseminating the use of this new tool in perioperative setting.

Secondly, this is a retrospective study, with data collected from information present in *queries* sent by participating centers. In order to reduce the missing data, we chose to select only hospitals that had a digital system and where the requested data are recorded in routine clinical care.

Finally, although the Ex-Care model aims to objectively estimate the probability of death within 30 days postsurgery, for its composition, two subjective variables were used (ASA-PS and surgical severity). Nevertheless, the ASA-PS is a classification widely used in the clinical setting and, for the variable surgery severity, a comprehensive review of the literature and consultation with specialists was carried out.

Implications

We believe that an updated Ex-Care model will be a helpful tool to accurately stratify the risk of death to which patients operated in Brazil are subjected, supporting professionals involved in perioperative care to identify high-risk surgical patients and to better plan therapeutic strategies. Also, in order to encourage the use of perioperative risk scores and facilitate access to the Ex-Care model, we will create and make available to professionals engaged in the care of surgical patients a smartphone application that contemplates the new model.

Conclusion

To date, there is no surgical risk model developed for the Brazilian population. This study protocol outlines the methodology that will be used to national derivation and validation of the Ex-Care Model, a tool that aims to accurately estimate the probability of in-hospital death within 30 postoperative days.

Ethics approval

This study is performed in accordance with the declaration of Helsinki and follows the resolutions of the Brazilian National Health Council. Ethical approval was granted by the HCPA Postgraduate Research Group Ethics Committee (Project Number: 2019.0192). Moreover, all other participating centers obtained approval from their own ethics committees. As this is a retrospective observational study and follows standard care for surgical patients, the HCPA Ethics Committee exempted the need for a consent form for participants. A Data Usage Commitment Term was prepared requesting all researchers to ensure data confidentiality.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Perioperative goal-directed fluid management using noninvasive hemodynamic monitoring in gynecologic oncology



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KEYWORDS
Fluid therapy;
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Gynecologic debulking surgery

Abstract

Background: Intraoperative fluid management is important for the prevention of perioperative morbidity and mortality. Our study aimed to investigate the perioperative feasibility and benefits of Goal-Directed Fluid Management (GDFM) using noninvasive hemodynamic monitoring in gynecologic oncology patients with acute blood loss and severe fluid loss. We assessed the effects of GDFM on hemodynamics, organ perfusion, complications, and mortality outcomes.

Methods: This randomized prospective study included 104 patients over the age of 18 years, including 56 patients with endometrial cancer and 48 patients with ovarian cancer who had open surgery. The anesthetic approach was standardized for all patients. We compared the perioperative results of the subjects who were randomized into GDFM (n = 51) and Liberal Fluid Management (LFM) (n = 53) groups using a computer program.

Results: The median perioperative crystalloid replacement (2000 vs. 2700; $p < 0.001$) and total volume of fluid (2260 vs. 3200; $p < 0.001$) were lower in the GDFM group compared to the LFM group. The hemodynamic findings and the HCO_3 and lactate levels of the GDFM group did not significantly change perioperatively. The heart rate, mean arterial pressure, and HCO_3 levels of the LFM group decreased and serum lactate levels increased perioperatively. The hospitalization rate in ICU (7.8% vs. 28.3%; $p = 0.010$), rate of patients with comorbidity conditions indicated in ICU (2% vs. 17%; $p = 0.024$), and rate of complications (17.6% vs. 35.8%; $p = 0.047$) were lower in the GDFM group compared to the LFM group.

Conclusion: The amount of intraoperatively administered crystalloid solution and complication rates were significantly lower in gynecologic oncologic surgery patients who received GDFM.

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Besides, hemodynamic findings, and lactate levels of the GDFM group did not change significantly during the perioperative period.
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Introduction

Intraoperative fluid management is important for the prevention of peri- and postoperative complications, morbidity, and mortality, particularly in gynecologic oncological operations involving multi-organ resection for tumors. Surgery can lead to significant fluid loss due to prolonged peritoneal air exposure, significant blood loss, and acute drainage of tumor-associated ascites. Intraoperative drainage of ascites is followed by reduced fluids in vessels, which may require the administration of large volumes of fluid for replacement.[1] While planning fluid management, the anesthesiologist needs to ensure adequate blood flow for adequate and safe tissue oxygenation and the capacity of the cardiac output to meet metabolic requirements.

Goal-Directed Fluid Management (GDFM) includes the evaluation of fluid sensitivity and cardiac functions using dynamic and static parameters to measure cardiac output in order to optimize oxygen supply to tissues during surgery. Randomized controlled trials and meta-analyses have reported superior outcomes for GDFM in terms of organ damage, mortality, wound healing, length of hospital stay, and length of ICU stay compared to Liberal Fluid Management (LFM).[2,3] The established advantages of GDFM compared to LFM and the subsequent financial benefits have led to GDFM being recommended as the standard of care by a large number of scientific communities and being included in treatment guidelines.[4,5]

Patients undergoing gynecologic oncologic surgery are prone to significant fluid shift and blood loss and therefore are at risk for hypovolemia, end-organ hypoperfusion, and adverse postoperative outcomes.[6] Although GDFM has been frequently investigated in patients undergoing major abdominal surgery, it has been rarely investigated in patients undergoing major gynecologic surgery. In addition, intravascular volume depletion and acute hemorrhage are important problems in gynecological oncology cases. In these cases, management of perioperative GDFM with minimal therapeutic procedures is essential. Therefore, in this study, we investigated the effects of GDFM on hemodynamic morbidity using PVI and investigated the effects of GDFM on mortality.

Methods

Study design and population

This prospective study was conducted between May 2019 and December 2019 at the Gynecological Oncology Clinic of the Health Sciences University Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital. One hundred and twenty seven adult patients with an American Society of Anesthesiologists (ASA) physical status of II—III presenting for major abdominal oncologic surgery (expected duration $\geq$ 2 h) were evaluated. The exclusion criterias were as follows: patients younger than 18 years, Body Mass Index (BMI) $\geq$ 35 kg.m^{-2}, laparoscopic surgery, peripheral artery disease, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, arrhythmia, advanced kidney or liver failure, decompensated heart failure (ejection fraction of $<$ 30%), and not being able to tolerate a tidal volume of 8 mL.kg^{-1} in mechanical ventilation (for accuracy of the Pleth Variability Index). Twenty three patients who met the exclusion criteria were excluded from the study. A total of 104 patients, including 56 patients with endometrial cancer and 48 patients with ovarian cancer, who met the inclusion criteria were included in the study (Figure 1).

The study was planned as per the 2013 Brazil revision of the Helsinki Declaration. All patients signed informed consent forms. The study was granted ethical approval by the local ethics committee (2019\152) and was registered as a clinical trial (NCT03956901).

Assuming an alpha of 0.05, a power of 0.80, and consistent with previous reports[7] with 10% lower complication rate in the GDFM group, the estimated sample size was at least 50 patients in both protocol groups. Age and body mass index were evaluated as potential confounders. According to this, patients were single-blindly assigned to the targeted fluid therapy or liberal fluid therapy branches by computer stratified randomization analysis with a ratio of 1:1 in the STATA program (StataCorp LLC, Texas, USA). Anesthesiologists were not blinded to group assignments. However, patients, surgeons, PACU and surgical nurses, and those who provided the data analysis were blinded. The data of the patients were obtained by saving them on the memory card of the monitor at the end of the case.

Anesthesia initiation

The anesthetic approach was standardized for all patients. Patients were allowed clear fluid intake up to 2 hours and solid food intake up to 6 hours before the operation. In the operating room, heart rate, oxygen saturation, Central Venous Pressure (CVP), and invasive and noninvasive arterial pressure measurements were made with a Datex S/5 monitor (Datex Ohmeda®, GE Healthcare, Chicago, IL, USA). In the GDFM group, hemodynamic fluid responsiveness was achieved by Pleth Variability Index (PVI) monitoring with a finger sensor (in the arm without invasive arterial cannulation, using the finger probe from the 4th finger and covered in an opaque manner) (Masimo Corporation, Radikal 7, USA). Vascular access was opened with a 16—18G catheter for all patients. Before anesthesia induction, 0.03 mg.kg^{-1} midazolam was administered, and epidural catheter was inserted for postoperative analgesia. No medication was administered to the patients through the intraoperative epidural

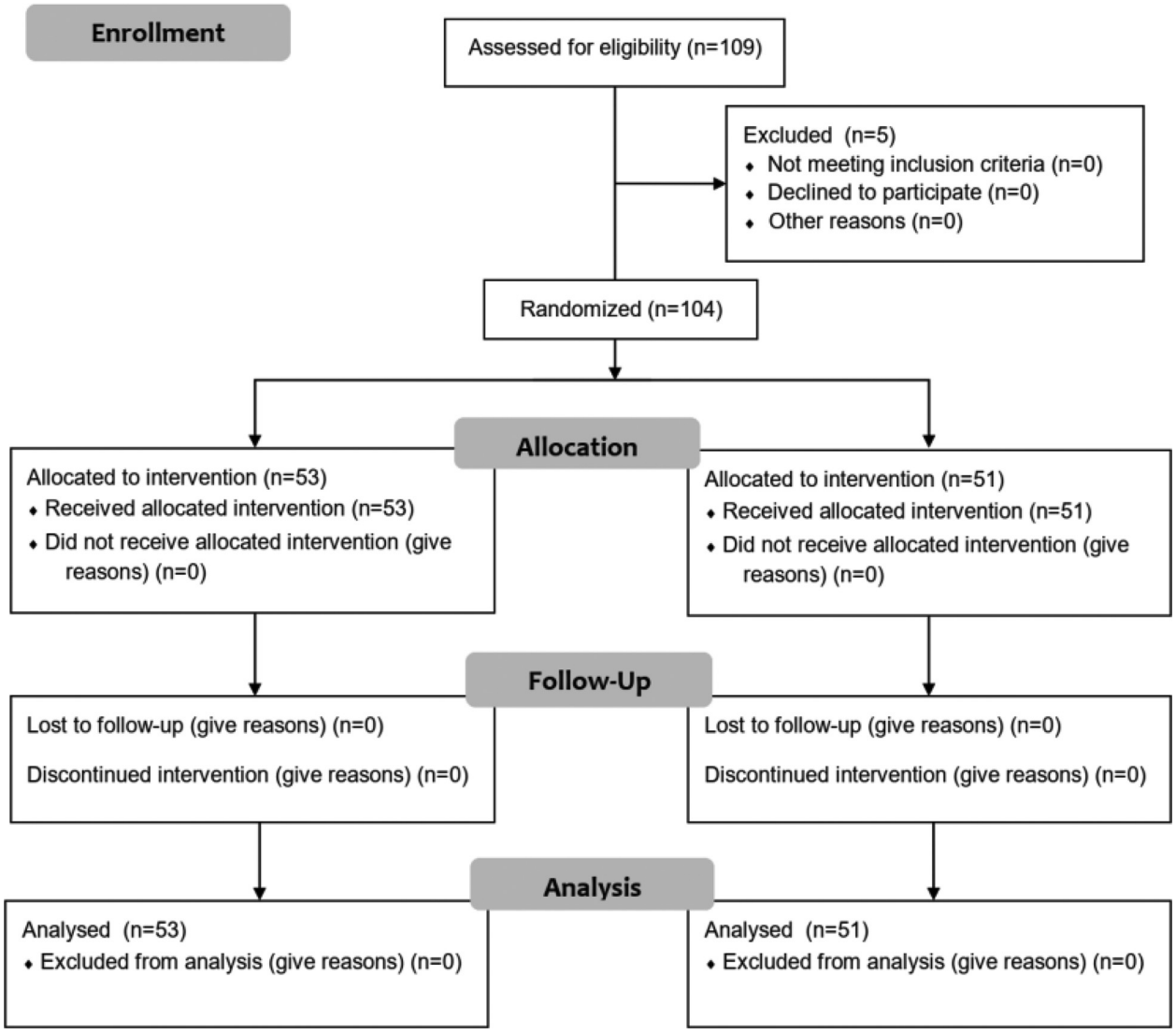

Figure 1 Trial profile. (GDFM, Goal-Directed Fluid Management; LFM, Liberal Fluid Management; MAP, Mean Arterial Pressure; NE, Norepinephrine, PVI, Pleth Variability Index).

catheter. All patients had an arterial line for arterial blood gas monitoring.

After anesthesia induction with 1 $\mu g.kg^{-1}$ fentanyl and 2–3 $mg.kg^{-1}$ propofol, the patient was curarized with 0.6 $mg.kg^{-1}$ rocuronium and connected to a ventilator. Mechanical ventilation was set to the volume-controlled mode with I:E 1:2, tidal volume 8 $mL.kg^{-1}$ of ideal body weight, and respiratory frequency adjusted according to end-tidal CO_2 (ECO_2 35–45 mmHg). Mechanical ventilation was maintained with a fresh gas flow rate of 3 $L.min^{-1}$ with 40% oxygen. Anesthesia was maintained with 1 MAC sevoflurane, 0.01–0.2 $\mu g.kg^{-1}.min^{-1}$ remifentanil infusion, and rocuronium as needed.

Perioperative fluid management

LFM application

A crystalloid fluid bolus (Ringer's lactate solution) of 500 mL was infused together with the induction of anesthesia, followed by a maintenance infusion of 4–8 $mL.kg^{-1}.h^{-1}$. Maintenance fluid therapy was continued in patients with MAP > 65 mmHg. If Mean Arterial Pressure (MAP) was < 65 mmHg, the patient was administered a 250 mL bolus of crystalloid solution and 1–2 μg bolus Norepinephrine (NE). Afterwards, MAP was followed at 5-minute intervals. If MAP was still < 65 mmHg after subsequent measurements, the patient was given 250 mL of crystalloid solution. In continuing hemodynamic follow-ups, if MAP < 65 mmHg despite mini fluid challenge, NE 0.1–1 $\mu g.kg^{-1}.min^{-1}$ (from a solution at a concentration of 0.08 $mg.mL^{-1}$) infusion was started and MAP adjusted to > 65 mmHg.

GDFM application

A crystalloid fluid bolus (Ringer's lactate solution) of 500 mL was infused together with the induction of anesthesia, followed by 2 $mL.kg^{-1}$ crystalloid fluid infusion. If the PVI was < 13% and MAP > 65 mmHg, the fluid infusion of the patients was continued at the adjusted dose. If PVI was < 13% and MAP was < 65 mmHg, fluid infusion was continued, and a 1–2 μg bolus NE was administered. Similar to the LFM

Table 1 Preoperative demographic, clinical, and laboratory findings.

Variables	All population n = 104	GDFM n = 51	LFM n = 53	*p*
Age, years	57.1±12.3	55.5±12.5	58.6±12.1	0.191
BMI, $kg.m^{-2}$	31.4±9.0	30.3±6.0	32.4±11.1	0.245
ASA, n (%)				
II	69 (66.3)	35 (68.6)	34 (64.2)	0.681
III	35 (33.7)	16 (31.4)	19 (35.8)	
Surgery time, minutes	307.5 (120–550)	300 (120–550)	350 (145–510)	0.098
Diagnosis, n (%)				
Endometrial	57 (54.8)	27 (52.9)	30 (56.6)	0.844
Ovarian	47 (45.2)	24 (47.1)	23 (43.4)	
Types of procedures, n (%)				
Endometrial	n = 57	n = 27	n = 30	
Hysterectomy	57 (100)	27 (100)	30 (100)	-
Bilateral BSO	57 (100)	27 (100)	30 (100)	-
PPALND	57 (100)	27 (100)	30 (100)	-
Ovarian	n = 47	n = 24	n = 23	
PPALND	44 (93.6)	22 (91.7)	22 (95.7)	
DPS/R	13 (27.7)	8 (33.3)	5 (21.7)	0.574
Bowel resection	8 (17.0)	5 (20.8)	3 (13.0)	0.747
LWR	4 (8.5)	2 (8.3)	2 (8.7)	0.999
Splenectomy	4 (8.5)	2 (8.3)	2 (8.7)	0.999
VATS	2 (4.3)	–	2 (8.7)	0.451
Ascites fluid, n (%)				
No	83 (79.8)	41 (80.4)	42 (79.2)	0.999
Yes	21 (20.2)	10 (19.6)	11 (20.8)	
Hemoglobin, $g.dL^{-1}$	11.4±1.6	11.4±1.5	11.5±1.7	0.724
Albumine, $mg.dL^{-1}$	37.6±4.6	37.1±4.9	38.0±4.2	0.349
Creatinine, $mg.dL^{-1}$	0.6 (0.3−9.4)	0.6 (0.3−9.4)	0.6 (0.3−1.7)	0.554

Numerical variables with normal distribution were shown as mean ± standard deviation. Numerical variables that do not show normal distribution are shown as median (min−max). Categorical variables were shown as numbers (%).
ASA, American Society of Anesthesiologists physical status; BMI, Body Mass Index; Ca, Cancer; GDFM, Goal-Directed Fluid Management; LFM, Liberal Fluid Management; ICU, Intensive Care Unit; PPALND, Pelvic Paraaortic Lymph Node Dissection; DPS/R, Diaphragmatic Peritoneal Stripping/Resection; LWR, Liver Wedge Resection; VATS, Video-Assisted Thoracoscopic Surgery.

group, MAP was followed at 5-minute intervals. If PVI was < 13% and MAP was < 65 mmHg after subsequent measurements, a repeat dose of NE bolus was administered. In repeated measurements, NE infusion of 0.1−1 $\mu g.kg^{-1}.min^{-1}$ (from a solution with a concentration of 0.08 $mg.mL^{-1}$) was started in patients with MAP < 65 mmHg. If PVI was > 13% and MAP was < 65 mmHg, the patient was administered a 250 mL crystalloid fluid bolus. If MAP < 65 mmHg persisted, 1−2 μg bolus NE was administered. If the PVI was > 13% and MAP was < 65 mmHg in subsequent measurements, a 250 mL crystalloid bolus was repeated for the last time. NE infusion of 0.1−1 $\mu g.kg^{-1}.min^{-1}$ (0.08 $mg.mL^{-1}$ solution) was started in patients with MAP < 65 mmHg on repeated measurements, and fluid infusion was continued until PVI was < 13%. The total fluid administered was recorded.

In patients with bleeding, if arterial blood gas, a target hemoglobin concentration within the target range (7−9 $g.dL^{-1}$), and PVI > 13%, they received erythrocyte suspension.[8] If more than 1,000 mL of ascitic fluid was aspirated in patients with ascites in the GDFM group, to maintain oncotic pressure, 1−2 units of Fresh Frozen Plasma (FFP) or 20% human albumin at 3 $mL.kg^{-1}$ were used targeting PVI < 13%.[9] In the LFM group, the amount of FFP and albumin were determined according to MAP, presence of tachycardia, and urine output findings. In these groups, the choice between using balanced crystalloids or colloids (albumin 100 mL) was left to the attending anesthesiologist.

Following perioperative hemodynamic stabilization, we recorded PVI, blood gas values, perioperative blood loss, and the amount of administered fluids at T0 (15 minutes after anesthesia induction), T1 (hour 1), T2 (hour 2), and after extubation. At the end of the operation, the patients were assessed to decide between extubation or admission to the ICU according to hemodynamic findings. NE infusion was evaluated and decided considering ongoing hemodynamic instability, respiratory distress, massive blood transfusion, and additional comorbidities (uncontrolled diabetes, uncontrolled hypertension) for ICU admission.

On the postoperative 24th hour, we recorded fever, creatinine, length of ICU stay, and length of hospital stay (the length of hospital stay was defined as the postoperative follow-up in bed until discharge). The patients were reached by phone on postoperative day 30 to confirm survival.

Statistical analysis

Data were analyzed using SPSS 20 for Windows (IBM Corp., Armonk, NY, USA). The normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. The normally distributed variables were presented as mean ± standard deviation while the non-normally distributed variables were presented as median (min–max). Categorical variables were presented as numbers and percentages. We used Student's *t*-test for the intergroup comparison of normally distributed variables and the Mann-Whitney U test for the intergroup comparison of non-normally distributed variables. Chi-Square and Fisher's exact tests were used for the intergroup comparison of categorical variables. The changes in laboratory findings before and after the operation were evaluated using the Generalized Linear Mixed Model (GLMM) for the analysis of longitudinal data with repeated measures for all patients and the two groups (GDFM and LFM). Values of $p < 0.05$ were considered statistically significant.

Results

The mean age of the subjects was 57.1 ± 12.3 years, and 66.3% (n = 69) were ASA II. There was no significant difference between the groups in terms of demographic characteristics and preoperative clinical and laboratory findings. Table 1 presents the relevant data in detail.

The median amount of crystalloid solution (2000 vs. 2700; $p < 0.001$) and median total volume of fluid (2260 vs. 3200; $p < 0.001$) were lower in the GDFM group compared to the LFM group. Other perioperative clinical findings were not significantly different for the GDFM and LFM groups (Table 2).

The mean Heart Rate (HR), mean MAP, and median serum lactate levels were similar for the two groups at T0 and T1, whereas they were higher in the LFM group at T2. Other perioperative laboratory findings were not significantly different for the two groups (Table 3).

The decrease in mean HR and mean MAP and the increase in median lactate levels and median base excess were significantly higher in the LFM group. The changes in other perioperative laboratory parameters were not significantly different (Table 3).

When preoperative and postoperative mean hemoglobin, mean albumin, and median creatinine levels were compared, and the changes observed were similar in the GDFM and LFM groups (Table 4).

The postoperative findings are shown in detail in Table 5. The hospitalization rate in ICU (7.8% vs. 28.3%; $p = 0.010$), rate of patients with comorbidities in ICU (2% vs. 17%; $p = 0.024$), and rate of complications (17.6% vs. 35.8%; $p = 0.047$) were lower in the GDFM group compared to the LFM group. Other postoperative events and mortality outcomes were not statistically different (Table 5).

Discussion

In this cohort of gynecologic oncologic surgery patients, we applied a pulse contour analysis-guided hemodynamic and static management protocol. We found that GDFM provides

Table 2 Perioperative clinical findings.

Variables	All population n = 104	GDFM n = 51	LFM n = 53	*p*
Blood loss, mL	400 (50–3000)	350 (50–3000)	500 (50–2000)	0.484
Urine output, mL	150 (25–1500)	150 (25–1500)	175 (50–1100)	0.169
Administered NE infusion, n (%)	9 (8.7)	2 (3.9)	7 (13.2)	0.182
Intravenous fluid replacement				
Crystalloid solution, n (%)	104 (100.0)	51 (100.0)	53 (100.0)	–
Volume, mL	2500 (812–6000)	2000 (812–5000)	2700 (1000–6000)	< 0.001[a]
Colloid solution, n (%)	49(47.1)	20(39.2)	29(54.7)	0.122
Volume, mL	500 (500–1000)	500 (500–1000)	500 (500–1000)	0.204
Total fluid volume, mL	2750 (812–8400)	2260 (812–7400)	3200 (1500–8400)	< 0.001[a]
Erythrocyte replacement, n (%)				0.074
None	74 (71.2)	39 (76.5)	35 (66.0)	
1 unit	8 (7.7)	6 (11.8)	2 (3.8)	
2 units	13 (12.5)	3 (5.9)	10 (18.9)	
3 units	9 (8.7)	3 (5.9)	6 (11.3)	
Fresh Frozen Plasma, n (%)				0.335
None	67 (64.4)	35 (68.6)	32 (60.4)	
1 unit	5 (4.8)	4 (7.8)	1 (1.9)	
2 units	19 (18.3)	8 (15.7)	11 (20.8)	
3 units	6 (5.8)	3 (5.9)	3 (5.7)	
4 units	5 (4.8)	1 (2.0)	4 (7.5)	
5 units	2 (1.9)	–	2 (3.8)	

Numerical variables with normal distribution were shown as mean ± standard deviation. Numerical variables that do not show normal distribution are shown as median (min–max). Categorical variables were shown as numbers (%).
GDFM, Goal-Directed Fluid Management; LFM, Liberal Fluid Management.
[a] $p < 0.05$ shows statistical significance.

Table 3 Perioperative laboratory findings.

Variables	All population n = 104	GDFM n = 51	LFM n = 53	*p*
Hemoglobin, g.dL^{-1}				
T0	10.8±1.5	11.0±1.5	10.7±1.6	0.356
T1	10.8±1.6	10.9±1.5	10.6±1.7	0.333
T2	10.7±1.7	10.9±2.0	10.6±1.4	0.322
Postextubation	11.0±1.3	11.1±1.4	11.0±1.2	0.808
p_r	0.140	0.845	0.102	
p_d		0.805		
Hearth rate, beats.min^{-1}				
T0	**78.4±15.4**	**79.6±17.6**	77.3±13.1	0.444
T1	68.9±12.2	71.9±14.3	**66.0±9.1**	0.014[a]
T2	69.1±12.5	72.3±13.3	**66.2±10.9**	0.012[a]
Postextubation	**84.1±14.3**	**89.3±15.7**	79.2±10.8	<0.001[a]
p_r	< 0.001[a]	< 0.001[a]	< 0.001[a]	
p_d		0.016[a]		
Mean arterial pressure, mmHg				
T0	79.2±14.2	82.7±18.0	75.8±8.0	<0.001[a]
T1	77.8±14.4	83.5±15.1	**69.3±6.6**	<0.001[a]
T2	75.9±13.9	82.6±15.5	**69.4±8.1**	<0.001[a]
Postextubation	**85.1±14.9**	**93.2±14.3**	77.3±10.9	<0.001[a]
p_r	< 0.001[a]	0.003[a]	< 0.001[a]	
p_d		0.003[a]		
pH				
T0	**7.5±0.1**	**7.5±0.1**	**7.5±0.1**	0.777
T1	7.4±0.1	7.4±0.1	7.4±0.1	0.279
T2	7.4±0.1	7.4±0.1	7.4±0.1	0.107
Postextubation	7.4±0.1	7.4±0.1	7.4±0.1	0.198
p_r	< 0.001[a]	< 0.001[a]	< 0.001[a]	
p_d		0.138		
HCO_3, mmoL.L^{-1}				
T0	24.5±2.3	24.7±2.5	**24.3±2.1**	0.335
T1	24.0±3.6	24.9±4.2	23.2±2.6	0.013[a]
T2	23.9±3.3	24.8±3.9	23.2±2.4	0.013[a]
Postextubation	23.4±3.0	24.0±3.2	23.0±2.7	0.070
p_r	0.004[a]	0.361	< 0.001[a]	
p_d		0.048[a]		
Lactate, mEq.L^{-1}				
T0	1.1 (0.1–3.2)	1.1 (0.5–2.8)	1.1 (0.1–3.2)	0.698
T1	1.1 (0.5–3.5)	1.1 (0.5–3.3)	1.1 (0.5–3.5)	0.573
T2	1.2 (0.4–6.3)	1.2 (0.4–3.8)	**1.4 (0.6–6.3)**	0.042[a]
Postextubation	1.7 (0.7–6.5)	**1.8 (0.7–6.4)**	**1.8 (0.7–6.5)**	0.665
p_r	< 0.001[a]	< 0.001[a]	< 0.001[a]	
p_d		0.047[a]		
Base excess, mEq.L^{-1}				
T0	**-0.1((-8.9)–(6.9))**	-0.1((-4.1)–(5.3))	**0.1((-8.9)–(6.9))**	0.610
T1	-0.9((-14)–(6.9))	-0.3((-4.9)–(5.4))	-1.3((-14)–(6.9))	0.107
T2	-0.5((-11)–(4.5))	-0.3((-6.7)–(4.5))	-0.6((-11)–(3.6))	0.105
Postextubation	-1.3((-13)–(7.5))	-0.4((-5.1)–(5.9))	-1.7((-13.0)–(7.5))	0.192
p_r	< 0.001[a]	0.121	< 0.001[a]	
p_d		0.032[a]		

Numerical variables with normal distribution were shown as mean ± standard deviation. Numerical variables that do not show normal distribution are shown as median (min−max). Categorical variables were shown as numbers (%).
HCO_3, Bicarbonate; GDFM, Goal-Directed Fluid Management; LFM, Liberal Fluid Management; pH, power of Hydrogen, T0, perioperative baseline, T1, 1-hour later; T2, 2-hour later.
[a] $p < 0.05$ shows statistical significance. p_r, Statistical difference of changes in laboratory findings in the group. p_d, Statistical difference of changes in laboratory findings between groups.

Table 4 Preoperative vs. postoperative laboratory findings.

Variables	GDFM (n = 51)	p_r	LFM (n = 53)	p_r	Δp
Hemoglobin, g.dL^{-1}					
Preoperative	11.4±1.5	< 0.001[a]	11.5±1.7	< 0.001[a]	0.818
Postoperative	10.5±1.3		10.6±1.3		
Albumin, mg.dL^{-1}					
Preoperative	37.1±4.9	< 0.001[a]	38.0±4.2	< 0.001[a]	0.230
Postoperative	28.8±3.5		28.6±4.5		
Creatinine, mg.dL^{-1}					
Preoperative	0.6 (0.3–9.4)	0.989	0.6 (0.3–1.7)	0.101	0.605
Postoperative	0.7 (0.3–8.6)		0.7 (0.4–2.3)		

Numerical variables with normal distribution were shown as mean ± standard deviation. Numerical variables that do not show normal distribution are shown as median (min–max). Categorical variables were shown as numbers (%).
GDFM, Goal-Directed Fluid Management; LFM, Liberal Fluid Management; pH, power of Hydrogen; WBC, White Blood Cell; CRP, C-Reactive Protein.
[a] $p < 0.05$ shows statistical significance. p_r, Statistical difference of changes in laboratory findings in the group. Δp, Statistical difference of changes in laboratory findings between groups.

favorable tissue oxygenation (such as stable serum lactate values) and reduces the amount of perioperative fluid administration due to its hemodynamic effects (such as stable MAP) compared to LFM, and GDFM was associated with reduced ICU admissions and postoperative complications.

Excess preoperative fluid administration in major abdominal and thoracic surgeries is associated with postoperative complications. Liberal and restrictive fluid management have been shown to be hazardous for high-risk surgical patients due to the risk of hypovolemia.[10] Therefore, for the possibility of safely limiting and personalizing fluid administration in high-risk surgical patients, GDFM is being recommended as the standard of care in relevant guidelines.[4,5]

Goal-directed fluid therapy suggests that reducing fluid administration when hemodynamic targets are met can help avoid inadequate fluid replacement.[11] Our results are consistent with the literature. In our study, we administered a crystalloid solution to all patients, but the amount of administered crystalloid solution was lower in the GDFM group compared to the LFM group. The use of crystalloid solutions alone may result in inadequate intravenous fluid replacement and iatrogenic fluid loading,[12] which may place patients at risk. Moreover, the GDFM method can reduce the risk of tissue edema that may result from excessive crystalloid fluid administration.[13] At the same time, the proportion of patients given both colloid solution and FFP in the LFM

Table 5 Event and mortality findings after the operation.

Variables	All population (n = 104)	GDFM (n = 51)	LFM (n = 53)	p
Hospitalization in ICU, n (%)	19 (18.3)	4 (7.8)	15 (28.3)	0.010[a]
Duration of stay in ICU, days	1 (1–10)	2 (1–10)	1 (1–9)	0.242
Indications of ICU, n (%)				
Comorbidity	10 (9.6)	1 (2.0)	9 (17.0)	0.024[a]
Closer hemodynamic monitoring	5 (4.8)	1 (2.0)	4 (7.5)	0.383
Inotropic therapy	11 (10.6)	2 (3.9)	9 (17.0)	0.065
Hemodynamic instability	3 (2.9)	2 (3.9)	1 (1.9)	0.973
Duration of stay in hospital, days	8 (0–30)	7 (2–30)	9 (2–28)	0.078
Fever, n (%)	8 (7.7)	4 (7.8)	4 (7.5)	0.999
Complication, n (%)	28 (26.9)	9 (17.6)	19 (35.8)	0.047[a]
Wound infection	15 (14.4)	6 (11.8)	9 (17.0)	0.579
Pulmonary edema	4 (3.8)	–	4 (7.5)	0.136
Evisceration	3 (2.9)	2 (3.9)	1 (1.9)	0.973
Acute renal failure	2 (1.9)	1 (2.0)	1 (1.9)	0.999
Retroperitoneal hematoma	2 (1.9)	1 (2.0)	1 (1.9)	0.999
Postoperative ileus	2 (1.9)	1 (2.0)	1 (1.9)	0.999
Urethral stricture	1 (1.0)	–	1 (1.9)	0.999
Anastomotic leak	1 (1.0)	–	1 (1.9)	0.999
Mortality, n (%)	1 (1.0)	–	1(1.9)	0.999

Numerical variables that do not show normal distribution are shown as median (min–max). Categorical variables were shown as numbers (%).
GDFM, Goal-Directed Fluid Management; LFM, Liberal Fluid Management; ICU, Intensive Care Unit.
[a] $p < 0.05$ shows statistical significance.

group was partially higher than the GDFM group. This situation supports the need for more fluid replacement to provide hemodynamic stability in the LFM group, in line with the literature.[7,9] In addition, although the proportion of patients with ascitic fluid was similar in both groups, these patients corresponded to half of the patients given colloid solution and FFP. It has been suggested that FFP transfusion in patients with malignant ascites may help restore hemodynamic stability.[14]

Dynamic variables based on ventilation-induced changes in cardiac output help predict fluid response. Timely interventions based on the individual needs of the patient can prevent hypotension and hemodynamic imbalance.[15,16] Arterial pulse pressure variation is cited as one of the most useful dynamic variables in guiding volume replacement.[15,17] In our study, perioperative decreases in MAP and HR were significantly higher in the LFM group compared to the GDFM group. The benefits of GDFM may be associated with the administration of fluids at the right time, helping avoid hypovolemia and hypoperfusion. Another advantage of the GDFM protocol is using NE as the first-line intervention for hypotension, independently of stroke volume variation.[18]

In our study, the comparative norepinephrine usage rate was approximately 1:3 for the GDFM and LFM groups, even though this finding was not statistically significant. These findings support the idea that the risk of hypotension is lower for GDFM, and the patient is less likely to require NE intervention.

The perioperative tissue perfusion outcomes of GDFM are superior to those of LFM approaches. When oxygen supply is insufficient, pyruvate cannot enter the Krebs cycle and is shunted to lactate. Therefore, serum lactate levels reflect anaerobic cellular metabolism that results from tissue hypoxia.[19] Serum lactate levels increase when oxygen supply is insufficient to meet tissue metabolism requirements. Latent hypoperfusion without clinical symptoms of shock elevates serum lactate levels.[20] These are solid parameters for the assessment of inadequate oxygen perfusion. In our study, serum lactate levels did not change in the GDFM group but increased in the LFM group. Forget et al.[16] demonstrated that GDFM with PVI applied during major abdominal surgery was associated with lower lactate levels and that these patients required significantly less crystalloid fluid administration. The results of our cohort of patients undergoing gynecologic oncological surgery suggest that GDFM is superior to LFM as demonstrated by more stable serum lactate levels and reduced fluid replacement.

Morbidity and mortality are significantly higher in patients who undergo high-risk surgeries. Most of these patients have clinically significant dehydration preoperatively, and patients lose varying volumes of fluid intraoperatively. Insufficient intravascular volume reduces pulse volume and cardiac output, resulting in inadequate tissue and organ perfusion. This can result in the development of serious complications, longer-term hospitalization, and, without the appropriate interventions, even death. For this reason, intraoperative fluid therapy is important both for surveillance and for preventing postoperative complications. In our study, ICU admission and complication rates were lower in the GDFM group, consistent with the literature.[2,10,12,21] Also, the complication rate of the LFM group was almost double that of the GDFM group. In our study, the distribution of patients with wound infection in the LFM and GDFM groups was similar. This is consistent with the conclusion in a meta-analysis that complementary hydration alone does not affect wound infection rate, regardless of any specific hemodynamic goal.[22] However, when the amount of perioperatively applied fluids is aimed at increasing subcutaneous oxygen tension, a greater amount of collagen in wound healing has been observed.[23] In particular, anastomotic leak, pulmonary edema, and urethral stricture were observed only in the LFM group. A recent study has shown that patients treated with a non-guided restrictive fluid administration protocol had a higher risk of postoperatively developing acute kidney injury and that this was associated with lower intraoperative urine output.[24] Large amounts of IV fluid replacement can exacerbate capillary leakage associated with the systemic inflammatory response to surgery and may contribute to the development of intestinal anastomotic edema.[25] Therefore, the complications that were observed only in the LFM group may have been due to the unsteady mucosal perfusion that resulted from unstable fluid therapy.[26,27] However, in our study, the distribution of complication types determined in both groups did not differ significantly. In our study, the complication rates in the GDFM group were consistent with GDFM applications presented in similar gynecologic surgery cohorts.[12,28] One patient died during the 30-day follow-up. This patient was in the LFM group and died due to a postoperative ileus complication. Postoperative ileus is a common complication of intra-abdominal surgeries. However, it is suggested that targeted fluid therapy may not be an effective strategy in reducing the risk of postoperative ileus.[29] Also, a longer-term follow-up would possibly change the postoperative mortality rate.

The major limitations of the present study are the relatively small number of patients and the results are based on a single center experience. In addition, we evaluated only 30-day short term survival outcomes. Another important limitation is the intensive care indications due to the preoperative comorbidities of the patients. The higher ICU hospitalization rate observed especially in the LFM group may be due to comorbidity including ICU indication. On the other hand, the BMI level was slightly higher in the LFM group. In our study, calculating the tidal volume based on ideal body weight, is appropriate to exclude patients with very high BMI. Various metabolic and neurohormonal changes commonly associated with overweight or obesity may have contributed to abnormalities in cardiac morphology and function.[30] One of the important limitations of our study is that muscle relaxation was not monitored. We used rocuronium as a muscle relaxant in our patients. Monitoring and maintenance of a constant level of muscle paralysis could have minimized the possibility that muscular contraction influenced on lung mechanics.

We conclude that the clinical use of GDFM in gynecologic oncological surgery is beneficial for limiting the amount of intraoperatively administered crystalloid solution without causing hypovolemia, hypotension, or serum lactate elevation. This may be associated with rapid recovery of bowel function, wound healing, and reduced ICU admission, length of hospital stay, and complication rates.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Perioperative management of patients undergoing tracheal resection and reconstruction: a retrospective observational study

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KEYWORDS
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Abstract
Background: Perioperative management of Tracheal Resection and Reconstruction (TRR) presents many challenges to the physicians involved in airway management. Factors related to postoperative outcomes can be identified as early as the preoperative setting and can even be linked to demographic characteristics of patients affected by tracheal stenosis. The primary aim of this study is to describe the experience of patients undergoing TRR at our hospital from an anesthesiology perspective, describing as a second aim demography, preoperative conditions, and postoperative complications.
Methods: This was a single institution retrospective review of patients who underwent TRR between 2009 and 2020. We did a post-hoc exploratory analysis to identify possible associations between perioperative complications and perioperative management.
Results: Forty-three ASA I—IV adult patients aged 18—72 years who underwent TRR were included. Prolonged intubation (72%) is the primary cause of tracheal stenosis. Intraoperative management: intravenous induction and laryngeal masks are now the most frequently used for airway management, especially in subglottic stenosis. Perioperative complications were vocal cord paralysis (25.6%), postoperative ventilatory support (20.9%), and need for surgical reintervention (20.9%). One patient (2%) died in the postoperative period due to anastomotic complication. After resection, dexmedetomidine is the preferred choice (48.8%) for sedoanalgesia in the ICU.
Conclusions: Perioperative management of TRR at our hospital has a low mortality and high morbidity rate. We did not find an association between perioperative anesthetic interventions and postoperative complications. Further studies are needed to evaluate which anesthetic interventions may be associated with better outcomes.
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Introduction

Tracheal Resection and Reconstruction (TRR) is the treatment of choice for many patients diagnosed with primary tracheal tumors and for those presenting with tracheal stenosis.[1] Sixty-five percent of tracheal stenosis cases around the world correspond to postintubation injuries, affecting women and men equally, with relevant predictors associated with complications of the tracheal anastomosis. These complications derive either from prior medical conditions (diabetes mellitus, tracheostomy before surgery), from intraoperative factors such as extended resections ($\geq$ 4 cm), or those requiring additional laryngeal resection.[2]

Current recommendations for perioperative management of TRR are mostly grounded on clinical experience and observational studies from a surgical standpoint with little attention to perioperative anesthetic interventions.[2-7] This surgical procedure presents many challenges to the anesthesiologist managing the patient because the risk of losing the airway is lingering throughout the perioperative period. During surgical resection, the airway is shared and manipulated by the surgeon, and at the end of the intervention, extubation, and postoperative management add further challenges because some patients must remain with prolonged cervical flexion, and Valsalva maneuvers, such as coughing or nausea, must be avoided given the risk of tracheal anastomosis rupture.[1,8-10]

There are numerous descriptions about the preferred airway approach for patients scheduled for TRR. Most commonly, a small-size endotracheal tube is positioned proximal to the stenosis; however, other alternatives such as the use of Laryngeal Mask Airways (LMA) for cervical tracheal resection and reconstruction, and catheter-based high-frequency jet ventilation have also been successfully used.[11] The anesthetic technique also varies, but it is usually performed under general anesthesia with total intravenous or balanced techniques.[12] Therefore, anesthetic management can be a concealed factor concerning postoperative outcomes of patients undergoing TRR. The main objective of this study is to describe our experience in the perioperative anesthetic management of patients with tracheal stenosis undergoing TRR.

Methods

After obtaining the approval of the Ethics and Research Committee and the Department of Anesthesiology of the Hospital Universitario San Ignacio, a retrospective analysis of the medical records was performed to identify patients over 18 years of age with tracheal stenosis undergoing TRR in the past ten years (June 1, 2009, to May 31, 2020).

Our primary objective is to describe the perioperative anesthetic management of patients with tracheal stenosis undergoing TRR. Secondary objectives are to describe the demography, preoperative condition, and postoperative complications after TRR. Finally, we did an exploratory analysis to identify possible risks factors for postoperative complications after TRR procedures; the analysis was performed between postoperative complications and the following variables: previous balloon dilation, laser resection, the severity of the stenosis, preoperative tracheostomy, duration of surgery, number of rings resected, cervical flexion, airway approach, and anesthetic induction.

For the statistical analysis, categorical variables were presented as percentages and continuous variables as mean and standard deviation. For the post-hoc exploratory analysis described above, we did a bivariate analysis with Student's *t*-test, Chi-Square test, and Fisher's exact test. Statistical significance was set for a p-value less than 0.05.

Two researchers reviewed the preanesthetic assessments records, anesthesia records, and surgical descriptions. Medical, nursing, and respiratory therapy records were also reviewed until hospital discharge and up to one year after surgery.

Exclusion criteria were patients on mechanical ventilation, surgical reintervention, carinal resection, and cases where the anesthesia record in the electronic or physical medical records was not available. This article adheres to the applicable STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Results

Forty-three patients undergoing TRR were analyzed, evidencing prolonged intubation as the primary cause (72%) for tracheal stenosis, which was found to be of variable degrees of severity. Distribution by sex and age was homogeneous with an average age of 41 years for both genders; their preoperative demographic variables are summarized in Tables 1 and 2. Due to the low number of observations, the statistical tests can be negative secondary to a low power of the study to find difference with a statistical and clinical significance. In every case, the power was below 50%.

Preoperative period

Most frequent symptoms referred before surgery were dyspnea/shortness of breath with exertion (76%), stridor (39%), and dysphonia (13%). Fourteen percent of patients presented with vocal cord paralysis and another 30% had been tracheostomized approximately 36 months (SD $\pm$34) before TRR. Post-hoc analysis did not find an association of postoperative surgical reintervention for patients who had undergone preoperative tracheostomy (p = 1.000).

For preoperative pulmonary function testing, 11% of patients had a normal forced expiratory volume in the first second, with 72% of patients presenting an obstructive ventilatory pattern. Pneumatic balloon dilation (51%) and laser resection (31%) were performed before TRR; 13% and 18% required surgical reintervention, respectively, after TRR. However, in the post-hoc analysis, we did not find an association between previous dilation or laser resection and surgical reintervention (p = 0.229 and p = 0.787).

Intraoperative period

All patients were monitored in accordance with the American Society of Anesthesiologists (ASA) standards, with 37% requiring additional intra-arterial blood pressure measurement. The induction technique was either intravenous (70%) or inhalational (18%), and 2% of patients required awake intubation; dexamethasone and lidocaine were also

Table 1 Patient characteristics.

Characteristics	Number of patients (n = 43)
Sex	
M (%)	21 (48.8)
F (%)	22 (51.1)
Age (mean in yr, ±SD)	41 (17.4)
BMI (mean in Kg.m^{-2}, ±SD)	26.3 (6.7)
ASA	
I (%)	5 (11.6)
II (%)	22 (51.2)
III (%)	14 (32.6)
IV (%)	2 (4.6)
Stridor (%)	17 (39.5)
Dyspnoea on exertion (%)	33 (76.7)
Time of tracheostomy before TRR (mean in months, ±SD)	36 (34)
Comorbidities	
Preoperative tracheostomy (%)	13 (30.2)
Arterial hypertension (%)	14 (32.6)
Coronary heart disease (%)	5 (11.6)
Asthma/COPD (%)	8 (19)
Congestive heart failure (%)	3 (7)
Active smoking (%)	8 (18.6)

BMI, Body Mass Index; ASA, American Society of Anaesthesiologists physical status; TRR, Tracheal Resection and Reconstruction; COPD, Chronic Pulmonary Disease; SD, Standard Deviation.

Table 3 Intraoperative characteristics.

Characteristics	Number of patients (n = 43)
Surgical time (mean in minutes, ±SD)	186.5 (63)
Airway	
Laryngeal mask (%)	16 (37.2)
OTI (%)	17 (39.5)
Intubation through tracheostomy (%)	10 (23.3)
Arterial line (%)	16 (37.2)
Rings resected	
2	8 (18.6%)
3	16 (37.2%)
4	12 (27.9%)
5	3 (7%)
6	3 (7%)
10	1 (2.3%)
Maintenance of anaesthesia	
TIVA (%)	11 (26.2)
Balanced (%)	32 (74.4)
Operating room extubation (%)	35 (81.4)
Intraoperative complications	
None (%)	39 (90.7)
Intraoperative cardiac arrest (%)	1 (2.3)
Tracheostomy (%)	2 (4.7)

TIVA, Total Intravenous Anaesthesia; OTI, Orotracheal Intubation.

administered in 88% and 49% of patients, respectively. Endotracheal intubation (either pre-stenosis or trans-stenosis) was performed in 39% of cases, an LMA approach was used in 37% of patients, and stoma site intubation was done in 23% of patients undergoing TRR. In a post-hoc analysis, we did not find an association between airway management and reoperation (p = 0.556). Seventy-six percent of patients received remifentanil and 77% dexmedetomidine during surgery. The intraoperative characteristics are summarized in Table 3.

Table 2 Pre-operative characteristics.

Characteristics	Number of patients (n = 43)
Distance from stenosis to vocal cords (mean in cm, ±SD)	2.99 (1.57)
Stenosis diameter (%)	
0	8 (18.6%)
1−50	5 (11.6%)
51−70	7 (16.3%)
71−99	8 (18.6%)
100	15 (34.9%)
Basal obstructive FEV1 (%)	13 (72.2)
Preoperative pneumatic dilation (%)	22 (51.2)
Preoperative laser resection (%)	17 (39.5)
Etiology of stenosis	
Idiopathic (%)	1 (2.33)
Oncological (%)	11 (25.6)
Previous intubation (%)	31 (72.1)

FEV1, Forced Expiratory Volume in 1 second.

The surgical technique consisted of resection of the tracheal segments involved with termino-terminal anastomosis, performed in an average of 186 minutes (SD ±63). In all the cases, the distal airway was also intubated on the field to achieve cross-field ventilation and allow tracheal dissection and suturing in a clear field. This was discontinued right after the suture of the posterior wall, and a small size orotracheal tube was advanced into the distal airway to complete the anterior anastomosis.

In 71% of cases, sevoflurane and intravenous infusion of remifentanil were used for maintenance of general anesthesia, titrating FiO_2 to achieve oxygen saturations of about 90% and decrease fire-risk related to oxygen. In this cohort, two patients required preventive tracheostomy at the end of the surgery, one because of previous vocal cord paralysis due to thyroid tumoral infiltration, and the other as a result of an extensive resection (10 rings). One patient had an intraoperative spontaneous tension pneumothorax, requiring cardiopulmonary resuscitation and tracheostomy at the end of the surgery.

Postoperative period

In the Intensive Care Unit (ICU), 49% of patients received an infusion of dexmedetomidine for sedation and analgesia, without reports of respiratory depression. Food and fluids were withheld for an average of 2.5 days. Average length of

Table 4 Postoperative characteristics.

Characteristics	Number of patients (n = 43)
Dexmedetomidine (%)	21 (48.8)
Head flexion (%)	30 (69.8)
Head flexion (mean in days, ±SD)	5 (2)
Fasting (mean in days, ±SD)	2.5 (2)
ICU (mean in days, ±SD)	6.9 (12.52)
Length of hospital stay (mean in days, ±SD)	12.1 (15.2)
Postoperative complications	
Ventilatory support (%)	9 (20.9)
Vocal cord paralysis (%)	11 (25.6)
Suture dehiscence (%)	3 (7)
Surgical site infection (%)	5 (11.6)
Postoperative tracheostomy (%)	6 (14)
Mortality in 30 days (%)	1 (2.3)

ICU, Intensive Care Unit.



Figure 1 Cervical flexion with chin-sternum suture and cervical stability, HUSI technique. Soucer: Authors.

ICU stay and following inpatient care were 6.9 and 12.1 days, respectively.

Major postoperative complications were vocal cord paralysis (25.6%), postoperative ventilatory support (20.9%), and need for surgical reintervention (20.9%). One patient died in the postoperative period due to massive hemoptysis and neck hematoma Table 4. depicts the postoperative characteristics of patients undergoing TRR.

Among those patients, 53.48% had Myer-Cotton grade III and IV tracheal stenosis,[13] 17.39% of them required reoperation; however, we did not find a statistical association between severity of the stenosis and reintervention (p = 0.478). Reoperation occurred among 8.3% of patients with resection of fewer than four rings and 36.8% of patients with more than four rings resected. However, no association was found between the number of rings resected and reintervention (p = 0.163). In 69.77% of cases, cervical flexion with the head in a neutral position was required (Fig. 1), but no association was found between flexion and surgical reintervention (p = 0.820). Finally, patients who did not require surgical reintervention had shorter surgical time than the patients who required surgical reintervention (95% CI -108, -18.9; p = 0.006).

Discussion

Preoperative assessment

Our principal cause of TRR was previous intubation, which is consistent with what has been described in previous literature.[2,3] Demographic findings (age, sex, and BMI) support the observations of the previous cohort reported by Wright et al., where men are equally affected compared to women and age distribution is mainly in middle-aged adults.[2]

Interestingly, a significant majority of our patients had none or optimally controlled comorbidities (ASA I and II), while other authors report the presence of chronic diseases but fail to specify their ASA physical status.[2-4,9,14] Diabetes mellitus is a well-documented risk factor for postoperative complications (OR = 3.32)[2] due to the microvascular injuries and decreases in perfusion to the tracheal anastomoses; however, we could not report associations because none of our patients had this diagnosis.

In this cohort, patients with a history of prolonged ICU length of stay had a previous tracheostomy to secure the airway and then were referred to our institution for TRR. Nonetheless, previous tracheostomy was not associated with postoperative reintervention in contrast to Wright's larger cohort in which preoperative tracheostomy was indeed linked to anastomotic complications (OR = 1.79).[2]

It is unclear if TRR was an urgent procedure in previous cohorts reported.[2-4,9,14] All our TRR were elective surgeries, whereas urgent preoperative interventions were tracheostomy, balloon dilation, or laser resection. These interventions permit maintaining a patent airway and may allow a period for medical optimization before TRR.[12]

Surgical planning in our hospital includes preoperative flexible bronchoscopy to evaluate vocal cord dysfunction, establish the distance from the vocal cords to the stenosis, and its severity. Interestingly, our patients' stenosis diameters were not associated with the need for reintervention, but more extensive studies are needed to evaluate this association and if it has a clinical significance.

Even though we performed preoperative balloon dilation and laser resection with a flexible bronchoscope through a LMA, other authors report these procedures with the use of a rigid bronchoscope.[15] This analysis did not find an association between previous dilation or laser resection with surgical reintervention; those results are following Hentze et al., who found that preoperative intervention is not a risk factor for postoperative complications.[14]

Intraoperative management

There are different anesthesia induction techniques described in the literature for severe stenosis.[12,16] Our intraoperative complications were not linked to anesthetic induction, which supports the observation of the previous cohort reported by Krecmerova et al.[9] Although our principal anesthetic induction was intravenous (79.07%) with no adverse events reported, it is unclear which technique is best suited for severe stenosis. Another study performed spirometry before and after anesthetic induction in patients undergoing TRR for laryngotracheal stenosis and found that intravenous induction with neuromuscular relaxation, LMA, and positive pressure volume ventilation have better air flows through severe extra thoracic stenosis compared to the spontaneous breathing efforts of the awake patient.[17] Therefore, we consider that further studies are necessary to evaluate if anesthetic induction has a clinical significance or if it is associated with intra- or postoperative complications.

In our study, different types of airway approaches were performed, and no relationship was found with postoperative reintervention. However, in recent years we have favored the use of LMAs, especially for subglottic stenosis where intubation may be difficult, without adverse events, which is consistent with Krecmerova's cohort. The authors suggest that LMA can be an option for airway management because it allows a patent airway and a fiberoptic view through the device, without an increased risk of serious complications (i.e., pulmonary aspiration, early postoperative bleeding, or suture dehiscence).[9] The potential advantages of using LMAs are that tracheal intubation is not required,[18] there may be better exposure and visualization of the surgical field, decrease in the operating time,[19] and LMA can be used with high-frequency jet ventilation.[6] Besides, possible risks associated with tracheal intubation in tracheal stenosis are avoided: hypoperfusion of the mucosa at the site of the cuff, and injury by ischemia and reperfusion.[20]

We do not have experience with other anesthetic approaches previously reported such as: regional anesthesia (cervical epidural, nerve blocks like bilateral superficial cervical plexus, thoracic paravertebral, vagal nerve, or phrenic nerve block), sedation with spontaneous ventilation, or extracorporeal support, that have an overall failure rate of 1.8% as reported in the literature.[7,11] There might be some advantages like feasible and faster anastomosis and high level of patient satisfaction with no difference in postoperative complications; however, the benefits of non-intubated airway surgery over intubated surgery remain unclear.[19,21,22]

All our patients had cross-field ventilation, which is consistent with what has been previously described in 93.2% of cases.[11] Cuff rupture is a possible complication of this ventilation that can be present in up to 20% of cases;[11] however, we did not find any complications related to it.

Despite the existing controversy about the use of steroids and the potential risk of suture dehiscence,[23] 88% of our patients received dexamethasone intraoperatively (4−8 mg) for prevention of postoperative nausea and vomiting and post-extubation laryngeal edema.[23,24] Among the three cases who had suture dehiscence, only one patient received steroids. This supports the observations of the previous cohort reported by Wright et al where the use of steroids was not a risk factor for anastomotic complications.[2]

The average time of surgery was 186 minutes; we found no difference in duration over the years. There was a statically significant difference in the time of surgery among those patients who required reintervention and those who did not; moreover, in thoracic surgery, prolonged operative time (≥ 240 min) is associated with an increased risk of complications (OR = 2.51).[25] In our cohort, the patients who required prolonged surgeries had an average of more than four tracheal rings resected. However, although we did not find an association between the number of rings resected and postoperative surgical reintervention, resections ≥ 4 cm have been described as a risk factor of postoperative complications (OR = 2.01).[2]

Postoperative outcomes

In this cohort, dexmedetomidine was our first line of treatment in the ICU for analgesia and conscious sedation without having any respiratory depression events. These findings follow the observation described by Fiorelli et al., where dexmedetomidine provided safe and effective sedation after TRR. It is paramount to bear in mind that dexmedetomidine significantly decreases mean arterial pressure and heart rate.[26] However, further studies are needed to compare the best treatment strategy for analgesia and sedation in the postoperative care of these patients.

Most patients had cervical flexion with chin to chest sutures to decrease mobility (neck extension) and secondary tension in the tracheal anastomosis.[27] A posterior splint for maintaining the neutral position was described by Mueller DK et al. as an alternative method to decrease movement of the cervicothoracic area while reducing lateral movement. They use the splint for an average of one week, similar to the flexion times used in our patients.[28] In our case, in addition to fixation sutures, pneumatic bags are used to prevent lateral movement (Fig. 1).

Interestingly, many of our patients were extubated in the operating room as other authors reported without presenting immediate adverse events.[9,14] These findings contrast with other authors' cohorts, where an uncuffed nasal endotracheal tube is left in place during the first postoperative day and then removed after bronchoscopic review of the anastomosis.[26] Early extubation avoids positive pressure or endotracheal tube cuff trauma to the new anastomosis, factors that may contribute to anastomotic complications. If extubation cannot be performed, keeping spontaneous ventilation with a small-caliber tube without insufflating the cuff is recommended, with another extubation attempt 24 hours later, under direct supervision. If this attempt fails, it is suggested to perform a tracheostomy 2-cm distal from the anastomosis.[12] However, it remains unclear whether early extubation has, in fact, any benefits over late extubation.

TRR has a success rate greater than 95% and a mortality of 1−2%, similar to what was found in our study.[2-4,9,29] The patient who died in our institution had an anastomotic complication. Despite a low mortality rate, this surgery has a high frequency of complications (15−39%), which could possibly be related to anastomotic-related issues.[2,29,30] Non-anastomotic complications are infection, bleeding, vocal

cord dysfunction, edema, pneumonia, arrhythmias, myocardial infarction, and pulmonary embolism. Anastomotic complications are dehiscence, granulomas, and restenosis, with an incidence of 9% and a mortality of 7.4%.[2] However, we did not find an association between our anesthetic management and postoperative complications. Therefore, there is uncertainty about the impact of anesthetic interventions on anastomotic or non-anastomotic complications.

Our study has several limitations. First, although we describe our ten years of experience, a small sample size could reflect a lower experience of our service in this type of surgery than a more specialized center. Second, it is a retrospective analysis and might have an underlying reporting bias. Finally, perioperative anesthetic management has changed over the years, reflecting heterogeneity in patient management; thus, it may explain why we did not find the associations in the analysis described above.

In conclusion, perioperative management of TRR at our hospital has a low mortality and high morbidity rate. We did not find an association between perioperative anesthetic interventions and postoperative complications. Moreover, to reflect possible evidence gaps, this article highlights several differences in contemporary practice. Therefore, we acknowledge that additional studies are needed to evaluate if anesthetic interventions (airway management, anesthetic induction, early extubation, or postoperative sedoanalgesia) may be associated with better outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Anesthesia technique and postpartum hemorrhage: a prospective cohort study



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KEYWORDS
Obstetrical anesthesia;
Postpartum hemorrhage;
Obstetric delivery

Abstract
Background and objective: During the past few years, an increased number of postpartum hemorrhages have been noticed, even in high-income countries. It has been suggested that this escalation could be associated with increased obstetric interventions. Among such interventions, anesthesia is one of the most prevalent. The present study aimed to investigate the influence of peripartum anesthesia on total blood loss during the 24 hours after delivery.
Methods: We performed a complementary analysis from a prospective cohort study that evaluated postpartum bleeding within 24 hours after birth. The study was performed between February 1st, 2015 and March 31st, 2016 at the Women's Hospital at the Universidade Estadual de Campinas, Brazil. Postpartum bleeding was measured using a calibrated drape and summing the blood contained in the compresses and pads used for 24 hours. We calculated means, percentages, and standard deviation and performed Mann-Whitney analysis for the relation of anesthesia with Postpartum Hemorrhage (PPH) and logistic regression for drugs used in the anesthesia with PPH, using SAS 9.4 software.
Results: We included 270 women in the study; of these, 168 received anesthesia for delivery and almost 50% of them had spinal and epidural anesthesia. The mean blood loss within 24 hours after delivery did not show differences between those who did and those who did not receive obstetrical anesthesia (579.0 ± 361.6 vs. 556.6 ± 360.6; $p = 0.57$). Logistic regression showed that anesthesia, the type of anesthesia, and the drug used did not influence the PPH above 500 mL and above 1000 mL within 2 hours ($p > 0.05$).
Conclusion: Anesthesia did not influence postpartum bleeding after vaginal delivery.
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Introduction

Postpartum Hemorrhage (PPH) is the leading cause of maternal mortality worldwide, mainly in low/middle-income countries.[1] In the last few years, an increased number of cases of PPH due to atony have been noticed, even in high-income countries, together with the need for procedures related to the treatment for PPH, such as surgery, hysterectomy, blood transfusion, arterial ligation, and embolization.[2,3]

It has been suggested that this escalation could be associated with the increased number of obstetric interventions.[4] Among such interventions during childbirth, anesthesia is one of the most prevalent, especially in middle- and high-income settings. The literature contains some controversial data about the safety of anesthetic procedures in influencing the incidence of PPH.[4–6] While some studies show that epidural anesthesia does not influence postpartum bleeding,[4,6] others show a protective effect,[3] or even a worsening of the incidence of PPH.[5,7] Nevertheless, the majority of studies involving PPH have used a visual estimation of blood loss for its diagnosis, which has been discussed.[8–10]

The present study aimed to investigate whether peripartum anesthesia increased the incidence of PPH during the 24 hours after delivery using an objective method of measurement of total blood loss.

Methods

We performed a complementary analysis from a prospective cohort study that evaluated postpartum bleeding objectively during the 24 hours after childbirth. The results from the original aim of the study were published on Borovac-Pinheiro A, Cecatti JG, de Carvalho Pacagnella R. Ability of shock index and heart rate to predict the percentage of body blood volume lost after vaginal delivery as an indicator of severity: results from a prospective cohort study. J Glob Health. 2019;9(2):020432. doi:10.7189/jogh.09.020432.

This study was performed between February 1st, 2015 and March 31st, 2016 at the Women's Hospital – a tertiary hospital at the Universidade Estadual de Campinas (Unicamp), São Paulo, Brazil. We invited all women in labor at 34 weeks gestation or above, in a singleton pregnancy, to participate. Those who accepted read and signed an informed consent form. We excluded women that had C-section, or who had one of the following conditions: hypertension, hypo- or hyperthyroidism without treatment, any cardiac disease, infections with fever or sepsis, or history of coagulopathy.

Immediately after delivery, we put a calibrated drape (BRASSS_V drape, Maternova®) under the women's buttocks to measure objectively the postpartum bleeding while the women were in the birthing position and, in addition, we collected all compresses used during the procedure (for example, for suture of lacerations). Over 24 hours, all compresses or sanitary pads used by the women were collected, stored in plastic bags, and weighed to measure blood loss by subtracting the dry weight of the materials. The blood density was considered 1 $g.dL^{-1}$.[9] All women received prophylactically 10 IU of oxytocin intravenous (IV) after birth as an institutional protocol. Health providers were able to see the blood collected in the drapes and only received information about the total blood loss if requested. The primary outcome was to evaluate whether changes in vital signs were correlated with PPH (already published). One of the secondary outcomes was to evaluate whether Obstetrical Anesthesia (OA) could influence postpartum bleeding.

The sample size was estimated by considering the need for 28 women with blood loss over 1000 mL to demonstrate performance of the vital signs by the area under the ROC curve (AUC) of 0.800 with a 95% Confidence Interval.[11]

We calculated means, percentages, and standard deviation. We performed a Shapiro-Wilk test to evaluate the distribution of blood loss after delivery, Mann-Whitney analysis for the relationship of anesthesia with PPH, and logistic regression for the drugs used and type of anesthesia with PPH above 500 mL and above 1000 mL, using SAS 9.4 software. We defined a significance level of 5% for all analyses.

The Institutional Review Board approved the study (CAEE: 26787114.3.0000.5404). This research was funded by Faepex–Unicamp but they played no role in the study design or interpretation of the results.

Table 1 Sociodemographic and obstetric characteristics of the women.

Characteristics	n (%)	Mean ± SD
Age	270	24.67 ± 6.19
Parity[a]	264	0.81 ± 1.14
Gestational age	270	38.93 ± 1.47
BMI[b]	244	28.85 ± 4.61
Ethnicity[c]		
White	178 (65.92%)	
Non-white	85 (31.48%)	
Onset of labor		
Spontaneous	203 (75.19%)	
Induced	67 (24.81%)	
Anesthesia		
None	102 (37.78%)	
Spinal	13 (4.81%)	
Epidural	22 (8.15%)	
Spinal + Epidural	133 (49.26%)	
Mode of Delivery		
Vaginal	247 (91.5%)	
Forceps	23 (8.5%)	
Episiotomy[d]		
No	164 (60.74%)	
Yes	96 (35.55%)	
PPH and severe PPH in 2 hours		
≥ 500 mL	84 (31.11%)	
≥ 1000 mL	22 (8.14%)	
PPH and severe PPH in 24 hours		
≥ 500 mL	120 (44.44%)	
≥ 1000 mL	34 (12.59%)	

Missing: [a]6, [b]26, [b]7, [d]10.

Results

We included 270 women. One hundred and sixty-eight (67%) women received anesthesia for delivery, and 133 (49%) received spinal plus epidural anesthesia. Table 1 illustrates

Table 2 Postpartum bleeding comparison between who did and those who did not receive anesthesia for delivery.

Blood loss	Anesthesia	n	Mean ± SD (mL)	*p*-value[a]
Within 2 h	Yes	168	434.7 ± 339.4	0.63
	No	102	415.9 ± 330.9	
Within 24 h	Yes	165	579.0 ± 361.6	0.57
	No	99	556.6 ± 360.6	

[a] Mann-Whitney test.

the sociodemographic and obstetric characteristics of the women.

The mean blood losses at 2 and 24 hours were 427.49 ± 335.57 mL and 570.66 ± 360.04 mL, respectively. Blood loss after delivery was not normally distributed – *p*-value < 0.0001. The major quantity of the blood loss occurred within 2 hours after birth, a period when 91% of women bled 90% of their total blood loss measured over 24 hours. Therefore, data analyses were performed within two periods of postpartum bleeding: 2 and 24 hours. No women had ICU admission or received surgical procedures. Only four women had a blood transfusion.

Table 2 illustrates data comparing mean postpartum bleeding between those who did and those who did not receive anesthesia for delivery. There were no statistically significant differences between the two groups within 2 or 24 hours after birth.

The drugs most often used were bupivacaine as a local anesthetic and sufentanil as an opioid. Among women who underwent spinal anesthesia, bupivacaine and sufentanil were used by 136 (87%) and 133 (86%) women, respectively. Among those who underwent epidural anesthesia, bupivacaine and fentanyl were used by 58 (40%) and 16 (6%) women, respectively.

We performed a binary logistic regression to identify whether anesthesia and the drug combination could influence postpartum bleeding above 500 mL and above 1000 mL within 2 hours after birth (Table 3). None of the factors studied influenced PPH.

Discussion

Our study aimed to identify whether OA could influence postpartum bleeding measured objectively. We found that OA did not influence the amount of blood loss after delivery.

Although the incidence of PPH has increased recently, several factors that could be related to PPH are the main factors associated with obstetric procedures, such as instrumental delivery, induction of labor, C-section, retained placenta and anesthesia.[3,4,12] Nevertheless, the role of OA in the incidence of PPH is not well established. Some studies have found results similar to ours. Rossen et al. found no relationship of severe PPH and OA in a retrospective study involving 10 years and 41,365 deliveries.[4] Mousa et al., in a study of more than 20,000 deliveries, found no influence of OA on PPH.[13] Biguzi, in a study involving more than 6,000 deliveries, also found no influence of OA on PPH.[6]

On the other hand, a population-based cohort study from Canada of 2,193,425 deliveries found that OA could be protective for blood transfusion due to PPH.[3] These findings are similar to our results; nevertheless, all studies included C-sections, while our study included only vaginal deliveries.

The negative impact of OA in increasing the incidence of PPH is related to general anesthesia.[14,15] In our study, no women received general anesthesia and all women had vaginal delivery.

We also found a higher incidence of PPH according to the WHO definition.[16] The differences found by other studies could be explained by the different methods and periods of measuring blood loss after delivery.[17–20] Some studies have demonstrated that visual estimation tends to underestimate total blood loss and the best way to access the total blood loss after birth is to use a calibrated drape.[10,17,21,22] In our study, the rigorous method of capturing all blood loss may have played a role in the overall prevalence of PPH.

To the best of our knowledge, this is the first study that evaluates the influence of OA on postpartum bleeding measured objectively. Nevertheless, this is a complementary analysis of a prospective cohort study for which the first goal was to evaluate the role of clinical signs in the diagnosis of PPH and not to evaluate OA. Therefore, the limitations of the study were that the type of anesthesia, its duration, and the drugs used were not controlled. Moreover, the indication of OA is not clear. Some differences may be found when the indication was treatment of a dystocia and pain relief only. Further studies evaluating PPH and OA should include comparisons of the types of anesthesia and drugs used, and doses of those drugs.

Table 3 Univariate logistic regression for factors related to anesthesia and postpartum bleeding above 500 mL and above 1000 mL within 2 hours.

Blood loss		OR (95% CI)[a]	*p*-value	n
≥ 500 mL within 2 h	Anesthesia Yes vs. No	0.81 (0.43–1.56)	0.54	236
	Epidural vs. Spinal + Epidural	2.71 (0.54–13.48)	0.22	137
	Spinal vs. Spinal + Epidural	0.98 (0.37–2.58)	0.96	137
	Bup + FNT vs. Bup + SFNT	0.24 (0.03–1.82)	0.17	137
≥ 1000 mL within 2 h	Anesthesia Yes vs. No	0.56 (0.18–1.67)	0.29	236
	Epidural vs. Spinal + Epidural	1.01 (0.04–24.70)	0.99	137
	Spinal vs. Spinal + Epidural	1.25 (0.22–7.04)	0.80	137
	Bup + FNT vs. Bup + SFNT	3.16 (0.15–67.84)	0.46	137

[a] Adjusted for BMI, morbidities, forceps, and episiotomy (BUP, Bupivacaine; FNT, Fentanyl; SFNT, Sufentanil).

Conclusion

In conclusion, from these analyses of a prospective cohort study evaluating blood loss measured objectively during 24 hours after vaginal delivery, obstetric anesthesia did not influence postpartum bleeding.

Authors' contributions

Anderson Borovac-Pinheiro: Helped in conceiving and designing the study, acquiring data, interpreting the data analysis, and drafting the manuscript.

Maria Jose Nascimento Brandão: Helped in acquiring data and drafting the manuscript.

Juliana Luz Passos Argenton: Involved in data analysis and interpretation and revised the manuscript.

Thales Daniel Alves Barbosa: Helped in acquiring data and its interpretation.

Rodolfo Carvalho Pacagnella: Helped in conceiving and designing the study, interpreting the data analysis, and drafting the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Comparison of the suprainguinal fascia iliaca compartment block with continuous epidural analgesia in patients undergoing hip surgeries: a retrospective study

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KEYWORDS
Hip arthroplasty;
Nerve blocks;
Epidural analgesia

Abstract
Background and objective: Pain control is one of the major concerns after major hip surgeries. Suprainguinal fascia iliaca compartment block (S-FICB) is an alternative analgesic technique that can be considered as an effective and less invasive method than epidural analgesia (EA). In this retrospective study, we compared postoperative analgesic efficacy of single shot ultrasound guided S-FICB and EA after major hip surgery.
Methods: We retrospectively examined 150 patients who underwent major hip surgeries and who received S-FICB or EA. Seventy-two patients submitted to EA and 78 patients who received S-FICB were included and their medical records retrospectively reviewed. Morphine consumptions, VAS scores, and side effects were recorded. Patients under antiplatelet or anticoagulant theraphy were also registered. Morphine consumption and VAS scores were the primary endpoints, succes rate and complications were the secondary endpoints of our study. *P*-values less than 0.05 were considered statistically significant.
Results: Morphine consumption was lower at the emergence in the EA group but there was no statistically significant difference between the two groups according to total opioid consumption (0 [0-0] vs 0 [0-0]; $p = 0.52$). There was no difference between VAS scores in the first 18 hours. Hypotension was significantly higher in the EA group (9 vs 21; $p = 0.04$).
Conclusion: In conclusion, S-FICB can provide comparable analgesia with EA in the early postoperative period after hip surgery but VAS scores were found lower in the EA group than S-FICB group after 18th hour. Hypotension has occured more frequently in patients receiving EA.
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Introduction

Pain control is one of the major concerns after hip surgeries. Patients often experience moderate to severe pain after these procedures, and pain control has a significant impact on functional recovery after joint arthroplasty.[1,2] Effective pain control is reported to increase patient satisfaction.[3] Poor pain control is associated with the prolonged rehabilitation time.[3] Delayed recovery increases the risk of postoperative complications and postoperative pain emerges as a serious problem after the hip surgeries.[3]

Peripheral nerve blocks have been increasingly used in recent years to improve pain control and reduce complications.[4,5] Both single and continuous nerve blocks can be used as part of a multimodal analgesia protocol. Multimodal approaches include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, infiltration analgesia, and neuraxial techniques in combination with peripheral nerve blocks and are recommended for better pain control without the serious side effects of opioid and NSAIDs following surgery.[4] Epidural analgesia (EA) is suitable for major hip surgeries but is subject to technical difficulties and has contraindications such as anticoagulation.[6] This technique is also associated with many adverse effects.

Fascia iliaca compartment block (FICB) is an alternative to neuraxial blocks and provides adequate unilateral analgesia with fewer adverse effects than EA.[2] Hebbard et al. described and Desmet et al. modified a new approach, suprainguinal fascia iliaca compartment block (S-FICB), which enables more effective cranial spread of the local anesthetics than conventional FICB.[7,8] FICB has been associated with reductions in both opiate consumption and pain scores in many studies, but a recent systematic review has reported that further research is needed to investigate the technique and administered volume for FICB.[3] To date, there has been few studies reported focusing on the effectiveness of the S-FCIB after hip surgeries.[3]

In this retrospective cohort study, we compared the effectiveness of a single injection ultrasound-guided S-FICB with continuous lumbar EA in patients undergoing hip surgery. We hypothesized that the US-guided S-FICB would provide postoperative analgesia comparable to the EA. The primary outcomes were opioid consumption, static, and dynamic visual analog scale (VAS) pain scores. Secondary outcomes included success rate of two techniques and occurrence of side effects.

Methods

Study design

This retrospective cohort study included 150 patients and was approved by the local ethics committee (Mersin University Clinical Research Ethics Committee, Nº: 2018-81). Data were collected from the medical records of patients who underwent hip surgery between August 1, 2017 and January 30, 2018. Inclusion criteria were patients undergoing primary hip arthroplasty under general anesthesia either with EA (n = 78) or with S-FICB (n = 72) performed by the same anesthesiologist (MA) for the postoperative analgesia. Patients receiving spinal or combined spinal-epidural anesthesia, using chronic analgesic drugs, having neurological deficits in the lower extremities and illnesses that interfered with communication skills such as mechanical ventilation requirement and patients having insufficient data were excluded from the study. Patients with unsuccessful blocks were also excluded from the final evaluation. A flow chart demonstrating patient selection is presented in Figure 1. Although we have a standard protocol for postoperative analgesia, there was no standard preoperative analgesia protocol in our institution; meperidine or morphine treatment was used with acetaminophen intravenously in the hip fractured patients. Patients who were not treated according to this standard analgesia protocol (see below) were also excluded. Anesthesia and postoperative analgesia protocols for S-FICB and EA patients were as follows:

Anesthesia protocol

No premedication was applied to the patients before operation. All patients were monitored with electrocardiogram (ECG), invasive blood pressure (IBP), pulse oximetry (SaO2), and end-tidal carbon dioxide ($EtCO_2$) in the operation room. General anesthesia was induced with propofol 0.5–2.0 $mg.kg^{-1}$ or thiopental 3–5 $mg.kg^{-1}$. Remifentanil 0.2–0.5 $mcg.kg^{-1}$ and rocuronium 0.5–0.6 $mg.kg^{-1}$ were administered to facilitate tracheal intubation. Anesthesia was maintained with O_2/N_2O 50/50 fresh gas, and 0.5–2% sevoflurane. Neuromuscular blockade was antagonized with 0.05 $mg.kg^{-1}$ neostigmine and 0,015 $mg.kg^{-1}$ atropine before extubation.

Postoperative analgesia protocol for S-FICB and EA after hip surgeries

FICB and epidural catheter techniques which applied for postoperative analgesia were explained to the patients before surgery. The analgesic technique was preferred by the patients if there was no any contraindication. Epidural catheter was the first choice in suitable patients who were undecided about the analgesic method. S-FICB was the first choice for patients who could not inserted an epidural catheter due to the use of anticoagulants or technical difficulties. All patients received intravenous (IV) acetaminophen 20 $mg.kg^{-1}$ during the operation. Morphine or meperidine was administered as needed during extubation and opioid doses were recorded. Our pain management team has visited patients at 6-h intervals. The target VAS-R score was ≤ 3. Static VAS (VAS-R) was evaluated during resting and dynamic VAS (VAS-M) was evaluated with active leg lifting to 15 degrees. The orthopedic ward nurse called our team if the patients complained of pain between scheduled visits.

EA: The epidural catheter was placed using the classical landmark technique during surgery after intubation and injection of 10 mL of 0.25% bupivacaine. Imaging techniques (fluoroscopy or US-guidance) were not used routinely. If VAS score was > 3, additional local anesthetic was administered and switched to infusion method (5–10 $mL.h^{-1}$) after catheter location was verified. Patient-controlled analgesia (PCA) was initiated if there was a problem with the catheter site and set to 0.5 mg morphine IV on demand with 15-minute lockout interval. Additional morphine or acetaminophen was administered as needed during the entire postoperative

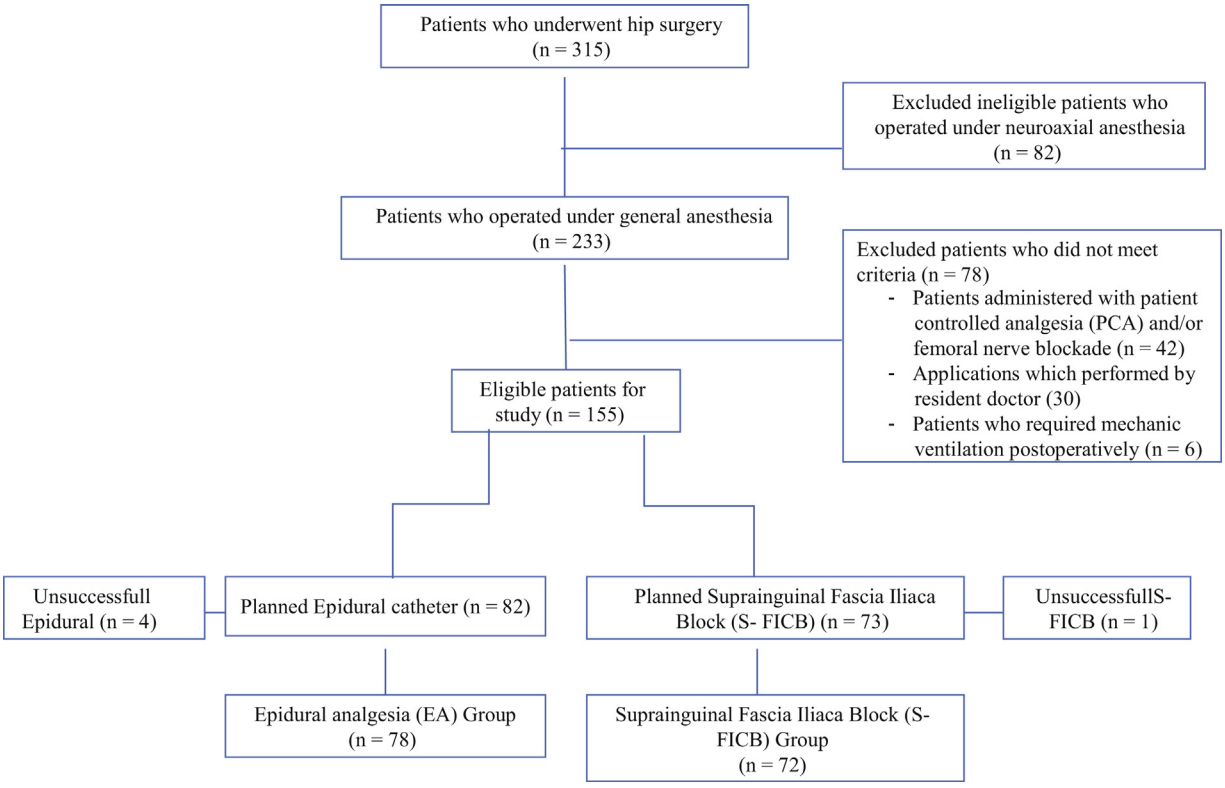

Figure 1 Flow diagram of the patient selection for the comparison between the two groups.

follow-up period. Patients were mobilized on the first postoperative day. If the patients complained of weakness, the epidural washout method with saline was used and the infusion rate was decreased.

S-FICB: Single-shot US guided S-FICB was administered after intubation and before surgery was initiated. An injection 0.40–0.60 mL.kg^{-1} of 0.25% bupivacaine was given using the US-guided longitudinal suprainguinal approach described by Desmet et al.[8] Additional volume was administered if sufficient local anesthetic distribution was not observed. If VAS score was > 3 after extubation, it was considered a failed block. Acetaminophen was administered at 20 mg.kg^{-1} every 6 hours, except for patients without pain during the first postoperative 48 hours. In addition, if VAS score was > 3 at any time postoperatively, PCA was set to 0.5 mg morphine on demand with 15-minute lockout interval or equivalent dose of meperidine.

All patients were monitorized at least 30 minutes in the PACU after surgery. Therefore, first assessment was carried out and pain measurement, morphine consumption, and side effects at ''zero hour'' were also recorded in the PACU. Patients who had pain were given 0.5 mg intravenous morphine with the target **VAS**: Three in this period. Pain levels and morphin consumptions were evaluated by an anesthetist (SA) in the postoperative pain management team at the intensive care unit (ICU) and ward. Standard VAS (0–10 cm) was used for pain assessment. VAS scores were recorded while at rest (VAS-R) and during active movement (VAS-M) at postoperative 6th, 12th, 24th, and 48th hours. Daily morphine consumption at postoperative 6th, 12th, 24th, and 48th hours were also recorded. Meperidine was converted to morphine equivalent (7.5 mg IV meperidine = 1 mg IV morphine). Vital signs were tracked by using patient follow chart which recorded hourly by nurse in the ICU or ward. Hypotension (systolic blood pressure < 90), hypoxia (SpO_2 < 90%), and nausea-vomiting complaints which required any treatment were reported. Walking ability was evaluated to test quadriceps weakness on the second day, in patients with complaints associated with walking were evaluated with manual muscle test. Postoperative length of hospital stay and adverse events attributed to opioid use were compared. In addition, medical history of antiplatelet or anticoagulant drug use and the number of patients for whom the analgesic intervention failed were also recorded.

Statistical analysis

Sample size was calculated with using data for EA in a previous study and was found 67 patients per group needed to detect 30% change of morphine consumption between EA and S-FICB patients with a power of 80% and a risk of 0.05 for type 1 error.[9] Shapiro-Wilk test was used for normality and comparisons were performed using the Mann-Whitney U test between the two groups because of non-normally distributed data. Fisher's exact test was used to compare for categorical variables. Continous variables were expressed as median and interquartiles, categorical variables were expressed as frequency and percentage. Statistical analysis was performed with www.e-picos.com New York Software and Medcalc Statistical Package program. A *p*-value < 0.05 was determined statistically significant.

Table 1 Patients demographics and operation characteristics.

	S-FICB (n = 72)	EA (n = 78)	*p*
Age (years)	70.50 [65.00–77.75]	69.00 [65.00–78.25]	0.83
Gender			
Male	32 (44%)	42 (53%)	
Female	40 (56%)	36 (47%)	0.25
Comorbid diseases			
Hypertension	31 (43.0%)	31 (39.7%)	
Diabetes Mellitus	26 (36.1%)	22 (28.2%)	
Coronary artery disease	16 (22.2%)	12 (15.3%)	
Cerebrovascular disease	5 (6.9%)	4 (5.1%)	0.71
Renal failure	6 (8.3%)	5 (6.4%)	
Electrolyte imbalance	1 (1.3%)	1 (1.2%)	
COPD	2 (2.6%)	5 (6.4%)	
Hypo/hyperthyroidism	2 (2.6%)	3 (3.8%)	
ASA			
I	1 (1.3%)	6 (7.6%)	
II	29 (40.2%)	34 (43.5%)	0.26
III	35 (48.6%)	32 (41.0%)	
IV	7 (9.7%)	6 (7.6%)	
Preoperative analgesic treatment			
No need any treatment	31 (43%)	40 (51.2%)	
Acetaminophen	11 (15.2%)	7 (8.9%)	
Meperidine infusion 10 $mg.h^{-1}$	20 (27.7%)	21 (26.9%)	0.72
Morphine infusion 1 $mg.h^{-1}$	10 (13.8%)	10 (12.8%)	
1-year mortality	8/72 (11.1%)	11/78 (14.1%)	0.63
Waiting time for urgent surgery (days)	0 0–1	0 0–1	0.38
Surgery duration (h)	120 [106–130]	120 [110–135]	0.58
Length of stay (days)	3 [3–4]	3 [3–4]	0.94
Acetaminophen dose (vial)	3.00 [2.00–3.00]	0.00 [0.00–0.25]	0.00 *
Used erythrocyte pack	2 [2–3]	2 [2–3]	0.73
Postoperative hematocrit level ($mg.dL^{-1}$)	9.50 [9.12–9.90]	9.40 [9.20–9.60]	0.36
Surgery			
Total hip replacement	21 (29.2%)	29 (37.2%)	
Partial hip replacement	30 (41.6%)	23 (29.5%)	0.28
Internal nail	12 (16.7%)	19 (24.3%)	
Plate-screw	9 (12.5%)	7 (9.0%)	

S-FICB, suprainguinal fascia iliaca compartment block; EA, epidural analgesia; ASA, American Society of Anesthesiologists; COPD, Chronic Obstructive Pulmonary Disease.
Values were presented as median [Q1–Q3] or %.

Results

We retrospectively analyzed data from a total of 150 patients. For comparison, the patients were divided into S-FICB group (n = 72) and EA group (n = 78) according to the postoperative analgesia they received. The patients' demographic and surgical characteristics are summarized in Table 1. There were no statistically significant differences between the two groups with respect to age, gender, comorbid dissease, American Society of Anesthesiologists (ASA) physical status, wait time for surgery, transfused red blood cell, postoperative hemoglobin level or operative time ($p > 0.05$ for all) (Table 1). The use of acetaminophen was found higher in the S-FICB group than the EA (3.00 [2.00–3.00] vs 0.00 [0.00–0.25] respectively, $p < 0.05$).

Opioid consumption was lower at emergence in the EA group (0 [0–1] vs. 0 [0–0] mg respectively, $p < 0.05$). There was no statistically significant difference between two groups according to total opioid consumption (0 [0–0] vs. 0 [0–0] respectively, $p > 0.05$) (Table 2). Static and dynamic VAS scores were found similar in the first 18 hours, but VAS scores were significantly lower at 24th and 48th hours in the EA group ($p < 0.05$) (Tables 3 and 4).

While US-guided S-FICB was successfully performed in 72 (98%) patients, the number of successful interventions was found 78 (95%) in the EA group. In terms of the number of patients treated without opioid, more patients have received opioid therapy (51 vs. 72 patients respectively, $p < 0.01$). The incidence of hypotension was significantly higher in the EA group (9 vs. 21 respectively, $p < 0.05$). The incidence of nausea-vomiting, hypoxia, and muscle weakness were found similar between two groups (Table 5). S-FICB was successfully performed without any complication in six patients who received antiplatelet or anticoagulant drugs.

Table 2 Comparison of morphine consumption between the two groups.

	Group S-FICB		Group EA		
Time	Med [Q1-Q3]	Min-max	Med [Q1-Q3]	Min-max	*p*
0th h	0[0-1]	0-2	0[0-0]	0-3	$p < 0.05$*
6th h	0 [0-0]	0-3	0 [0-0]	0-6	$p > 0.05$
12th h	0 [0-0]	0-4	0 [0-0]	0-4	$p > 0.05$
18th h	0 [0-0]	0-3	0 [0-0]	0-3	$p > 0.05$
24th h	0 [0-0]	0-3	0 [0-0]	0-3	$p > 0.05$
48th h	0 [0-0]	0-2	0 [0-0]	0-3	$p > 0.05$
Total	0 [0-0]	0-12	0 [0-0]	0-16	$p > 0.05$

S-FICB, suprainguinal fascia iliaca compartment block; EA, epidural analgesia.
* Statistically significant value.

Table 3 Comparison of Static VAS scores between the two groups.

	Group S-FICB		Group EA		
Time	Med [Q1-Q3]	Min-max	Med [Q1-Q3]	Min-max	*p*
0th h	1 [0-2]	0-3	0 [0-2]	0-4	> 0.05
6th h	1 [0-2]	0-3	0 [0-2]	0-4	> 0.05
12th h	1 [0-2]	0-4	1 [0-2]	0-3	> 0.05
18th h	1 [0-2]	0-3	0 [0-2]	0-3	> 0.05
24th h	0 [0-2]	0-3	0 [0-1]	0-3	< 0.05*
48th h	0 [0-2]	0-3	0 [0-0]	0-2	< 0.05*

S-FICB, suprainguinal fascia iliaca compartment block; EA, epidural analgesia.
* Statistically significant value.

Table 4 Comparison of Dynamic VAS scores between the two groups.

	Group S-FICB		Group EA		
Time	Med [Q1-Q3]	Min-Max	Med [Q1-Q3]	Min-Max	*p*
0th h	3 [3-4]	0-6	3 [3-4]	0-6	> 0.05
6th h	3 [2-4]	0-6	3 [2-4]	0-6	> 0.05
12th h	3 [3-4]	0-7	3 [2-4]	0-5	> 0.05
18th h	3 [2-4]	0-5	3 [2-4]	0-5	> 0.05
24th h	3 [2-4]	0-5	2 [2-3]	0-5	< 0.05*
48th h	3 [2-4]	0-5	2 [0-3]	0-4	< 0.05*

S-FICB, suprainguinal fascia iliaca compartment block; EA, epidural analgesia.
* Statistically significant value.

Table 5 Comparison to success rate and side effects in the patient groups.

	S-FICB (n = 72)	EA (n = 78)	*p*
Successful block	72/73 (98%)	78/82 (95%)	0.21
Accidental catheter removal	N/A	2	–
No. of patients without morphine administered	51/72 (70%)	72/82 (92%)	< 0.01*
Nausea–vomiting	6 (8%)	11 (14%)	0.25
Hypotension	9	21	0.04*
Hypoxia	4	6	0.60
Muscle weakness	0	0	1

S-FICB, suprainguinal fascia iliaca compartment block; EA, epidural analgesia.
* Statistically significant value.

Discussion

We observed from our study that US-guided S-FICB provided analgesia equal to the EA technique after hip surgeries in the early postoperative period, but that the EA provided significantly better analgesia after 18 hours. Morphine consumption was statistically equal at all measured time points except emergence, as was total morphine consumption. Hypotension was observed more frequent in patients receiving EA. S-FICB was successfully administered with no complications in patients under antiplatelet or anticoagulant therapy.

A meta-analysis suggested that the analgesic efficacy of single-shot FICB lasts up to 24 hours.[9] Temelkovska et al. reported that the analgesic effect of single-shot FICB begins to decrease after 12 hours.[10] There are few studies comparing S-FICB with other analgesia methods in the literature. Our results indicated that single-shot S-FICB can provide adequate early postoperative analgesia after hip surgery. However, we found that it has limited duration of action compared to the EA technique, which can provide long-term pain control with infusion or repeated doses. Although morphine administered before extubation may have resulted in higher morphine consumption in the S-FICB group during emergence, total morphine consumption was similar between the two groups in our study. Regular acetaminophen reduces VAS pain score, opioid consumption, and opioid-related adverse effects.[11] Average acetaminophen use was found to be higher in the S-FICB group than EA. The administration of acetaminophen may have contributed to the effectiveness of the analgesia in our S-FICB group.

Conventional FICB may offer better analgesia and reduce morphine consumption compared to a control group after hip surgeries.[12] There are only two conflicting studies in the literature comparing conventional FICB and EA. Rashwan et al. found that patients in the EA group had lower pain score and tramadol consumption than patients who received continuous FICB after femur neck fracture surgery.[13] However, Nooh et al. reported that both techniques had similar analgesic effect after hip and knee surgeries.[14] Conventional FICB was administered using an unguided technique in both studies. Although FICB can be performed blind, US-guidance increases block success by ensuring injection in the correct space and allows monitoring for adequate distribution, resulting in better analgesia than the blind technique.[15] In addition, the recommended volume is 30–40 mL for FICB, but 30 mL of local anesthetic was used in these studies. In the present study, the mean volume was 30.7 mL, but local anesthetic was administered with US-guidance and no patient received a volume less than 0.4 mL.kg^{-1}. Furthermore, we performed FICB via proximal suprainguinal approach, which provides better analgesia than the conventional method.[16]

There is no gold standard anesthetic method for hip surgery. In terms of mortality, the advantage of neuroaxial techniques over general anesthesia has not been proven.[17] If the patient prefers, neuroaxial anesthesia is the first choice in our clinic. However, general anesthesia is preferred in anticoagulant/antiplatelet drug use, serious heart valve diseases or operations that are known to last long. EA is the one of the best methods of pain management after hip arthroplasty. It is frequently implemented by catheter after these surgeries and optimal pain control is sustained even into the late postoperative period. It has been suggested that although EA provides better analgesia during movement than IV opioid administration, the lower pain score advantage of EA at rest is limited to the first 4–6 hours.[18] The use of opioid added local anesthetics may provide better analgesia during neuraxial interventions but it may cause also more frequent side effects. EA may also have better analgesic effect than nerve blocks during exercise.[19] However, peripheral nerve blocks may provide equal postoperative analgesia to the EA with fewer complications after lower extremity surgeries.[18,20] A study comparing the analgesic efficacy of these three methods showed that continuous 3-in-1 block could have a similar effect to EA and IV opioid administration with fewer side effects.[21]

US guidance is used when administering neuraxial or peripheral nerve blocks and increases rates of success. In the present study, the success rate for S-FICB was 98%. A review reported 99% success of epidural catheter placement using the landmark technique, but adequate anesthesia/analgesia may be achieved at a rate of only 76% at the lumbar epidural level.[22] We determined a 93.8% success rate of EA in our study. However, factors such as misplacement or migration of the catheter and individual variations in the structure of the epidural area reduce the effectiveness of the EA in pain control.[23] Accidental catheter removal is one of the problems associated with catheter techniques. This occurred in two patients in the EA group in our study. While fewer patients needed opioid treatment in the EA group, the mean VAS scores and total morphine consumption were similar in the two groups. This suggests that patients whose catheters were misplaced or accidentally removed may have increased the overall morphine consumption of the EA group in our study.

Although it provides better pain control than many other techniques, continuous EA causes certain adverse effects such as urinary retention, hypotension, and bilateral muscle weakness.[2,18] Hypotension is a common side effect of EA due to vascular dilation caused by sympathetic denervation. Hypotension occurs more frequently with the epidural technique than systemic analgesia and nerve blocks. Consistent with the literature, in our study hypotension was significantly more common in the EA group than the S-FICB group. All other adverse effects occurred at the same frequency in both groups.

Muscle weakness is attributed to both FICB and the EA. Behrends et al. suggested that preoperative FICB did not improve pain control after hip arthroscopy but may cause quadriceps weakness.[24] However, the results of a meta-analysis are inconsistent with this finding.[3] It was suggested that the programmed intermittent epidural bolus technique may provide greater dermatomal spread and lower pain scores compared to continuous administration.[25] Moreover, adding continuous infusion to epidural PCA may increase analgesic quality but also increase the incidence of muscle weakness.[26] Recent studies showed that a programmed intermittent bolus regimen provides better pain control and less motor blockade than continuous infusion via both EA and lumbar plexus catheter.[25] But, this undesirable event could be ceased by repositioning the catheter or reducing anesthetic concentration by suspending infusion and using

washout technique.[27,28] The intermittent bolus method was used in our patients according to our analgesia protocol and no patient suffered muscle weakness in either group on the first postoperative day.

There is no consensus regarding the timing of surgery for hip fracture patients who are being treated with anticoagulant drugs. In orthopedic surgery guidelines, the moderate recommendation is that fracture patients undergo surgery within the first 48 hours to reduce mortality.[29] However, the epidural technique is not suitable for patients using anticoagulant therapy without delay. Neuraxial block is contraindicated in patients receiving antiplatelet or anticoagulant, whereas peripheral nerve block may be administered in compressible regions.[6] The injection site for S-FICB is distant from major nerves and blood vessels; therefore, US-guided S-FICB can be considered safe in this patient group. Almeida et al. showed that FICB under sedation was sufficient for surgery in hip fracture patients receiving anticoagulant drugs.[30] We believe that US-guided S-FICB may be used in patients using antiplatelet or anticoagulant drugs and could offer a substantial advantage for both anesthesia and analgesia for hip fracture surgery. These patients should be monitored more closely due to the development of hematoma in addition to the described complications.

We conducted a retrospective study, and it was major limitation of our study. Data was collected from well-structured follow-up records kept by the postoperative pain management team. Nevertheless, we could report only clinically observed side effects. Secondly, urinary retention could not be evaluated because urinary catheter was inserted as standard during the follow-up period. Additionally, there was no standard preoperative analgesia management for hip fracture patients. Finally, VAS scores and opioid consumption amounts were recorded only once during the emergence period.

Conclusion

In conclusion, single-shot S-FICB may provide similar postoperative pain control as compared to EA in the first 18 hours after hip surgery. However, VAS scores were lower in the EA group than S-FICB group after the 18th hour. There was no statistically significant difference between the two groups according to total opioid consumption in the first 48 hours. Hypotension has occured more frequently in patients receiving EA but other side effects were similar between two groups.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Evaluation of skin test indications for general anesthetics in real life: a prospective cohort study☆

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Abstract
Background: In daily practice, atopic patients and those who have other drug allergies are referred to allergy clinics for evaluation of possible general anesthetic allergy despite the fact that it is not recommended in recent guidelines.
Objective: The aim of this prospective study is to determine the negative predictive value of skin tests for common general anesthetic drugs prior to general anesthesia in atopic patients and in patients who had drug allergies by including the data of those who had previously tolerated or reacted to general anesthesia.
Methods: A database program was constituted to collect the preoperative skin test data of patients referred to our clinic between 2013 and 2018. Demographic and clinical history, medications implemented during perioperative period, reactions, and results of skin tests performed with anesthetic drugs and latex were evaluated.
Results: Four hundred fifty-nine out of the total 1167 patients referred fulfilled the inclusion criteria for further evaluation. Nearly 75% of the patients were female and mean age was 46.3 ± 14.3 years. History of hypersensitivity reactions (HRs) due to NSAIDs and/or antibiotics, radiocontrast agents, local anesthetics, and food were present in the 53.1%, 4.1%, 1.5%, and 2.0%, respectively. The negative predictive values of skin tests for general anesthetics were in the range of 80–100%. Only 4 patients (0,87%) experienced HRs during operation.

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Conclusion: These real-life data reveal high rates of negative predictive value of skin tests with general anesthetic drugs and a low reaction rate in atopic patients and in patients with allergy to other drugs.
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Introduction

Hypersensitivity reactions (HRs) during general anesthesia are rare, however life-threatening conditions involving multiple organ systems can be seen.[1] Regardless of the mechanism, the clinical spectrum ranges from mild urticaria to severe anaphylaxis, which can lead to cardiovascular and/or pulmonary collapse and even death.[2] Possible pathomechanisms of perioperative hypersensitivity reactions can be determined in two groups: one is the allergic Immunoglobulin E (IgE)-mediated reactions, for which there is an identifiable culprit and high risk of recurrence on re-exposure, and the other group is the remainder of immediate perioperative reactions, which are either related to the pharmacological effects of anesthetic drugs or surgical management or fall in the category of nonallergic, nonspecific activation of mast cells and basophils, or other pathways.[2] One such mast cell activation can occur via the recently discovered Mas-related G protein-coupled receptor-X2 (MRGPRX2) receptor.[3] The exact mechanisms and risk of recurrence on re-exposure are poorly described for these reactions. Patients with clonal or nonclonal mast cell disorders can have an increased risk of severe reactions elicited either by specific triggers or via nonspecific activation.[4,5] Interestingly, clinical manifestations are usually more severe in IgE-mediated reactions.[6,7] The estimated incidence of HRs during general anesthesia varies widely among studies ranging from 1 in 353 to 1 in 18,600 procedures.[8–10] Prospective studies suggest incidences of 1:3180 in France[11] and 1:1480 in Spain.[12] Since a relatively high mortality rate (4–9%) of anesthetic agent-induced HRs has been reported, deciphering the predisposing risk factors for HRs, thereby the prevention of HRs in subsequent anesthesia, is of extreme importance.

Although clinical assessment is essential to understand the culprit agent and the reaction type, there are some factors complicating the true diagnosis of an HR during general anesthesia. During anesthesia, several potential culprits including drugs, such as neuromuscular blocking agents (NMBAs), antibiotics, analgesics, diagnostic dyes, and volume replacement solutions, are almost simultaneously administered and patients are concomitantly exposed to latex. The unconscious patient cannot warn the physician about unexpected symptoms, and therefore early signs and symptoms can easily be overlooked by the surgeons. Furthermore, some important findings of anaphylaxis such as hypotension can easily be confused with the pharmacologic effects of drugs used during anesthesia.[13]

Considering these circumstances, gathering clinical information related to allergy history before anesthesia is essential to decrease the risk of severe HRs. According to the recent European Academy of Allergy and Clinical Immunology (EAACI) guideline, preoperative allergological evaluation is strongly recommended for the patients who have experienced HRs or an unexplained event during previous anesthesia and who are to undergo an operation, but not for those with atopic diseases or other drug allergies.[2] Anesthesiologists are often concerned also for the patients who are atopic and especially for those having other drug allergies; consequently, they frequently request allergological consultation in these situations as a daily routine in order not to face with patients seeking for legal redress against them when there is a severe reaction afterwards. Although the recent guideline gives insight to physicians in their decision, the grade of evidence for skin testing in atopic diseases and other drug allergies is low, and mostly rely on old case-controlled descriptive studies.[2,14–18] The aim of our prospective study relying on real-life data is to determine the diagnostic value of skin tests for general anesthetic drugs in atopic patients and in patients who have drug allergies other than anesthetics, even if they have previously tolerated general anesthesia. The negative predictive value of tests for each drug is evaluated in detail.

Methods

A local database evaluating the incidence and risk factors of perioperative immediate drug hypersensitivity reactions was established in collaboration with departments of adult allergy and anesthesiology at our tertiary referral university hospital and was prospectively used by these departments between 2013 and 2018. It reflected the scope of Scandinavian, Great Britain, and Irish perioperative anaphylaxis guidelines.[15,19] Anesthesiologists added all individual patient information prior to and during surgery, including demographic data, their anesthesiology plan, medications implemented in the perioperative period, currently used drugs, detailed clinical history, atopy, drug allergies and allergic reactions developed during perioperative and postoperative periods, onto the database. In parallel, allergists prospectively included the allergic diagnostic workup information of every patient prior to surgery. We utilized the database for all patients including those who are only atopic or having any drug allergy history.

Patients in the 18 to 65 age bracket were included in the study. Patients without a full perioperative information record, individuals who underwent emergency surgery, and pregnant women were excluded. All patients prospectively underwent skin prick tests and intradermal tests with most commonly used NMBAs (i.e., mivacurium, atracurium, suxamethonium, cisatracurium, vecuronium, and rocuronium), thiopental sodium, morphine, fentanyl, remifentanil, midazolam, ketamine, propofol, tramadol, morphine as well as other agents requested to be tested by the anesthesiologist,

and latex, with the exception of volatile agents in suggested concentrations.[2,20,21] Depending on the severity of the HRs in the history, tests were started with more diluted concentrations up to the maximum nonirritant concentrations.

Suspected HRs to antibiotics and/or nonsteroidal anti-inflammatory drugs were evaluated according to recommendations of European Network on Drud Allergy (ENDA).[22] Where appropriate, penicillin skin testing was applied according to the published guidelines. For skin prick tests, 10 mg.mL^{-1} of histamine and physiologic saline solution were used as positive and negative controls, respectively. When skin prick test was negative, intradermal tests using increasing concentrations of the drugs were performed. Tests were assessed after 20 minutes according to published guidelines.[20] Atopy was defined as at least one positivity on skin prick tests with common inhalant allergens (ALK Abello, Denmark). Skin tests were defined as positive if there was a wheal of at least 3 mm greater than negative control.[23] The classification of clinical severity of perioperative immediate hypersensitivity was performed according to the modified Ring and Messmer four-step grading scale.[24,25]

The study was approved by Istanbul University, Istanbul Faculty of Medicine Ethics Committee (EK-2018/950) in June 2018, in accordance with the Declaration of Helsinki. A written informed consent for allergy skin testing was obtained from each patient as a daily routine practice in our adult outpatient clinic.

Statistical analysis

All statistical analyses were performed with SPSS version 21.0. Demographic and clinical features of the patients were evaluated with descriptive statistics including percentages and mean ± standard deviation. The *p*-values less than 0.05 were considered as statistically significant. After each operation, history of possible reactions during anesthesia was carefully assessed and all possible reactions were recorded in order to evaluate the number of patients with true or false negative skin test results. Negative predictive value was calculated as follows: Negative predictive value (NPV) = true negative / (true negative + false negative) x 100.

Results

Of the 1167 patients whose preoperative data were recorded, 708 were excluded due to missing perioperative data and/or the overlap between group 1(patients with other drug allergies) and group 2 (patients with atopy). Finally, total 459 patients were suitable for full assessment to form two groups that did not overlap with each other (Fig. 1). Of these 459 patients, nearly 75% (n = 344) were female and the mean age was 46,3 ± 14,3 years. In detailed clinical history of these patients, additional allergic conditions were found to be present in some patients, such as chronic spontaneous urticaria in 75 patients (16.33%), local anesthetic agent allergy in 7 patients (1.52%) and radiocontrast agent allergy in 19 patients (4.13%). A total of 109 patients had comorbidities including coronary artery disease (n = 4), diabetes mellitus (n = 17), hypertension (n = 20) and malignancy (n = 68). Overall, 244 patients (53.15%) had a history of DHRs due to antibiotic and/or Nonsteroidal anti-

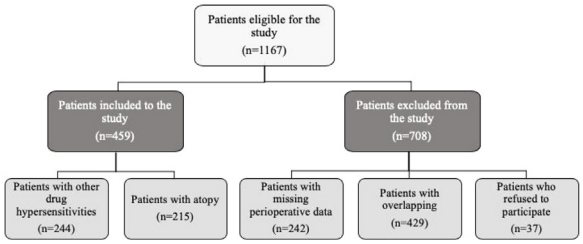

Figure 1 Flow chart of the patients included in the study.

inflammatory drugs (NSAIDs) and 215 patients (46.85%) had atopy. Of the 215 atopy patients, 123 patients had house dust mite sensitivity, 68 patients had pollen sensitivity, and 24 patients had both house dust mite and pollen sensitivity, with 9 of 24 patients having food poly-sensitivity by skin prick tests.

Nearly 65% of the patients (n = 297) were previously operated under general anesthesia and 41 of them had a history of hypersensitivity reaction during previous general anesthesia. However, which drugs induced the perioperative reactions in these patients were not known. Therefore, they were skin tested with the agents requested by anesthesiologists, starting with more diluted drug concentrations depending on the severity of their previous reactions. Five patients (12.2%) had positive skin test with latex and there was no general anesthetic drug positivity in these patients. While 4 patients had positive skin test with a single general anesthetic agent, 6 patients had positive skin test with multiple general anesthetic agents. The most common test positivity was found for propofol (14.6%). In 26 of 41 patients, no skin test positivity was found with any agent. In one of 2 patients with a history of perioperative anaphylaxis, propofol, midazolam, atracurium, thiopental, and morphine skin tests were positive. These agents were not used in the operation and no perioperative reaction was reported. The test results were shown in Fig. 2.

The skin test results were evaluated in all patients; skin test positivity with at least one agent was found in 66 of 459 patients (14.37%). The characteristics of these patients were as follows: nearly 76% (n = 66) of the patients were women, the mean age was 45.37 ± 14.1 years, 31.8% of the patients had never exposed a general anesthetic, 68.2% had a history of anesthesia in the past, and 22.7% had a previous history of hypersensitivity reaction with general anesthetics. The most common sensitizing agent was latex (9.2%). Among tested drugs, propofol was found as the most sensitizing drug (3.7%) (Fig. 3), whereas no skin test positivity was observed with cisatracurium. There was no statistically significant difference in the test positivity rate between patients with drug hypersensitivity and atopic patients or between patients who were previously exposed to general anesthetics and patients without a history of general anesthetic exposure. The test results of all patient groups and the negative predictive values of skin tests for general anesthetics in patients with atopy and other drug hypersensitivity were shown in Table 1 and Table 2, respectively.

Only four patients (female/male: 3:1, mean age: 44.75 ± 9.03 years) without a previous history of HR to general anesthesia experienced HRs during anesthesia. The demographic and clinical characteristics of these 4 patients

Table 1 Skin test results for general anesthetic drugs and negative predictive values of tests in patients with other drug hypersensitivities.

		Patients with other drug hypersensitivities[a] (n = 244)						
		Preoperative DST			Perioperative exposure to drug			NPV (%)
Agents		Total (n = 1613)	Positive (n = 43)	Negative (n = 1570)	Total (n = 1215)	Perioperative HR negative (n = 1213)	Perioperative HR positive (n = 2)	
IV anesthetics	Thiopental sodium	53	2	51	7	6	1	85.7
	Midazolam	227	1	226	221	221	0	100
	Ketamine	10	-	10	3	3	0	100
	Propofol	238	11	227	197	197	0	100
Opioids	Morphine	30	2	28	21	21	0	100
	Fentanyl	236	-	236	222	222	0	100
	Remifentanil	99	1	98	52	52	0	100
	Tramadol	188	1	187	70	70	0	100
NMBAs	Atracurium	48	3	45	5	4	1	80
	Mivacurium	41	1	40	8	8	0	100
	Vecuronium	11	1	10	2	2	0	100
	Rocuronium	236	1	235	181	181	0	100
	Cisatracurium	5	-	5	-	-	-	-
Depolarizing Muscle Relaxant	Suxamethonium	8	-	8	1	1	0	100
Latex		183	19	164	225	225	0	100

DST, drug skin test; IV, intravenous; NMBAs, Neuromuscular blocking agents; NPV, negative predictive value; HR, hypersensitivity reaction; n, number of patients.
[a] Antibiotics and/or NSAIDs.

Table 2 Skin test results for general anesthetic drugs and negative predictive values of tests in atopic patients.

	Atopic patients (n = 215)							
	Preoperative DST			Perioperative exposure to drug			NPV (%)	
Agents		Total (n = 1456)	Positive (n = 34)	Negative (n = 1422)	Total (n = 1116)	Perioperative HR negative (n = 1115)	Perioperative HR positive (n = 1)	
IV anesthetics	Thiopental sodium	**41**	-	**41**	**10**	**10**	**0**	**100**
	Midazolam	**206**	**3**	**203**	**193**	**193**	**0**	**100**
	Ketamine	**12**	**1**	**11**	**10**	**10**	**0**	**100**
	Propofol	**205**	**6**	**199**	**168**	**167**	**1**	**99.4**
Opioids	Morphine	**20**	-	**20**	**20**	**20**	**0**	**100**
	Fentanyl	**207**	**2**	**205**	**197**	**197**	**0**	**100**
	Remifentanil	**103**	-	**103**	**61**	**61**	**0**	**100**
	Tramadol	**163**	**1**	**162**	**43**	**43**	**0**	**100**
NMBAs	Atracurium	**48**	-	**48**	**2**	**2**	**0**	**100**
	Mivacurium	**29**	-	**29**	**2**	**2**	**0**	**100**
	Vecuronium	**22**	-	**22**	**1**	**1**	**0**	**100**
	Rocuronium	**205**	**1**	**204**	**182**	**182**	**0**	**100**
	Cisatracurium	**2**	-	**2**	**1**	**1**	**0**	**100**
Depolarizing Muscle Relaxant	Suxamethonium	**10**	**1**	**9**	**1**	**1**	**0**	**100**
Latex		**183**	**19**	**164**	**225**	**225**	**0**	**100**

DST, drug skin test; IV, intravenous; NMBAs, Neuromuscular blocking agents; NPV, negative predictive value; HR, hypersensitivity reaction; n, number of patients.

Table 3 Characteristics of patients who had perioperative reactions after allergological work up.

PATIENTS	SEX	AGE	ATOPY	DRUG ALLERGY HISTORY	EXPOSURE TO ANESTHESIA	PREOPERATIVE TEST RESULTS		DRUGS ADMINISTERED DURING ANESTHESIA	TYPE AND SEVERITY OF REACTIONS	POSTOPERATIVE TEST RESULTS
						Negative	Positive			
P1	M	37	Yes	No	1th time	Propofol Rocuronium Fentanyl Midazolam Tramadol Remifentanil Thiopenthal Latex		Propofol Rocuronium Fentanyl Midazolam Latex	Anaphylaxis (Grade 3)	Propofol was positive
P2	F	51	No	Yes	2nd time	Propofol Rocuronium Fentanyl Midazolam Atracurium Meperidin Remifentanil Latex		Midazolam Latex	Urticaria/ angioedema (Grade 1)	Could not be evaluated due to der-mographism
P3	F	54	Yes	No	3rd time	Rocuronium Tramadol Remifentanyl Atracurium Thiopenthal Morphine	Propofol Fentanyl Midazolam Latex	Atracurium Remifentanil Thiopenthal sodium	Urticaria (Grade 1)	Atracurium and thiopenthal were positive
P4	F	37	No	Yes	1th time	Propofol Rocuronium Fentanyl Remifentanil Midazolam Tramadol Latex		Propofol Rocuronium Fentanyl Remifentanyl Midazolam Neostigmin Atropin Latex	Urticaria/ angioedema/ hypotension (Grade 2)	Midazolam and remifentanil were positive

F, female; M, male.

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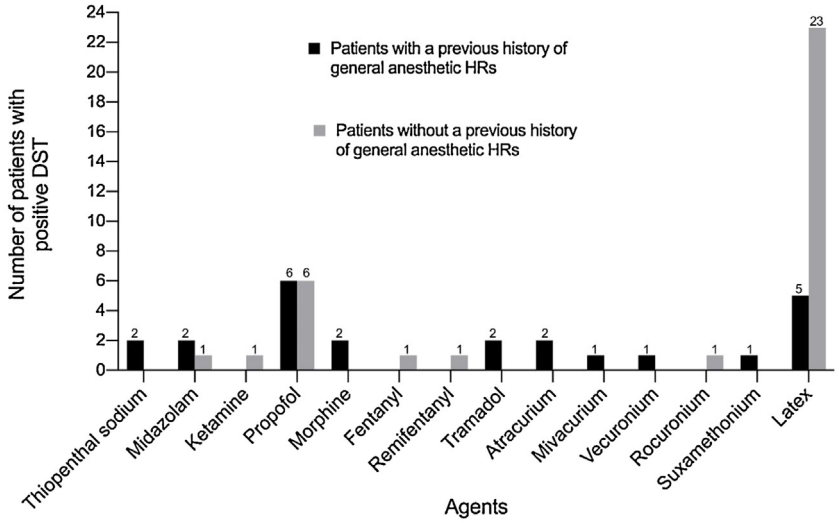

Figure 2 Number of preoperative positive skin test results of patients with or without a previous history of perioperative general anesthetic HRs. DST, drug skin test; HRs, hypersensitivity reactions.

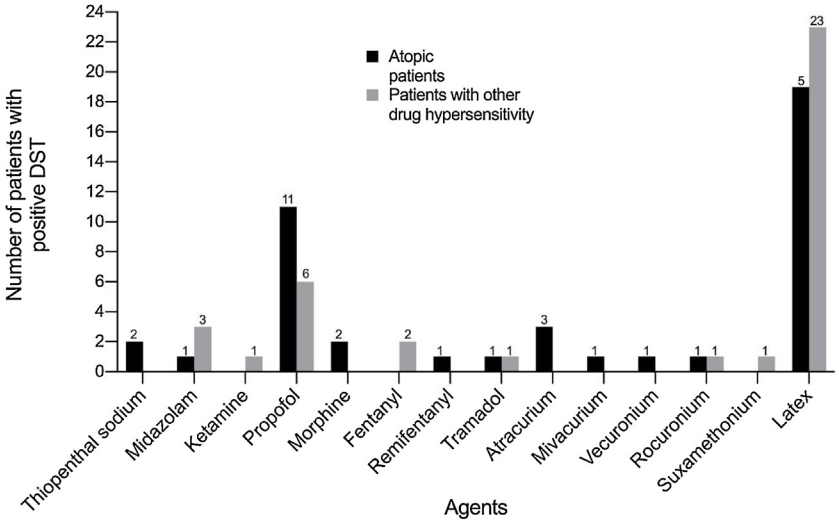

Figure 3 Results of preoperative skin tests in patients with atopy or other drug allergies. DST, drug skin test.

(P1-P4) are shown in detail in Table 3. Postoperative skin testing was performed to these patients with all the agents used during anesthesia including latex. All preoperative skin tests were negative in 3 patients (P1, P2 and P4). P3 received non-reactive anesthetics with cautions for latex-free environment during operation, because she reacted to some anesthetics and latex in skin tests (Table 3). Drug tests repeated after the operation showed new sensitizations in three patients (P1, P3, and P4) (Table 3).

Discussion

In this study, a large patient series was preoperatively evaluated with skin tests for multiple anesthetic drugs. This series was consisted of atopic patients and drug allergic patients without anesthesia related reaction history as well as those with perioperative drug allergy. Overall, skin test positivity rate was 14.37% (66 out of 459 patients), and the most frequent sensitizing agent was latex (9.2 %) followed by propofol (3.7 %). Due to ethical reasons, test positive drugs were not applied to the patients. Accordingly, we could not evaluate positive predictive value and sensitivity of these tests. However, skin test negative drugs were used without any adverse events in most of the patients with atopy or other drug allergies, indicating that negative predictive value of the skin tests was very high (above 90%). However, studies with a more homogeneous group with a greater number of patients would provide a more reliable interpretation of NPV.

Although avoidance of the agents with positive skin test results is recommended, there is not a specific suggestion for the agents with negative skin test results. The risk of false negative skin testing should be considered. In our study, we identified only 4 patients who did not have a previous HR history to general anesthetics, with negative skin testing,

displayed HRs during operation. Skin tests repeated after reactions yielded positive results in 3 of these patients. The possible explanation for this situation is either that preoperative skin test results were false negative or that these patients may be sensitized after the last exposure. So far, to our knowledge, there are no data reported about the risk of new sensitization with preoperative skin testing for general anesthetics, suggesting the necessity of more data for optimal recommendations after negative skin testing.

Among 41 patients with a previous history of HRs to general anesthetics, 2 had anaphylaxis and 15 (36.5%) reacted to different agents during preoperative skin tests, with propofol (14.6%) and latex (12.2%) as the most common sensitizing agents. None of these patients had any adverse events when re-exposed to general anesthesia, which was given according to the test results, indicating the reliability of negative skin tests with general anesthetics and latex.

In the recent EAACI guideline, it was reported that the only risk factor specifically identified for immediate perioperative anaphylactic reactions was a previous history of adverse reaction after exposure to general anesthetics.[2] In case control studies, no association between IgE-mediated reactions to general anesthetics and asthma, atopy, other drug hypersensitivities, or previous exposure to general anesthetics was reported.[9,14,15] In line with these findings, in our study, the majority of patients who did not have a previous reaction history with anesthetics and those who have atopic diseases and a drug hypersensitivity profile did not have a HR during general anesthesia. However, test positive drugs were avoided in such patients. Therefore, the positive predictive value of the positive skin test results could not be determined, nor utilized for the benefit of patients. We have to further keep in mind that although preoperative skin tests with anesthetics are recommended only for the patients who had a previous HR experience during anesthesia, a preoperative evaluation for other drugs such as antibiotics or NSAI analgesics, which are commonly used in preoperative or postoperative periods, are necessary for those who have drug allergy history.[12]

In our study, the culprit drugs were identified in 3 of the patients who had perioperative HRs. The relationship between the timing of the drug administration and the onset of the symptoms may help to determine the agents that caused the HRs. However, this is a suboptimal way, since during anesthesia, several drugs are concomitantly administered. There could be also other factors that mimic the clinical picture of anaphylaxis, such as direct mast cell mediator release and other causes of hypotension and bronchospasm, and that include the pharmacological actions of the anesthetic drugs themselves, which could complicate the detection of the culprit drugs.[26]

Nondepolarizing muscle relaxants are among the leading causes of perioperative anaphylaxis.[6,9] Sensitivity and specificity of skin testing to NMBAs are unknown. In our series, skin test positivity with muscle relaxants was very low (0.44–2%) in the patients with drug allergy history or atopy. In the patients with previous HR history with anesthetics, muscle relaxants revealed positive results in 1.08% while propofol was positive in 1.30%. As cited by the EAACI position paper, introduction of geographical environmental elements, such as pholcodine or cosmetics with quaternary substituted ammonium groups, could change incidence of NMBA hypersensitivity reactions upon first exposure.[2] Although our country also allows pholcodine use as antitussive in accordance with European Medicines Agency (EMA), we could not detect a high incidence of NMBA reactions. As mentioned above, the most common positive result in this group was observed with latex (12.2%). Similarly, latex skin test showed the highest test positivity among all the patients (9.2%). As latex allergy is among the most leading causes of perioperative anaphylaxis, to detect this sensitization before a major surgical intervention is of great importance. Of the patients, 297 had undergone general anesthesia without any problems; although this artificially reduces the likelihood of developing a perioperative hypersensitivity reaction upon re-exposure, these patients were not excluded from the study, especially since repeated encounters with latex may be a risk factor.

Perioperative hypersensitivity reactions were found significantly higher in women in previous studies.[27] HRs to anesthetic agents were reported to be more common in women, possibly related to sex hormones.[27] Furthermore, women were reported more often to be reactive to neuromuscular blocking drugs than men.[27] Although a female predominance (74.9%) was noticed in our study cohort, this was not significantly related with preoperative skin tests results.

Our study is novel, as it represents the first Turkish perioperative hypersensitivity reaction data and includes a large number of patients, but it has some limitations. Due to ethical and safety concerns, patients with positive skin test results to some general anesthetics did not further receive these drugs during operation, and therefore positive predictive value and sensitivity of these tests were not assessed. However, cooperation and data sharing between the allergists and anesthesiologists during the study resembling the real-life clinical practice and the prospective design of the study by presenting the real-life data strengthen the findings of the study. Lastly, this database only contains the information of elective surgical patients.

In conclusion, these real-life data confirm that skin testing with anesthetic agents in patients with atopy or in patients who have a drug allergy history for drugs other than general anesthetics is not necessary unless they had experienced a reaction during previous anesthesia. However, latex allergy should be evaluated carefully before any operation in high-risk groups.

Conflict of interest

The authors declare no conflict of interest.

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ORIGINAL INVESTIGATION

Airway management in general anesthesia for endovascular treatment of cerebral arteriovenous malformation: a retrospective observational study



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Abstract
Background and objective: This retrospective and observational study aimed to retrospectively evaluate the use of the endotracheal tube (ETT) and the Laryngeal Mask Airway (LMA) for the airway management with respect to airway safety, hemodynamic stability, adverse respiratory events, and recovery characteristics in patients who underwent endovascular treatment (EVT) for cerebrovascular arteriovenous malformation under general anesthesia between 2011 and 2018.
Methods: The study included data from the patient's electronic medical records and anesthesia files. The primary outcome measure was the incidence of hemodynamic disturbances and respiratory adverse events during airway management. The secondary outcome measure was the comparison of recovery characteristics.
Results: The airway was secured using ETT in 41 patients and LMA in 39 patients. Airway safety was established in all patients without a complication throughout the procedure. Mean arterial blood pressure and heart rate were increased to > 20% of baseline levels at intubation and extubation periods in more patients in the ETT group than the LMA group (27 vs. 3; $p = 0.07$, and 11 vs. 2; $p = 0.021$). Respiratory adverse events including straining and coughing were observed in ten patients in the ETT group but only in one patient in the LMA group ($p = 0.013$). Time to extubation, to neurological assessment, and to discharge from the angiography unit were similar ($p > 0.05$).

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Conclusion: It was concluded that LMA provided sufficient airway safety as with ETT and may be used as an alternative to ETT for EVTs under general anesthesia.
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Introduction

Endovascular Treatment (EVT) has been increasingly used in the past twenty years as a sole therapy or more frequently, as a component of the multimodal therapy for the treatment of brain Arteriovenous Malformations (AVMs) (1). The aim of EVT is to reduce the size and blood flow of the nidus of AVM to occlude its feeders via the application of Ethylene-Vinyl Alcohol Copolymer (EVOH) or Onyx through a microcatheter.[1,2] The anesthetic management of EVT for AVM involves general principles of the interventional neuroradiology (INR), which have been adopted mainly from the traditional neurosurgery: a) providing an immobile patient, b) maintaining hemodynamic stability, c) manipulation of arterial blood pressure (ABP) as necessary, d) smooth emergence from the anesthesia, e) early recovery as shown by a neurological assessment, and f) treatment of complications.[3,4]

Among the various anesthetic techniques such as conscious sedation, general anesthesia (GA), and neurolept anesthesia, GA is the most commonly used technique because it ensures both immobilization and airway safety during the procedure. Endotracheal intubation has been generally used for airway management in GA.[5-10] Although supraglottic airway devices are well-known tools for the airway management in GA, their use in the interventional neuroradiological procedures is limited. Only four reports exist in the literature.[11-14]

Endovascular treatments were begun for cerebrovascular aneurysm in 2008 and for arteriovenous malformation in 2011 in our hospital. We have been using both the endotracheal tube (ETT) and the Laryngeal Mask Airway (LMA) for the airway management in procedures under GA.

This study aimed to retrospectively evaluate the use of ETT and LMA for the airway management with respect to airway safety, hemodynamic stability, adverse respiratory events, and recovery characteristics in patients who underwent endovascular treatment for cerebrovascular arteriovenous malformation under general anesthesiabetween 2011 and 2018.

Methods

This observational and retrospective study was conducted in a tertiary hospital from January 2011 to April 2018. After obtaining hospitals ethic committee approval, data were retrospectively collected from the hospital's computerized data base (MedData^{TM} HBYS), medical and anesthesia files of all adult patients who underwent elective endovascular treatment for uncomplicated cerebrovascular AVM by a single neuroradiologist in the INR unit. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15-17] Obtaining informed consent was waived with respect to the retrospective design of the study.

The inclusion criteria were as follows: elective EVT for cerebral AVM under general anesthesia and American Society of Anesthesiologists (ASA) physical status I—II patients without neurological deficits. Exclusion criteria were a history of cerebrovascular surgery, neurological impairment before the procedure, difficult airway management, insufficient data, and lost to follow-up in the perioperative period.

Anesthetic technique

All patients were examined by the anesthesiologists before the intervention. A large-bore peripheral venous cannula was inserted in the forearm, and 8—10 mL.kg^{-1} saline or Ringer's lactate was given for prehydration during the fasting period, which lasted six hours for light meals and two hours for clear fluids. Patients were monitored with electrocardiography (ECG), pulse oximetry, and noninvasive blood pressure (NIBP) in the INR unit. Baseline vital parameters were recorded. An arterial catheter was placed in the left radial artery after local anesthetic infiltration to monitor arterial blood pressure and to take blood samples for activated clotting time (ACT) measurement.

GA was induced using 2—2.5 mg^{-1}kg^{-1} intravenous (IV) propofol and 1—2 μg^{-1}kg^{-1} fentanyl. 0.6 mg^{-1}kg^{-1} rocuronium was given to facilitate endotracheal intubation or LMA insertion, and 1.5 mg^{-1}kg^{-1} lidocaine (2%) was given to suppress airway reflexes. After three minutes of mask ventilation with 100% oxygen, an ETT (ID 6.5—8.0) was placed after direct laryngoscopy or a LMA (- no 3—5) was inserted (LMA-Classic^{TM}, Intavent Orthofix Ltd., Maidenhead, Berkshire, United Kingdom). LMA was inserted using the classical method described by Brain.[18] Volume inflated in the pneumatic cuff of the LMA was 15 mL for size 3, 20 mL for size 4, and 30 mL for size 5 to minimize the pressure on the pharynx. Patients were ventilated using positive pressure ventilation (PPV). Ventilator settings were adjusted to keep the end tidal CO_2 level between 25 and 29 mmHg (mild hypocapnia) and the peak airway pressure lower than 20 cmH_2O.

A total intravenous anesthesia (TIVA) technique using remifentanil and propofol infusions was used for the maintenance of anesthesia. Remifentanil was given with a constant infusion rate (2 μgkg^{-1}h^{-1}). Propofol infusion rate was changed in a range between 3—6 μg.kg^{-1}h^{-1} to maintain mean arterial pressure (MAP) between 60 and 70 mmHg until glue injection and between 20% and 30% below the baseline MAP during the glue injection to slow the blood circulation in the injection area.

The body temperature was monitored, and a forced air warming device was used to prevent hypothermia. An urine

catheter was placed, and urine output was monitored. The baseline activated clotting time (ACT) was measured, and heparin 100 U.kg^{-1} was given as a loading dose, and an infusion was started at a rate of 15 U.kg^{-1}h^{-1} to maintain the ACT between 2 and 3 times the normal rate after the femoral artery cannulation. A total of 1200 mg N-acetylcysteine and 50 mg ranitidine were given to prevent contrast-induced nephropathy and for gastric protection. After completion of EVT, TIVA and heparin infusions were discontinued. Ventilation was controlled with 100% oxygen until the return of spontaneous ventilation. IV 1.5 mg.kg^{-1} lidocaine was given to prevent airway reflexes during extubation, and 40 μg.kg^{-1} neostigmine and 20 μg.kg^{-1} atropine were given for the reversal of the neuromuscular blocking agent in both groups. ETT or LMA was removed when spontaneous respiration resumed (tidal volume > 4 mL.kg^{-1}) and when consciousness returned.

The following recovery and discharge times were recorded: time to extubation or to removal of LMA, time to the neurological assessment, and time to discharge from the angiography unit to the intensive care unit (ICU). The neurological status of the patient was assessed by the neuroradiologist using the Glasgow Coma Scale (GCS) who performed the EVT. Patients with stable neurological and hemodynamic status, a modified Aldrete recovery score > 9, and a dry femoral artery puncture site were discharged from the angiography unit to the ICU.

Systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), heart rate (HR), and end-tidal CO_2 ($etCO_2$) levels were monitored and recorded continuously throughout the procedure. Vital signs were recorded before induction (baseline), before (pre-intubation) and after endotracheal intubation or LMA insertion (post-intubation), after extubation or removal of LMA (post-extubation), and at 5 minutes intervals during the procedure. A bolus dose of 40 μg.kg^{-1} metoprolol was given when the MAP increased > 20% above baseline values to avoid further increments in ABP. Respiratory adverse events and other complications were assessed and recorded throughout the procedure.

The electronic medical records, medical and anesthesia files, and intensive care unit charts were evaluated to collect data including demographic characteristics, techniques of anesthesia and airway management, hemodynamic changes after airway management and extubation, respiratory adverse events throughout the procedure, recovery and discharge times after the procedure, and the other complications related to the EVT. The records with insufficient data were excluded from the study. Only the files of patients whose EVT was performed by the same neuroradiologist, and anesthesiologists were included.

The primary outcome measures were the incidence of hemodynamic disturbance that was defined as the hemodynamic parameters which were not between ±20% of baseline values and the incidence of adverse respiratory events including laryngospasm, apnea, cough, gagging, and straining. The secondary outcome measure was the comparison of recovery times after the procedure including time to extubation, time to neurological assessment, and time to discharge from the INR unit to the ICU (min).

A power analysis was conducted to calculate sample size based on a prior study using PASS 13 software.[14,19] A total sample size of 72 (36 cases for each group) was required to detect at least 30% difference in MAP between ETT and LMA groups with a power of 80% at the 5% significance level.

Statistical analysis

All records were analyzed for missing data. The patient who had partially missing data and was lost to follow-up after the intervention was excluded from the study. The data were analyzed using the Statistical Packages for Social Sciences for Windows version 11.5 pocket program (IBM Corp., Chicago, IL, USA). For intergroup comparisons, the Chi-Square test and Fisher's exact test were used to analyze nominal data, and the *t*-test for independent samples was used for quantitative data. Data were expressed as mean ± SD for continuous variables and numbers, and percentages for categorical variables. The value of $p < 0.05$ was considered significant.[20]

Results

Medical records of 80 patients were reviewed. There was no missing data and all patients have completed the follow-up period that lasted 38−42 hours (Fig. 1). Two groups were identified considering the airway management technique: the Endotracheal Tube group (group ETT ; n = 41) and the Laryngeal Mask Airway group (group LMA ; n = 39). The demographic characteristics were similar between the groups (Table 1).

Primary outcome measures

Respiratory complications related to the airway management including insufficient ventilation, desaturation, laryngospasm, or bronchospasm were not recorded. There were three periods throughout the procedure where hemodynamic changes in mean arterial blood pressure and heart rates were not ±20% of baseline values: a) After the induction of GA (pre-intubation), b) After airway management (post-intubation), and c) After extubation (post-extubation).

The pre-intubation MAP levels were lower than 20% of baseline values in 21 patients in the ETT group and in 19 patients in the LMA group ($p = 0.771$). Heart rate was reduced to < 20% of baseline levels in 11 patients in the ETT

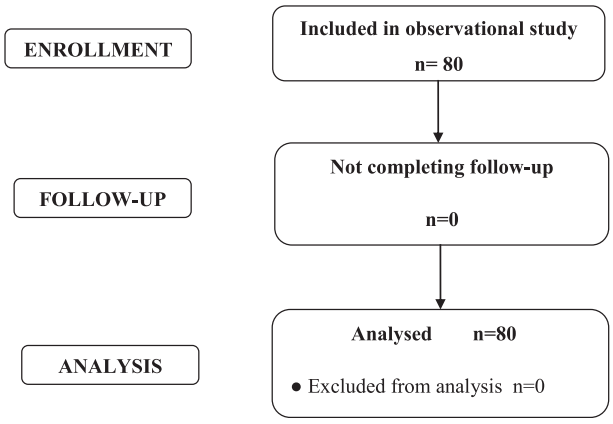

Figure 1 Flow diagram detailing participant flow through observational study.

Table 1 Patient baseline characteristics.

Parameters	Group ETT (n = 41)	Group LMA (n = 39)	*p*
Age (years)[a]	33.4 (10.3)	34.5 (11.8)	0.693
Gender (Female / Male)[b]	26 / 15	24 / 15	0.551
Body Mass Index ($kg.m^{-2}$)[a]	25.2 (2.3)	25.4 (2.0)	0.315
ASA physical status I / II[b]	36 / 5	33 /6	0.803
Mallampati Score I / II / III[b]	32 / 8 / 1	29 / 9 / 1	0.541

ETT, Endotracheal Tube; LMA, Laryngeal Mask Airway; ASA, American Society of Anesthesiologists.
[a] Data presented as mean (standard deviation).
[b] Data presented as absolute number (n).
$p < 0.05$ was considered as statistically significant.

Table 2 Comparison of changes in mean arterial blood pressure and heart rate between groups.

Parameters	ETT / LMA ± 20% of baseline	ETT / LMA < 20% of baseline	ETT / LMA > 20% of baseline	*p*
Mean Arterial Pressure[a]				
Preintubation	20 (48.8%) / 20 (51.3%)	21 (51.2%) / 19 (48.7%)	0 (0%) / 0 (0%)	0.771
Postintubation	14 (34.1%) / 36 (92.3%)	0 (0%) / 0 (0%)	27 (65.9%) / 3 (7.7%)	0.007
Postextubation	30 (73.2%) / 37 (94.9%)	0 (0%) / 0 (0%)	11 (26.8%) / 2 (5.1%)	0.021
Heart Rate[a]				
Preintubation	26 (63.4%) / 24 (61.5%)	11 (26.8%) / 12 (30.7%)	4 (9.8%) / 3 (7.6%)	0.563
Postintubation	12 (29.2%) / 30 (76.9%)	0 (0%) / 0 (0%)	29 (70.7%) / 9 (23.1%)	0.002
Postextubation	18 (43.9%) / 33 (84.6%)	0 (0%) / 0 (0%)	23 (56.1%) / 6 (15.4%)	0.002

ETT, Endotracheal Tube; LMA, Laryngeal Mask Airway.
[a] Data presented as absolute number and percentage, n (%).
$p < 0.05$ was considered as statistically significant.

group and in 12 patients in the LMA group before the intubation ($p = 0.563$) (Table 1). The pre-intubation MAP levels and heart rates were reduced to < 20% of baseline values in similar number of patients in both groups ($p = 0.771$ and $p = 0.563$, respectively) (Table 1). The post-intubation MAP levels and heart rates were increased to > 20% of baseline values in significantly more patients in the ETT group than in the LMA group (27 vs. 3; $p = 0.007$ and 29 vs. 9; $p = 0.002$, respectively) (Table 2). Similarly, the post-extubation MAP levels and heart rates were increased to > 20% of baseline values in more patients in the ETT group compared to the LMA group (11 vs. 2; $p = 0.021$ and 23 vs. 6; $p = 0.002$, respectively) (Table 2). Hemodynamic disturbances as elevation in MAP were managed successfully using metoprolol.

A total of eleven respiratory adverse events were recorded in all patients. Straining was recorded in one patient after intubation and in another five after extubation in the ETT group compared to one patient in the LMA group after extubation ($p = 0.002$). Coughing was recorded in 4 patients in the ETT group after extubation but was not recorded in the LMA group ($p = 0.001$) (Table 3). All respiratory adverse events were resolved spontaneously without an intervention and did not result in a further complication.

Secondary outcome measure

The mean duration of the procedure was 108.5±21.3 min and was not statistically different between the groups ($p > 0.05$). The mean time to extubation, time to the neurological assessment, and time to the discharge from the INR unit to ICU were not different in either group after the procedure ($p > 0.05$) (Table 3).

Table 3 Comparison of recovery times and respiratory adverse events between groups.

Parameters	Group ETT	Group LMA	*p*
Recovery Times (min)[a]			
Time to extubation	8.9 ± 1.8	9.1 ± 1.6	0.101
Time to neurological assessment	12.6 ± 2.9	12.8 ± 3.0	0.136
Time to discharge	17.5 ± 2.3	17.1 ± 1.4	0.214
Respiratory adverse events[b]			
Straining	6 (14.6%)	1 (2.5%)	0.002
Coughing	4 (9.7%)	0 (0%)	0.001

ETT, Endotracheal Tube; LMA, Laryngeal Mask Airway.
[a] Data presented as mean (standard deviation).
[b] Data presented as absolute number and percentage, n (%).
$p < 0.05$ was considered as statistically significant.

There was no procedure-related complication observed throughout the procedure. The patients were followed in the ICU for 14–22 hours, and then were transferred to the service. All patients were discharged from the hospital at the next day.

Discussion

The results of the study demonstrated that both ETT and LMA provided sufficient airway security without major complications including insufficient ventilation, desaturation,

laryngospasm, or bronchospasm. Hemodynamic disturbances were manageable and did not result in further complications. Recovery times were also similar that allowed rapid neurological assessment in the INR unit. The incidence of hemodynamic disturbance and respiratory adverse events were lower in the LMA group. According to the results, it can be stated that LMA may be safely used in patients who underwent endovascular treatments for cerebrovascular arteriovenous malformation under general anesthesia.

The anesthetic principles for EVT were developed mainly from intracranial neurosurgical anesthesia.[3-5] Endotracheal intubation is used to ensure the airway security in the intracranial surgeries because the patients are placed in the sitting, prone or lateral decubitus positions and the patient's head is sometimes fixed using a skull clamp head frame. The duration of the surgery lasts up to 3−5 hours and also painful.[4-6]

We have been also using routinely endotracheal intubation in general anesthesia for EVTs as recommended in the literature.[3-9] But, in our practice, the elevation of arterial blood pressure at intubation period induced by direct laryngoscopy, and cough and straining at the extubation periods were criticized by the neuroradiologist due to the risk for the development of an intracerebral hemorrhage, which is one of the leading factors causing morbidity and mortality.

As in neurosurgery, the maintenance of hemodynamic stability is very important in EVT. The rate of bleeding during AVM embolization has been reported to be 1.4%, and it has been found that the lack of hypotension is one of the clinical predictors of hemorrhage.[21,22] Anesthesiologists are responsible for establishing preventive measures against hemodynamic disturbances such as minimizing airway reflexes during airway management, manipulating ABP with hypotensive agents as necessary, and maintaining the anesthetic depth in a stable manner.[9] However, our efforts including intravenous lidocaine boluses to reduce airway reflexes were not always successful.

This issue directed us to investigate the availability of supraglottic airway devices in EVTs, which has been widely used as an alternative for endotracheal intubation in many other surgeries under general anesthesia. It was reported that hemodynamic disturbances were found to be significantly reduced with classical LMA than ETT during airway management at intubation and extubation periods.[23,24] Also, a systematic review and meta-analysis revealed that the incidence of laryngospasm, cough at removal, dysphagia or dysphonia, sore throat, and hoarseness was reduced with supraglottic airway devices.[25]

However, only one report existed in the literature which reported the use of LMA in three patients who underwent coiling of unruptured cerebral aneurysms under general anesthesia.[11] It was concluded that LMA may be a safe alternative by avoiding the hemodynamic effects of tracheal intubation.

Upon this, it was decided to try using LMA in the EVT of cerebrovascular aneurysms except in conditions where the use of LMA were contraindicated including history of obesity, chronic obstructive pulmonary disease, low pulmonary compliance, hiatal hernia, gastroparesis, inability to open the mouth, and an infection or pathologic abnormality in the oropharyngeal cavity.[26] As EVTs differ from the surgery, anesthetic requirements vary across both procedures at some points. The patients are in a supine position, the position of the head is neutral, and a skull clamp is not necessary to fix the head during the EVT procedure. The C-arm of the fluoroscope is turned around the head without a contact with patient's body. Those provide easy access to the airway during the procedure. It is reported that EVTs last up to 120 minutes, which is much shorter and also painless compared to the surgery.[2] Taking in the account all these factors, the conditions might not pose an additional risk to use the LMA in the EVT procedures.

The use of LMA was started first in EVTs of cerebrovascular aneurysm. After two years, it was continued in cerebrovascular AVM because there were no complications observed in the airway security related to the LMA and hemodynamic stability was established without an intervention.

There are few reports in the literature regarding the use of LMA and all were performed in the EVTs for cerebrovascular aneurysms. In a study, it was concluded that LMA ensured suitable conditions based on an analysis of cardiovascular stability in 26 patients.[12] LMA was used in another study which investigated the effect of dexmedetomidine on the recovery characteristics in 102 patients. It was reported that all patients were ventilated through LMA without a respiratory complication.[13] A retrospective study was conducted by the authors of this study in patients who underwent EVT during an eight-years period. It was concluded that LMA may be routinely used due to airway securing without respiratory complications and hemodynamic disturbance.[14]

A rapid and smooth recovery is also important for assessing of the neurological status and early diagnosis of the postprocedural complications including bleeding, vasospasm, stroke, and focal deficits.[6,7] In our study, the recovery and discharge times were similar in both groups. This is attributable to use propofol, fentanyl, and rocuronium, an intermedium acting neuromuscular blocking agent for the induction of anesthesia and a TIVA technique based on the propofol and remifentanil infusions for the maintenance. These anesthetic drugs provide stable hemodynamics and rapid recovery from anesthesia. This result is consistent with a study which found similar recovery and discharge times using remifentanil-propofolbased TIVA and an intermedium acting neuromuscular blocking drug (mivacurium) in patients undergoing elective orthopedic surgery with LMA or TT.[27]

The current study has several limitations. First, the retrospective nature of the study might have resulted in bias that affected the selection of the control group. Additionally, exposure to the interventions and outcomes may be difficult to control in both groups. To prevent this disadvantage, we used the same inclusion and exclusion criteria during the data collection period. Data were obtained from multiple sources including anesthesia files, electronic medical records, and ICU charts to reduce recall bias. A single neuroradiologist and the same anesthesiologists performed all interventions. The patient files with insufficient data were excluded. It should be noted that the study aimed to evaluate the data of the anesthetic experience with LMA and ETT focusing on the safety profile in EVT for cerebrovascular AVM which is a relatively new procedure for the anesthetic management. Therefore, we think that prospective and randomized studies are required to prove the availability of modern airway devices in this evolving area. Another limitation was the lack of the use of bispectral index and neuromuscular junction monitoring. They would provide real-time data about the depth of the anesthesia.[28,29]

It is concluded that LMA may be used as an alternative to endotracheal tube in the routine anesthetic practice for endovascular treatment of cerebral AVMs. LMA provided airway security as safe as ETT with attenuation of hemodynamic disturbance and minimal adverse respiratory events.

Author's contributions

MAS and MÖÖ conducted the study, collected the data, and contributed the writing of the manuscript. MÖÖ and COC analyzed the study results and contributed the revision of manuscript. MBE and BA assisted in analysis data and contributed the writing of the manuscript. MAS designed, directed, and reviewed the study.

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Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2021.12.004.

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ORIGINAL INVESTIGATION

The effects of dexketoprofen on renal ischemia-reperfusion injury: an experimental study

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KEYWORDS
Dexketoprofen;
Ischemia-reperfusion;
Kidney;
Malondialdehyde;
Reactive oxygen species

Abstract
Objective: Ischemia/reperfusion (I/R) may cause irreversible damage to tissues and organs. We evaluated the effects of dexketoprofen on a renal I/R model in rats.
Methods: The study included 30 male rats. Control group received 1 mL of saline. Dexketoprofen group received 1 mL (25 mg) of dexketoprofen intraperitoneally. After 60 minutes renal ischemia, 23 hours reperfusion was applied. In Sham group, laparotomy was performed with a medial line incision without any additional procedure. Changes in the plasma malondialdehyde (MDA), renal tissue MDA, plasma glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), BUN, creatinine and albumin levels, and histopathological changes were evaluated.
Results: CAT values were significantly lower in Control as compared with the Sham group. Plasma levels of MDA in the Control group were significantly higher than in the Dexketoprofen group. BUN and creatinine values were significantly higher in the Dexketoprofen group. The severity of tissue injury in the Dexketoprofen group was significantly higher than in Control and Sham groups
Conclusion: Although dexketoprofen reduces the I/R-induced systemic inflammation, it increases renal tissue damage.
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Introduction

Ischemia is a restriction or reduction of the blood flow into the tissues and reperfusion is the process of achieving renewed blood flow and reoxygenation. Renal ischemia and reperfusion (I/R) damage are among the pathological situations encountered in organ transplantation. The restriction of renal blood flow during ischemia leads to a reduction in oxygen and nutrient supply to the tissues and the pooling of harmful metabolites. As a consequence of reperfusion, reactive oxygen species (ROS) are produced in the tissues and an inflammatory response occurs.[1–3] These responses may cause irreversible tissue damage via the degradation of the nucleic acids, lipids and proteins in the cells. The cells respond to this damage through various enzymatic (glutathione peroxidase – GPx, superoxide dismutase – SOD, catalase – CAT) and non-enzymatic (alpha-tocopherol, ascorbic acid, melatonin, carotene, transferrin and ceruloplasmin) pathways.[4,5] These endogenous enzymes (GPx, SOD, CAT) activities increase to protect the tissue against the oxidative injury.[4] GPx, which is synthesized in mammalian cells, is generally considered the first line of defence against ROS. It is a sulphur containing tripeptide (glycine, cysteine, glutamine) that reduces hydrogen peroxide (H_2O_2) to water (H_2O) by using glutathione as a substrate. Superoxide dismutase, which is an oxido-reductase that contains copper, zinc or manganese at the active site, catalyses the dismutation of superoxide (O_2-) to oxygen (O_2), and H_2O_2. Catalase is a heme-protein located in peroxisomes that converts H_2O_2 to H_2O and O_2.[5] Malondialdehyde (MDA) is one of the markers for ROS and oxidative stress, and an increase in the MDA level indicates elevated levels of ROS and consequently organ damage.[6–8]

Dexketoprofen is a cyclooxygenase (COX) inhibitor that has recently come into use as a painkiller.[9,10] However, its efficacy in reducing ischemia/reperfusion damage has not been confirmed in current studies. In our study, we aimed to examine the biochemical and histopathological effects of dexketoprofen on the degree of ischemia/reperfusion damage in the rat kidney model.

Methods

Animals and experimental design

The study animals were obtained from the Experimental Animal Research Centre of Ondokuz Mayis University in Samsun, Turkey. Thirty male Wistar Albino rats weighing from 200 to 250 g were included in the study. We did not set any inclusion and exclusion criteria before the recent study except animals' unexpected death. All the subjects were cared for under appropriate conditions (temperature: 21 ± 1 °C, humidity: 40–70%, 12 hours of dark and 12 hours of light, and ad libitum feeding and access to water). The study protocol was approved by the Local Ethics Committee for Experimental Animals at Ondokuz Mayis University (Approval number: 2012/67).

The method of Altintas et al. was utilized to perform renal I/R.[2] The rats were anesthetized with ketamine – xylazine (100–20 mg.kg^{-1}). Animals were block randomized by random numbers (Microsoft Office 365 Excel, Microsoft, Redmond, WA, http://www.microsoft.com) and allocated to 3 treatment groups, with 10 rats in each group, as follows:

Group C (Control group): 1 mL of intraperitoneal saline was injected 40 minutes before the surgical procedure. Laparotomy was performed with a medial line incision. The right and left renal veins and arteries were clamped to induce 60 minutes of ischemia. At the end of the ischemia period, reperfusion was provided for 23 hours. After the reperfusion period the left kidney was removed for pathological evaluation and the right kidney was removed for biochemical analysis.

Group D (Dexketoprofen group): A total of 1 mL (25 mg) of dexketoprofen was injected 40 minutes before the surgical procedure. The rest of the procedure was as per that for Group C.

Group S (Sham group): Laparotomy was performed with a medial line incision, which was then closed without any additional procedures.

Three different investigators were involved as follows for each animal: a first investigator performed the anaesthetic and surgical procedure based on the randomization table. This investigator was the only person aware of the treatment group allocation. A second investigator was responsible for the biochemical analyses, and the third investigator performed the histopathological evaluation.

For postoperative pain management all rats received a subcutaneous injection of 0.1 mg.kg^{-1} buprenorphin (Temgesic; Schering-Plough, Brussels, Belgium). After the procedures were completed, blood was drawn via a cardiac puncture. Rats have immediately been euthanized at the end of cardiac puncture by intraperitoneal sodium thiopental (40 mg.kg^{-1} body weight) (Pental Sodium, İbrahim Etem, İstanbul, Turkey). The plasma MDA (MDA_p), renal tissue MDA (MDA_t), plasma GPx, CAT, SOD, blood urea nitrogen (BUN), creatinine (Cr), albumin levels and histopathological changes were evaluated.

Sample preparation and analyses

The extraction method of plasma malondialdehyde (MDAp)

The extraction method of plasma malondialdehyde was conducted according to the method described by Yoshioko et al.[11]

The extraction method of renal tissue malondialdehyde (MDAr)

The renal tissue samples were prepared according to the method of Celik and Suzek.[12] The tissues were homogenized for five minutes in 50 mM of cold KH_2PO_4 solution (1:5 w/v) by using a homogenizer (Dounce homogenizer Sigma-Aldrich Co. LLC, St. Louis, MO, USA). The homogenates were centrifuged at 3000 g for 20 minutes at 4 °C. To 0.5 mL of each sample; 2.5 mL of 20% TCA solution and 1 mL of 0.67% TBA solution were added. The MDA level was then determined by HPLC (High Performance Liquid Chromatography) method.

Instrumentation and chromatographic conditions

Renal tissue and plasma MDA levels were measured according to the method described by Agarwal and Chase.[13] The HPLC system consisted of multichannel pumps (LC 20AT), an

auto sampler (SIL 20ACHT) and fluorescence detector (FLD) (RF-10AXL) (Shimadzu, Kyoto, Japan). A reverse-phase C_{18} column (Inertsil® ODS-3V, 5 μm, 4.6 x 250 mm, GL Science, Tokyo, Japan) was used for the MDA determination. The mobile phases consisted of a 40:60 ratio (v/v) of methanol to 50 mM of potassium monobasic phosphate at pH 6.8, adjusted with potassium hydroxide. All the chemicals were purchased from Merck, Darmstad, Germany. The flow rate of the mobile phases was 1 $mL.min^{-1}$, and the column oven temperature was set at 30 °C. The FLD was set at an excitation wavelength of 515 nm and an emission wavelength of 553 nm. The injection volume was 20 μL and the run time was 10 minutes per analysis.

Biochemical analyses

Glutathione peroxidase

The analysis of the GPx level was conducted with the GPx assay kit, according to the instructions provided by the manufacturer (Cayman Chemical Company, USA). The absorbance values were read at the wavelength of 340 nm.

Superoxide dismutase

The analysis of the SOD level was conducted with the GPx assay kit, according to the instructions provided by the manufacturer (Cayman Chemical Company, USA). The absorbance values were read at 440 nm.

Catalase

The analysis of the SOD level was conducted with the GPx assay kit, according to the instructions provided by the manufacturer (Cayman Chemical Company, USA). Absorbance values were read at a wavelength of 540 nm.

The blood samples were centrifuged (Shimadzu UV160A, S. No: 28006648, Japan) at 3000 g for 10 minutes and the serums were stored at -80 °C. The stored samples were thawed at room temperature on the day of analysis. All assays were conducted according to the manufacturer's instructions.

The concentrations of BUN in the serums were analysed with by using commercially available kinetic UV assay kits (Roche Diagnostics GmbH, Ref.No.11729691, Mannheim, Germany).

The concentration of creatinine in the serum was analysed with Jaffe colorimetric assay kits (Roche Diagnostics GmbH, Ref.No.06407137, Mannheim, Germany). This kinetic colorimetric assay is based on the Jaffé method.[14]

The concentration of albumin in the serum was analysed with a Roche Hitachi Cobas 8000 device and by using a commercially available colorimetric assay kit (Roche Diagnostics GmbH Ref. No.05166861 Mannheim, Germany).

After the kidney tissues had been fixed for 24 hours in a 10% formaldehyde solution, they were dehydrated in ethanol and embedded in paraffin wax. Sections of 5 μm thickness were cut and stained with haematoxylin and eosin for histopathological evaluation. The kidney sections obtained from rats were examined under a light microscope (Nikon, Eclipse E600). Kidney damage was graded semi-quantitatively on a scale of 0–4, with: 0 (zero), normal histology; 1, tubular dilation; 2, degeneration only without necrosis; 3, tubular necrosis with adjacent structure intact; 4, when tubular necrosis with total loss of structure.

Sample size and statistical analysis

A power analysis was performed considering SOD values as a primary endpoint. The sample size was estimated in 10 rats per group in order to determine a mean difference of 2.11 ± 1.12 units/mL, with a 95% confidence interval and power of 95%.[2]

Statistical analyses were performed with SPSS 21.0 for windows. Data were presented as mean ± standard deviation (SD), or as median and interquartile range (IQR). The Shapiro–Wilk test was used to analyze the normal distribution of the quantitative outcomes. One-Way ANOVA followed by Tamhane test were used to analyze parametric data. Kruskal–Wallis analysis of variance was used to compare non parametric data, and then Mann Whitney U test with Bonferroni correction was used for pairwise comparison. A *p*-value less than 0.05 was considered statistically significant.

Results

Glutathione peroxidase, superoxide dismutase, and catalase levels in the blood

There was no statistically significant difference between groups regarding SOD and GPx levels ($p \geq 0.05$) (Table 1). The CAT values were significantly lower in Group C than in Group S ($p = 0.018$) (Table 1).

Malondialdehyde levels in kidney tissues

There was no statistically significant difference between groups regarding the tissues MDA levels ($p \geq 0.05$) (Table 1). The HPLC chromatogram for MDA for the kidney tissue samples is shown in Figure 1.

Plasma malondialdehyde levels

The plasma MDA levels were significantly higher in Group C than in Group D ($p = 0.001$) (Table 1). The HPLC chromatogram for MDA for plasma samples is shown in Figure 2.

Blood urea nitrogen, creatinine, and albumin levels

The BUN and Cr values were significantly higher in Group D than in Groups C and S ($p < 0.001$). These values were significantly higher in Group C than in Group S ($p < 0.001$). In addition, there were no significant differences among the groups regarding their albumin levels ($p \geq 0.05$) (Table 2).

Histopathological analysis

When the changes in the kidney tissues were histopathologically analysed under a light microscope in terms of necrosis, degeneration, tubular dilatation, protein cylinders and interstitial, lymphocyte infiltration, no pathological changes were observed in Group S. In Groups C and D which were subjected to I/R, degeneration, tubular dilatation, and

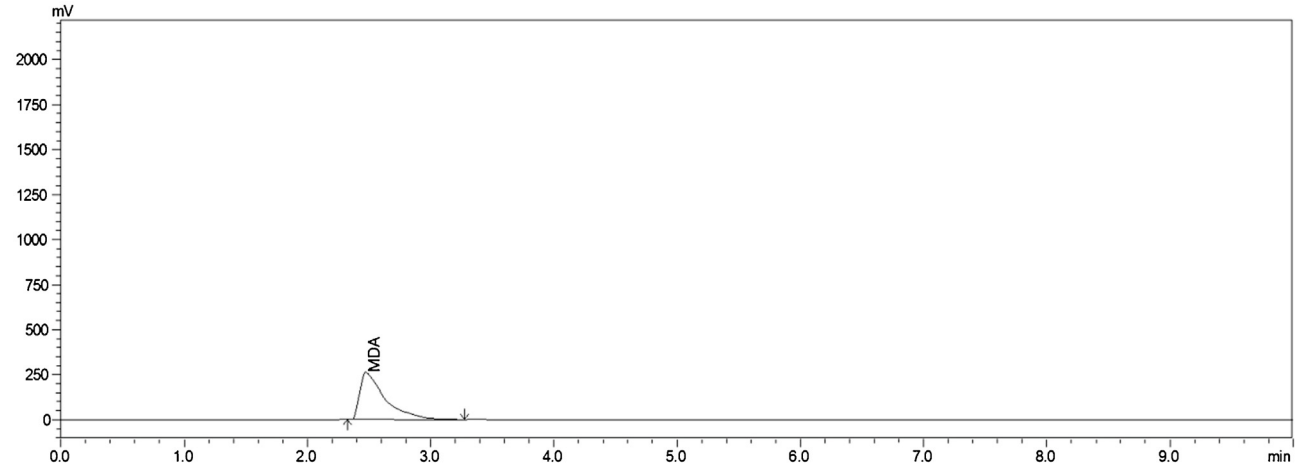

Figure 1 HPLC-FLD chromatogram for kidney tissue samples. HPLC-FLD, high performance liquid chromatography with fluorescence detection; MDA, malondialdehyde.

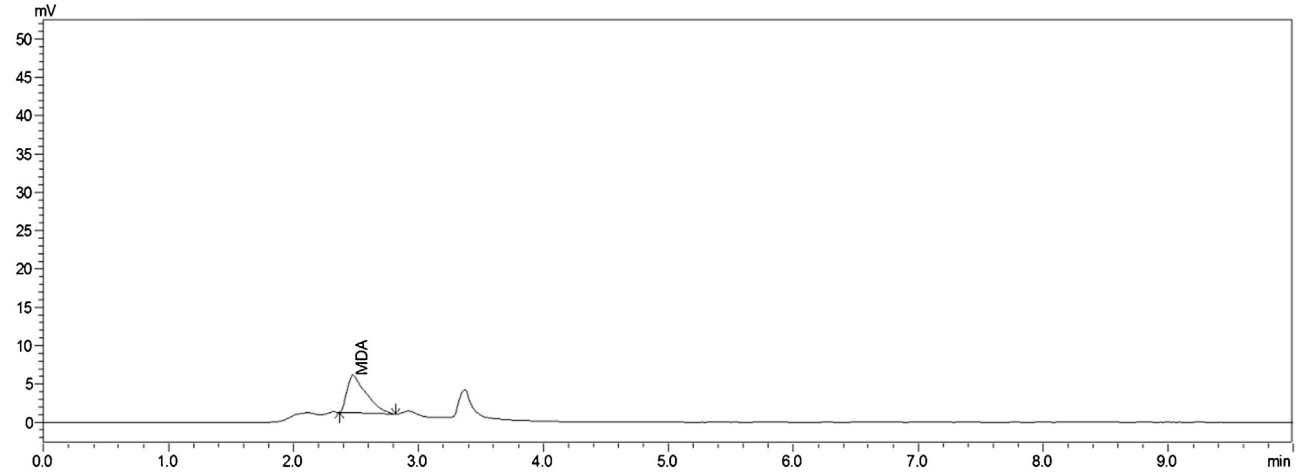

Figure 2 HPLC-FLD chromatogram for plasma samples. HPLC-FLD, high performance liquid chromatography with fluorescence detection; MDA, malondialdehyde.

protein cylinders were detected; these pathological changes were more prominent in Group D than in Group C (Fig. 3).

Kidney damage scores were higher in the Group D than in

Table 1 Results of CAT, SOD, GPx' and MDA analyses for *Wistar albino* rats.

	Group D	Group C	Group S	*p*
CAT ($nmol.min^{-1}.mL^{-1}$) Mean ± SD	158.4 ± 75.9	106.3 ± 39.4[a]	176.1 ± 57.4[b]	0.037
SOD ($units.mL^{-1}$) Median (Min–Max)	37.6 (32.3–44.4)	31.5 (23.9–43.1)	36.8 (29.5–63.3)	0.179
GPX ($nmol.min^{-1}.mL^{-1}$) Median (Min–Max)	30.5(23.4–49.9)	30.1(24.4–42.7)	32.6 (29.5–39.7)	0.212
MDAt ($\mu M.mg^{-1}$) Median (Min–Max)	0.08 (0.04–0.30)	0.10 (0.07–0.14)	0.09 (0,05–14)	0.067
MDAp ($\mu M.mL^{-1}$) Median (Min–Max)	0.87 (0.72–1.1)[b]	1.22 (0.95–1.67)	0.94 (0.78–1.94)	0.003

CAT, catalase; SOD, superoxide dismutase; GPx, glutathione peroxidase; MDAt, renal tissue malondialdehyde; MDAp, plasma malondialdehyde.

[a] $p < 0.05$ versus Group S.

[b] $p < 0.05$ versus Group C.

Table 2 Results of BUN, Cr and albumin analyses for *Wistar albino* rats.

	Group D	Group C	Group S	*p*
BUN ($mg.dL^{-1}$) Median (Min–Max)	119.6 (36.4–146.6)[a,b]	29.7 (21.8–115.8)[a,c]	18.9 (14.9–26.3)[b,c]	< 0.001
Cr ($mg.dL^{-1}$) Median (Min–Max)	1.98 (0.51–2.96)[a,b]	0.47 (0.28–1.89)[a,c]	0.28 (0.25–0.32)[b,c]	< 0.001
Albumin ($gr.dL^{-1}$) (Mean ± SD)	2.31 ± 0.58	2.42 ± 0.37	2.59 ± 0.65	0.527

BUN, blood urea nitrogen; Cr, creatinine.
[a] $p < 0.05$ versus Group S.
[b] $p < 0.05$ versus Group C.
[c] $p < 0.05$ versus Group D.

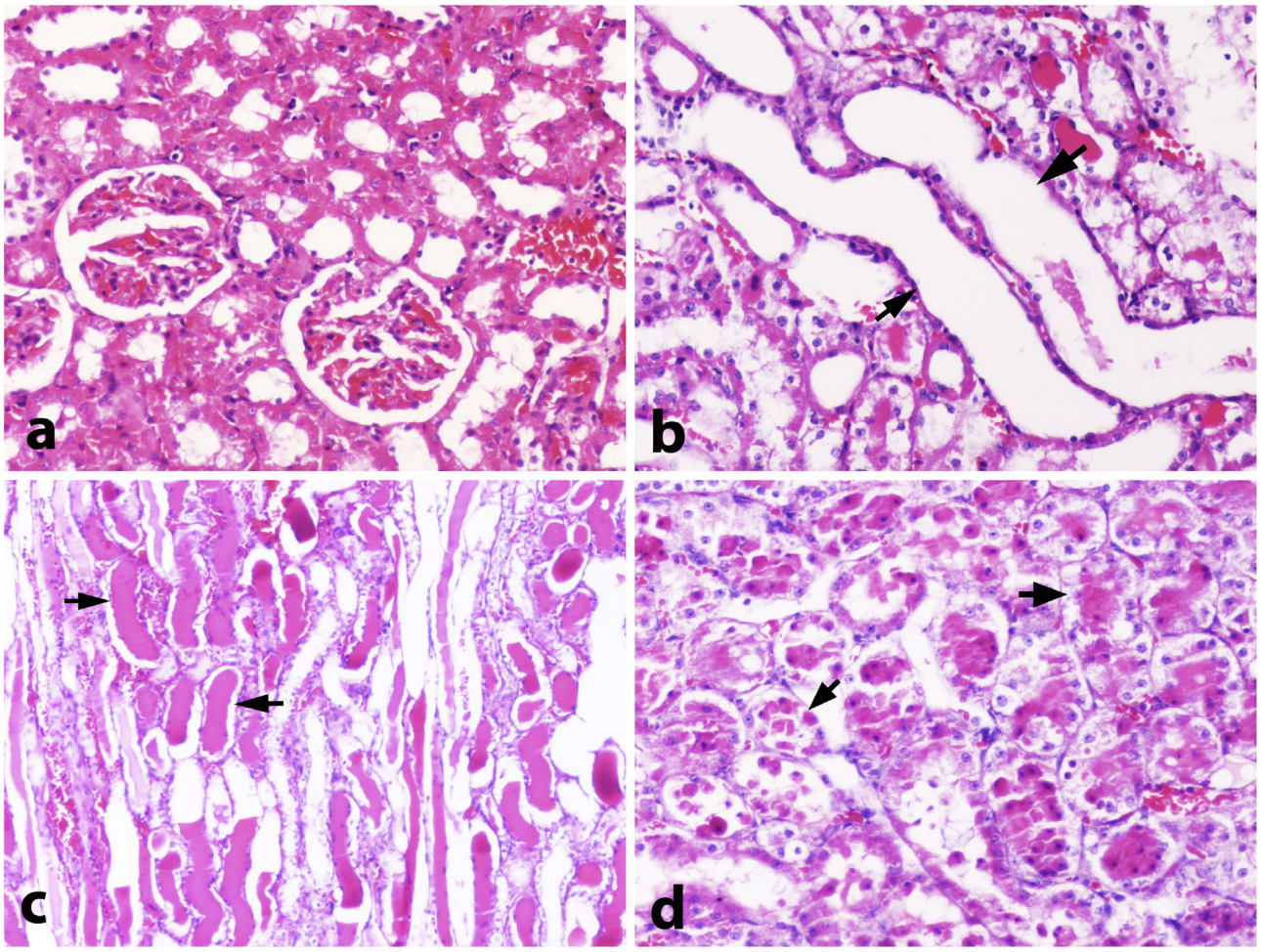

Figure 3 Appearance under light microscopy of kidney sections from the rats in Group C, S and D: (a) normal histological appearance in Group S, (b) mild tubular dilatation (arrowed) in Group C, (c) diffuse protein cylinders (arrowed) in tubule lumens in Group D, (d) diffuse necroses (arrowed) in tubule lumens in Group D (Haematoxylin&Eosin staining, a, b, d x240; c x120).

the Group C and S (median [Inter Quartile Range], 2 [2.25], 1 [0.00], 1 [0.00], respectively) ($p = 0.001$).

Discussion

This study has demonstrated that renal I/R caused an increase in plasma levels of MDA, BUN, and Cr and decrease in CAT plasma levels. However, plasma levels of GPx, SOD, albumin, and tissue MDA were not affected by renal I/R. The administration of dexketoprofen, in association with I/R, reduced plasma levels of MDA and increased BUN and Cr plasma levels. I/R caused major histopathological changes in the kidney tissues and dexketoprofen increased this damage.

The acute ischemia that occurs in situations such as kidney transplantation, trauma, surgery, and cardiopul-

monary bypass is among the major causes of acute kidney failure.[15,16] Ischemia initiates cellular damage because there is insufficient blood flow to sustain the cells' normal metabolic activities. Reperfusion leads to a higher rate of formation of ROS and increases the amount of tissue damage by triggering inflammation.[17] In the current study, we aimed to investigate the potential protective effects of dexketoprofen, which is an NSAID, against renal I/R damage.

Excessive production of ROS and oxidative stress play a major role in the pathophysiology of renal I/R damage because they negatively affect proteins, membrane lipids and nucleic acids in kidney tissues.[2,3] However, this harmful process is counteracted by GPx, SOD and CAT enzymes that reduce the kidney damage induced by I/R.[2] GPx, SOD and CAT, and that the administration of antioxidant and anti-inflammatory drugs provides relative protection of the levels of these enzymes by minimizing inflammation and reducing kidney damage.[2,3,18,19] Altıntaş et al.[2] showed in a renal I/R model that the SOD and CAT levels in rats that had been administered dexpanthenol were higher than those in the control group. Furthermore, Tasdemir et al.[3] demonstrated in a renal I/R model for rats that the immunomodulator, infliximab, increased both SOD and GSH levels. In addition, Süleyman et al.[18] administered the selective COX-2 inhibitor, etoricoxib, in a rat I/R model. In comparison with the control group, etoricoxib better maintained tGSH, SOD and CAT levels and hence reduced renal damage via its antioxidant, anti-inflammatory and anti-apoptotic effects.

MDA is an important indicator of oxidative stress. The blood and tissue levels of MDA increase in response to lipid peroxidation caused by I/R damage. Several studies have shown an increase in MDA levels due to lipid peroxidation caused by renal ischemia, and that this increase can be reduced by the administration of anti-inflammatory and antioxidant agents.[2,3,20,21] In our study, the plasma MDA levels increased in Group C but the administration of dexketoprofen significantly decreased the plasma MDA levels in Group D by suppressing lipid peroxidation.

NSAIDs have been commonly used for a long period but their side effects are frequently encountered. NSAID-related renal dysfunction is dependent on dosage and exposure time. Even their short-term usage may disrupt renal function in sensitive individuals. This disruption in renal function is evidenced by increases in serum BUN and Cr levels.[22–24] NSAIDs cause renal damage by inhibiting the synthesis of prostaglandin (PG).[22] Altıntaş et al.[2] demonstrated that renal I/R increases both BUN and Cr levels. Bolat et al.[23] demonstrated that diclofenac, which is an NSAID, increased BUN levels to a dose-dependent degree. Similarly, in the current study, BUN and Cr levels increased in response to I/R. Additionally, dexketoprofen caused higher BUN and Cr levels by increasing renal damage. In addition to I/R damage, the reduction of vasodilator PG synthesis due to the effects of dexketoprofen also increases renal damage by reducing glomerular capillary pressure.[24]

NSAIDs inhibit COX-1 and COX-2 activity which affects the renal vascular tonus.[25] The extent of renal damage depends on the accumulation of the reactive metabolites that are formed in response to I/R. The usage of NSAIDs may increase this damage by causing vasospasm in renal vascular structures, because they reduce the activity of reactive metabolites through COX inhibition.[24–26] In our study, I/R caused renal damage. The administration of dexketoprofen further increased the renal damage. This damage appears to have increased due to renal vascular spasms that occurred because of COX inhibition by dexketoprofen. The diffuse protein cylinders in the tubule lumens and diffuse necroses in the tubules of the kidney tissues in Group D also support this view.

There are a few limitations in this study. First, we could not test the immunohistochemistry of kidneys due to a lack of funds and equipment. Second, analyzing acute kidney injury biomarkers could have been beneficial.

Conclusions

In the present study, dexketoprofen reduced systemic inflammation related to a renal ischemia/reperfusion animal model, but it caused significant renal tissue damage. Therefore, we consider that its usage is not appropriate in the presence of renal hypoperfusion and ischemia. However, it may be useful to conduct further studies with different doses of dexketoprofen to better understand its role in the ischemia/reperfusion scenario.

Ethical approval

The experimental protocol of this study was reviewed and approved by the Animal Care and Use Committee of Ondokuz Mayis University, Samsun, Turkey (Ethical Committee Approval Number: 2012/67) and carried out according to the Animals in Research: Reporting In Vivo Experiments (ARRIVE) statement. Also this manuscript adheres to the Enhancing the Quality and Transparency of Health Research (EQUATOR) guidelines.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Is Jedi Grip efficient and effective in ultrasound-guided peripheral nerve blocking? A prospective, randomized, observer-blinded study

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KEYWORDS
Brachial plexus blockade;
Ultrasound, Interventional;
Anesthesia, Regional

Abstract
Background: In this prospective, randomized, controlled observer-blinded study, we aimed to compare the efficacy of a single-operator technique called the Jedi Grip and a conventional technique requiring a double operator in ultrasound–guided axillary brachial plexus blocking.
Methods: Ninety-two patients (ASA I–II; aged 18–65 years old) who underwent elective hand, wrist and forearm surgery were randomly assigned to Group Conventional (C) or Group Jedi (J). In both groups, axillary plexus blockade was performed by applying 5 cc of a mixture of 10 cc of 0.5% bupivacaine and 10 cc of 2% prilocaine to the ulnar, radial, median, and musculocutaneous nerves. Parameters such as the performance time and number of needle passes were recorded during the procedure. Subsequently, a blinded observer evaluated and recorded parameters related to the blockade success. The main outcome variables were the performance time and success rate (surgical anesthesia).
Results: The block performance time of the Jedi technique was slightly longer than that of the conventional technique (220 (50), 202 (78) s, respectively) (*median (IQR)*; $p = 0.05$). No significant difference was found between groups in terms of blocking success; 9 (20%) from the conventional group and 3 (6.4%) from the Jedi group were unsuccessful ($p = 0.053$). No differences were found in terms of arterial puncture, and no other complications occurred in either group. The motor-sensory block onset and termination times and initial analgesia requirements were similar.
Conclusion: The Jedi technique may be applied safely with similar block success and performance results as the conventional technique.
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Introduction

Ultrasound guidance has almost entirely changed and improved the practices of peripheral nerve blocks for the last two decades. However, ultrasound-guided block cannot eliminate complications such as accidental vascular injury, hemidiaphragm paralysis, and pneumothorax although it reduces these risks. Additionally, meta-analyses considering the relevant new literature cannot show evidence of reducing the incidence of peripheral neural injury.[1,2]

Ultrasound-guided regional anesthesia procedures are typically performed by two operators, one controlling both the ultrasound probe and peripheric block needle position, and the other assistant operator controlling the aspiration and injection of the local anesthetic (LA). Control of anesthetic injection is crucial to the success of the regional anesthesia. A disadvantage of this common habit is preventing the operator from perceiving the sense of resistance in the syringe plunger, indicating an intraneural needle tip position. Additionally, this technique requires an assistant who must have knowledge about the procedure and a good communication and coordination.[3,4] The absence or failure of the abovementioned elements might be a potential source of error while administering several small boluses as the needle tip is repositioned to optimize the spread of LA around nerves.

Several single-operator grip techniques of the needle and syringe for ultrasound (USG)-guided peripheral block have been described allowing the provider to perform independently to overcome the abovementioned situations, and these techniques have been criticized based on personal experience.[3–8] Although methods have been described in the literature, the classical method has not been compared with single-operator methods in any prospective, randomized controlled study. One of these techniques is called the Jedi Grip, defined by Pappin and Christie.[3] The peripheral block needle is held between the index finger and middle phalanx of the middle finger, and the syringe is held with fingers 4 and 5, with the plunger part to the thumb in the palm. The Jedi technique allows the operator to perform aspiration or injection by releasing the thumb.

In this study, we aimed to compare the Jedi technique and conventional peripheral block technique with an assistant in a prospective, randomized, controlled and observer-blinded study on patients who underwent elective hand, wrist and elbow surgery under axillary brachial plexus block in terms of various parameters including block success and the application time.

Methods

After obtaining ethics committee approval (SBU Ankara Numune SUAM Clinical Research Ethics Committee, numbered E-18-1955 and dated 25/04/2018) and written informed consent, this single-center, prospective, randomized, observer-blinded study was conducted between May 2018 and February 2019 at Ankara Numune Education and Research Hospital (Ankara). The trial was registered at Clinical Trials.gov (NCT04463329).

One hundred patients (aged between 18 and 65 years with American Society of Anesthesiologists [ASA] physical status I to II) undergoing elective hand, wrist and forearm surgery were prospectively enrolled. Eight patients were excluded from the study because of data loss. The inclusion criteria were age between 18 and 65 years, ASA I–II, and body mass index (BMI) between 18.5 and 35 $kg.m^{-2}$. The exclusion criteria of the study were as follows: hepatic or renal failure, serious cardiac or pulmonary disease, local or systemic infection, sepsis, coagulation disorder, neurological, muscular or psychiatric disease, body mass index (BMI) below 18.5 or above 35, drug and substance abuse, pregnancy, refusal of regional anesthesia, history of allergy to LA, mental-motor retardation (inability to consent or assess the visual analog scale [VAS] pain score), preoperative long-term non-steroidal anti-inflammatory drugs (NSAID) or opioid use, and prior surgery in the axillary regions.

After creating 2 sets of 50 unique numbers from 1 to 100 for each group using an internet-based program (www.randomize.org), the patients were randomly allocated to one of the two groups as Group C (n = 50, conventional two-operator axillary brachial plexus blockade) and Group J (n = 50, axillary brachial plexus block with a single operator using Jedi grip).

A peripheral intravenous cannula (20–22G) was placed in the upper limb contralateral to the surgical site, and 1–2 mg of midazolam was administered before transferring to the operation room. Standard ASA monitoring was applied throughout the procedure, including the noninvasive arterial blood pressure, heart rate, and pulse oximetry. As a safety precaution, the anesthesia machine was tested, and general anesthesia drugs were prepared.

All the blocks were performed by the same researcher who practiced the Jedi technique before starting the study using polymer gel position pads by targeting a point with air injection and using the Jedi technique for almost 2 months in clinical practice before the study.

The same peripheral block needle and ultrasound machine were used for all the patients (a 22G, 5-cm long, short-beveled, teflon-coated needle (Locoplex; Vygon, France) and linear 38-mm, high-frequency 6 to 13 MHz transducer (Logiq e; General Electric, United States).

The patients in both groups were placed in the supine position, the arm was abducted 90 degrees on the side of the block, the elbow was flexed 90 degrees, and the head was turned to the shoulder side where the procedure was not performed. Skin disinfection was performed with povidone iodine and the patient was covered with a sterile drape. The 5 to 12 Millihertz linear USG probe (Logiq e, General Electric, USA) was covered with a sterile transparent sheath. A mixture of 10 cc of 0.5% bupivacaine and 10 cc of 0.2% prilocaine was prepared for a 20-cc syringe.

The axillary brachial plexus block was applied to patients either by the conventional two-person technique or one-person Jedi technique according to the allocated group. In Group C, the operator used the probe and needle with different hands while an assistant controlled the syringe to aspirate or inject LA. In Group J, a single operator controlled the probe with one hand while controlling the needle and syringe with the Jedi technique. The needle was held between the index finger and the middle phalanx of middle finger, and the syringe was held with fingers 4 and 5, with the plunger part to the thumb in the palm. Before the injection, the needle was absolutely aspirated to ensure that the



Figure 1 An example of the Jedi Grip performed at our hospital.

needle was not in the vein. Injection and aspiration were performed with thumb (Fig. 1A and B).

The procedure was the same in both groups except for the needle-holding technique. The ultrasound probe was positioned in the axilla at the lateral border of the pectoralis major muscle and perpendicular to the axis of the arm to obtain a short-axis view of the axillary artery and its surrounding nerve bundle. Image quality was optimized with the selection of the appropriate depth (within 2–3 cm), focus range (within 1 cm) and gain. The hyperechoic median, ulnar, and radial nerves were visualized around the axillary artery. With slight proximal-distal movement of the transducer, the musculocutaneous nerve or plane between the coracobrachialis and biceps muscles were visualized. After obtaining a satisfactory image, the imaging time (defined as the time interval between contact of the ultrasound probe with the patient to visualization) was recorded.

The needle was inserted in-plane from the anterior aspect and directed toward the posterior aspect. Nerves were separately imaged, and a 5-cc LA mixture was administered first to the radial, ulnar, median, and musculocutaneous nerves in all the patients. After the end of LA injection, the needling time (defined as the time between the entry of the needle through the skin to the end of local anesthesia) was recorded. The performance time was defined as the sum of the imaging and needling times. The number of needle passes and complications, such as paresthesia and vascular puncture, were also recorded.

After completion of the block, a single–blinded observer recorded the demographic data and questioned the patients about pain related to the block procedure using a 10-cm visual analog scale (0 cm = no pain, 10 cm = worst imaginable pain). The patients were also questioned for symptoms related to LA toxicity.

Subsequently, measurements of the brachial plexus blockade were performed every 5 minutes until 30 minutes by the same single–blinded observer.

Sensory blockade was evaluated and graded from the lateral side of the forearm, volar face of the thumb, volar face of the 5th finger and lateral side of the hand back for the musculocutaneous, median, ulnar, and radial nerves, respectively. Grading was performed according to a previously validated 3-point scale using a cold test: 0 = no block, 1 = analgesia (patient can feel touch, not cold), and 2 = anesthesia (patient cannot feel touch).[9–11]

Motor blockade was evaluated and graded with elbow flexion, thumb abduction, thumb opposition, and thumb adduction for the musculocutaneous, radial, median, and ulnar nerves, respectively. Motor blockade grading was also performed according to a (validated) 3-point scale: 0 = no block, 1 = paresis, and 2 = paralysis.[9,11]

Motor and sensory examinations were performed for all four nerves every five minutes, and the sum of the results was recorded as the composite score. The overall maximal composite score was 16 points. When the total composite score was a minimum of 14 or higher (with a sensory component of 7 or more), the patient was considered ready for surgery. The time until the composite score was 14/16 and above was defined as the anesthesia onset time, i.e., the time to reach surgical anesthesia.[8,10]

The sensory block onset time was defined as the time from the end of block application until the sensory block score was at least 1 point in any of the radial, ulnar, median, or musculocutaneous nerves. The motor block onset time was defined as the time from the end of block application until the motor block score was at least 1 point in any of the radial, ulnar, median, or musculocutaneous nerves.

After the operation, the time to at least one point of regression in the sensory block and first analgesic requirement was measured, and the severity of pain was assessed with VAS. Patient satisfaction was also evaluated using a 4-point Likert scale as follows: 4: excellent; 3: good; 2: fair; and 1: poor.

Statistical analysis

The number of patients required for each group was determined using the G-Power 3.1.9.4 package program. Anticipating a 1-minute difference in the needling time was significant, and the estimated sample size was 45 per group with d = 0.60 (effect size), α = 0.05 and power = 80%. We planned to conduct the study with 100 patients to ensure adequate final numbers.

Table 1 Characteristics of the patients.

Variables	Conventional (n = 45)	Jedi (n = 47)
Age (year), Mean ± SD	38.82 ± 12.29	33.47 ± 11.66
Height (cm), Mean ± SD	170.98 ± 8.30	171.66 ± 8.16
Weight (kg), Mean ± SD	77.66 ± 14.36	72.87 ± 11.19
BMI ($kg.m^{-2}$)	26.52 ± 4.45	24.72 ± 3.65
Gender, n (%)		
Female	7 (15.6%)	9 (19.1%)
Male	38 (84.4%)	38 (80.9%)
Asa physical status, n (%)		
I	9 (20%)	13 (27.7%)
II	36 (80%)	34 (72.3%)

The IBM SPSS 20 statistical package program was used for data analysis. For all statistics, the significance limit was set at $p < 0.05$. Categorical data were expressed as absolute and relative frequencies. Continuous variables were expressed as means and standard deviation, when normally distributed, and as medians and quartiles or interquartile ranges for those without a normal distribution. The Shapiro-Wilk test was used to examine the compatibility of the data for normal distribution. Chi-squared test and Fisher's exact test were used to compare categorical variables between the two groups. Group comparisons of continuous data with a normal distribution were analyzed using *t*-test, and group comparisons of data did not show a normal distribution were analyzed using the Mann-Whitney U test.

Results

One hundred patients who underwent hand, wrist and forearm surgery were randomly assigned to 1 of 2 groups. Eight patients were excluded from the study because of incomplete data due to early discharge. Finally, 92 patients (Group C, n = 45; Group J, n = 47) were included in the study (Fig. 2).

The characteristics of patients are presented in Table 1. The weight, height, sex and ASA status were similar between groups ($p > 0.05$) but there was a statistically significant difference in age and body mass index (BMI) ($p < 0.05$) (Table 1).

The imaging times were similar between groups, but the needling and block performance times of the Jedi technique were slightly longer than those of the conventional technique ($p < 0.05$) (Table 2). No statistically significant difference was found between the two groups in terms of arterial puncture, number of needle entries, pain (VAS) during the procedure, block success or need for additional anesthesia ($p > 0.05$) (Table 3).

The onset times of sensory block, motor block and anesthesia were similar between the groups ($p > 0.05$). The sensory and motor block regression times were evaluated only in patients with successful block and were similar between groups ($p > 0.05$) (Table 3).

No statistically significant difference was found between the groups in terms of the postoperative VAS values (Group C 4.5 ± 2.08 and Group J 4.4 ± 2.16; $p = 0.478$). The postoperative VAS score was not assessed in patients with block failure.

No statistically significant difference was observed between the groups in terms of the time to first analgesia requirement. In both groups, the patients did not require analgesics for at least 10 hours after block (Group C: 10.72 ± 3.2 h, Group J: 10.61 ± 3.5 h; $p = 0.889$).

No statistically significant difference was found between the two groups in terms of patient satisfaction (Table 4). No differences were found in terms of arterial puncture, and no other complications occurred in either group during block and intraoperative or postoperative follow-up.

Discussion

Various single-operator ultrasound-guided peripheral block methods have been described in the literature.[3–8] These methods have been criticized based on personal experience.[7] However, to date, no prospective randomized controlled study has compared the classical two-operator method and single-operator methods.

Our results suggest that the Jedi technique achieves similar success rates with slightly longer block performance times than the conventional two-operator block technique. The anesthesia onset times were similar between groups.

Ultrasound guidance has been reported to reduce regional anesthesia-related complications.[1] In ultrasound-guided regional anesthesia, it is possible to determine the localization of the nerve and clearly observe the drug spread during the administration of LAs. Based on the relevant literature, it is reasonable to assume that the use of USG can lead to improvements in patient safety by reducing nerve damage, LA systemic toxicity (LAST), or other complications. However, the American Regional Anesthesia Association (ASRA) also states that the use of ultrasound does not reduce the incidence of regional neural injury associated with regional anesthesia.[1,2]

Although tactile pressure sensation in the injection piston is accepted as subjective data,[12,13] the use of various methods together would likely increase the safety level.

Conventionally, in ultrasound-guided peripheral nerve blocks, aspiration and injection are performed by an assis-

Table 2 Comparison of imaging, needling, and block performance times between groups.

Variables	Conventional (n = 45)	Jedi (n = 47)	Hodges Lehman estimate	95% CI		*p*-value
				Lower	Upper	
Imaging time (s)[a]	3 (1)	3 (2)	0	-1.00	0.00	0.081
Needling time (s)[a]	202 (78)	220 (50)	-30	-50	-5	0.010
Block performance time (s)[a]	205 (76)	227 (50)	-31	-52	-7	0.009

[a] The variable is expressed as median (IQR) and Mann-Whitney U test was used for comparison.

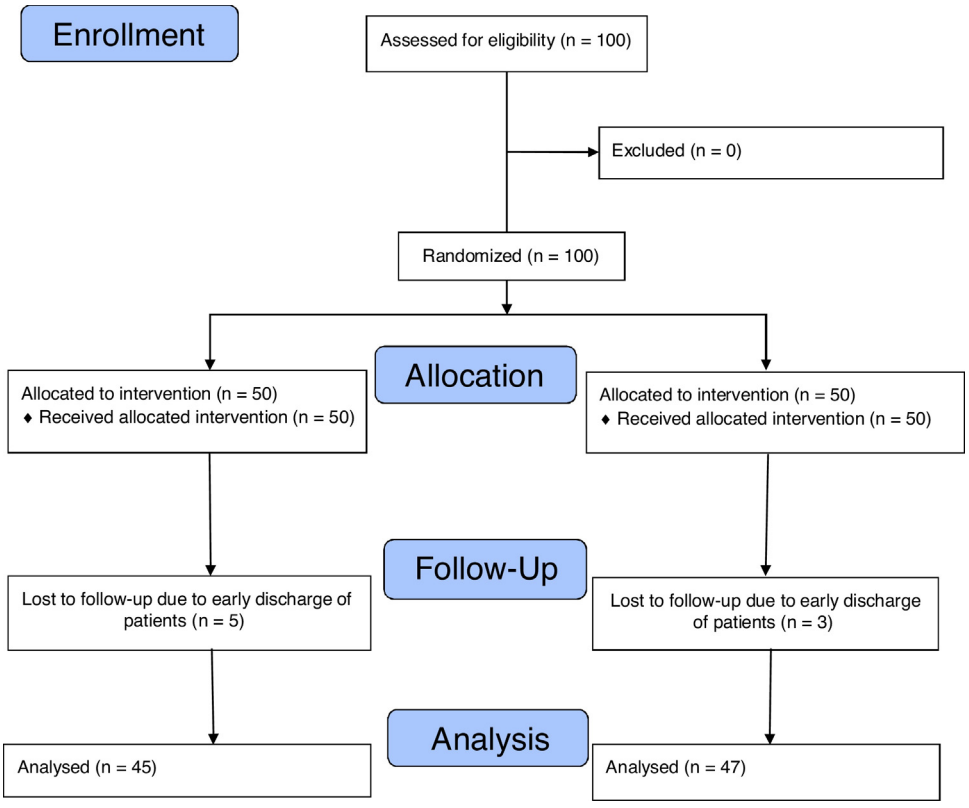

Figure 2 Flow chart of the study.

Table 3 Comparison of block characteristics and success between groups.

Block characteristics	Conventional (n = 45)	Jedi (n = 47)	*p*-value
Pain During Procedure (VAS)[a]	0 (1)	0 (1)	0.332
Number of Needle Entries, n (%)[b]			
1	44 (97.8%)	47 (100)	0.489
2	1 (2.2%)	0 (0)	
Arterial Puncture, n (%)[b]	6 (13.3%)	6 (12.8%)	0.936
Unsuccessful, n (%)[b]	9 (20%)	3 (6.4%)	0.053
Conversion to general anesthesia, n (%)[b]	9 (20%)	7 (14.9%)	0.518
Sensory block onset time (min)[a]	5 (0)	5 (0)	0.189
Motor block onset time (min)[a]	5 (5)	5 (5)	0.329
Anesthesia onset time (min)[a]	20 (4)	20 (5)	0.102
Sensory block regression time, n (%)[b]			
2–8 hours	27 (75%)	25 (56.8%)	0.090
8–18 hours	9 (25%)	19 (43.2%)	

[a] The variable is expressed as median (IQR) and Mann-Whitney U test was used for comparison.
[b] Chi-squared test or Fisher's exact test were used where appropriate.

tant while the anesthesiologist holds the USG probe in one hand and the peripheral block needle in the other. Singh et al.[14] reported the current practice among anesthesiologists from a closed Facebook group questionnaire. As expected, in this study, most of the participants used conventional techniques except for those using alternative single operator let-go techniques (17.3%). It can be assumed that the disadvantage of this technique is to drop the needle free at the injection stage without control.

Pappin and Christie[3] stated that the practitioner cannot sense the piston pressure of the syringe, indicating intraneural injection. They also indicated that smaller doses of bolus injections at different points around the nerve sheath are required to achieve LA spread in USG-guided blocks, leading to communication and coordination problems between the practitioner and assistant. They described the Jedi needle holding technique as a precaution against these problems. According to Pappin and Christie, the amount of LA injected can be reduced as the time and quantity of the injection

Table 4 Comparison of patient satisfaction between groups.

Variables	Conventional (n = 45)	Jedi (n = 47)	*p*-value
Patient satisfaction, n (%)			
Fair and poor	9 (20%)	3 (6.4%)	0.053
Good and excellent	36 (80%)	44 (93.6%)	

passes to the practitioner's control without the need for communication and coordination.[3,4]

The Jedi technique has been criticized based on personal experience because of the difficulty of using a 20-ml syringe and involuntary shift of the needle tip position during aspiration.[7] However, the justification of these criticisms in the literature has not been proven by prospective randomized controlled studies. The Jedi technique is the only single-operator technique that allows injection and aspiration without leaving control of the needle.

In this study, we aimed to compare the Jedi method described by Pappin[3] and the classical peripheral block method with an assistant in a prospective randomized and controlled study on patients who underwent axillary brachial plexus block in terms of various parameters, including block success and application time.

Thus, we found that the Jedi technique slightly increased the performance time. For all that, the Jedi technique did not increase the complications of arterial puncture, number of needle entries, or the patient's pain (VAS) during the procedure.

Sensory-motor block and the anesthesia onset time (time to reach surgical anesthesia) in the Jedi technique were not prolonged compared with those in the conventional technique.

The Jedi technique was found to be as efficient and effective as the classical method in terms of the block success rate.

The regression time of the sensory block, VAS values after the regression of the block, and time of the first analgesic requirement were similar. In both groups, patients did not require analgesics for at least 10 hours after the block. In both techniques, the patients' satisfaction with the procedure was similar. The Jedi technique did not increase the complication rate compared with the classical method.

Thus, one advantage of learning and the performing Jedi technique is that it provides the opportunity to perform regional anesthesia during working shifts with few and untrained staff.[15–17]

Several limitations of our study can be listed as follows. The operator was more experienced with the conventional technique. Therefore, before starting the study, the operator practiced the Jedi technique on gel pads for 2 months to minimize the difference in experience. The techniques should be compared with a large number of operators because, different operators' levels of success in both techniques may vary. Another limitation of the study was sample size insufficiency for interpreting complication rate because of the low expected occurrence of block complications and the calculation of sample size according to the block performing time.

Conclusions

The Jedi technique allows a single operator to perform peripheral nerve block by holding the syringe, peripheral block needle on one hand and ultrasound probe on the other hand. The technique excludes communication and coordination problems between the operator and assistant. It allows the operator to feel the applied pressure tactically in the piston, thereby achieving success rates similar to those of the conventional method. Studies are needed comparing the Jedi technique with other single-operator techniques and investigating whether the LA dose can be reduced with single-operator techniques.

Conflicts of interest

The authors declare no conflicts of interest.

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SYSTEMATIC REVIEW

Intraoperative transesophageal echocardiography following mitral valve repair: a systematic review



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KEYWORDS
Intraoperative transesophageal echocardiography;
TEE;
Mitral valve;
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Systematic review

Abstract
Objective: We aimed to examine the recent evidence and search for novel assessments on intraoperative TEE following mitral valve repair that can impact short and long-term outcomes.
Methods: The Ovid MEDLINE, PubMed, and EMBASE databases were searched from January 1, 2008, until January 27, 2021, for studies on patients with severe Mitral Valve Regurgitation (MR) undergoing Mitral Valve (MV) repair surgery with intraoperative Transesophageal Echocardiography (TEE) performed after the repair. Additional searches were conducted using Google search engine, Web of Science, and Cochrane Library.
Results: After reviewing 302 records, 8 retrospective and 22 prospective studies were included (n = 30). Due to clinical and methodological diversity, these studies are noncomparable and data were not amenable to quantitative synthesis.
Conclusion: Although technological advances allowed the objective assessment of geometric and dynamic alterations of the MV, the impact of the use of these technologies on short- or long-term outcomes was not studied. There is uncertainty and conflicting evidence on the ideal method and metrics to evaluate MV patency post-repair. Few isolated studies validated methods to assess coaptation surface and LV function post-repair.
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Introduction

Mitral valve Regurgitation (MR) is described as retrograde blood flow from the left ventricle into the left atrium during cardiac systole, due to a malfunction in any of the mitral valve apparatus components. Carpentier's classification is used to describe the mechanism of MR and is divided into Mitral Valves (MV) with normal leaflet movement (Class I), excessive leaflet movement or redundant tissue (Class II), or restrictive leaflet movement due to leaflet disease (Class III-a) or ventricle disease (Class III-b).[1] The leading causes of MR are degenerative, rheumatic, and ischemic heart disease. The prevalence of rheumatic heart disease is declining in high-income countries; however, degenerative, and ischemic heart disease remain significant.[2] Significant MR is

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associated with increased mortality and heart failure rehospitalization.[3]

Surgical repair of the MV is the preferred approach for the regurgitant mitral valve as it carries favorable outcomes compared with valve replacement.[4] Nonetheless, surgical repair of MR can be challenging, and many factors need to be considered to ascertain the feasibility of repair.[5]

If feasible, patients with significant mitral valve regurgitation often undergo a thorough preoperative assessment of the mitral valve apparatus to select an appropriate repair strategy. A comprehensive approach to intraoperative TEE examination of MV before Cardiopulmonary Bypass (CPB) was previously described and found useful for determining the mechanism of MR.[6] Post-CPB intraoperative TEE examination of the mitral valve, on the other hand, is vital since it offers an initial assessment of the adequacy of surgical repair. Observational studies have shown an association between the preoperative evaluation of MV pathology, intraoperative echocardiographic findings of surgical repair and long-term outcomes.[7-9]

We aimed to conduct a systematic review that examined the recent evidence and searched for novel assessments on intraoperative TEE following mitral valve repair that can positively impact short and long-term outcomes.

Methods

We followed the Cochrane and PRISMA standards for conducting and reporting systematic reviews.[10,11]

Data sources

A systematic search was conducted for studies published from January 1, 2008 to January 27, 2021. Initial search engines consisted of Ovid MEDLINE, PubMed, and EMBASE. Additional searches were conducted using Google search engine, Web of Science, and Cochrane Library. The search was limited to human studies published in the English language. At the reference manager stage, duplicates, letters, editorials, and pediatric studies were excluded. The complete search strategy is provided in the supplementary material.

Study selection

We included studies that investigated intraoperative TEE evaluation of the MV repair after separation from CPB in surgeries with either sternotomy or thoracotomy. A PRISMA flow diagram detailing the study selection process can be found in Figure 1.

We excluded: Case reports (n = 24) and review articles (n = 22); Studies not related to MV repair (n = 50); Studies investigating non-conventional mitral valve repairs due to MR (n = 59). These studies included Percutaneous MitraClip or other edge-to-edge interventions; Studies in which intraoperative TEE examination was not used to guide the outcome after surgical repair of the mitral valve (n = 97); Studies investigating pre-CPB predictors of complications or failure after MV repair (n = 6); Studies without details on the intraoperative TEE assessment of the MV repair (n = 13); and Pediatric studies (n = 1)

One Reviewer (RZ) screened titles and abstracts and excluded ineligible records. Two reviewers (II and AF) independently confirmed exclusions. The full texts of included records were further assessed for eligibility by one Reviewer (RZ) and confirmed by the two independent reviewers (II and AF). Disagreements were resolved by consensus. General study characteristics and outcome data were extracted by two reviewers (RZ and AP) and verified by reviewers II and AF. Among reviewers, both methods and content expertise were represented.

Critical appraisal and risk of bias assessment

Many publications describe a comprehensive and detailed intraoperative pre-repair evaluation of the MV with TEE, but a summarized and generic evaluation post-CPB. Thus, we employed a generic MV repair assessment when critically appraising the studies (to decrease the risk of bias in our assessment) and did not include studies without relevant information about the post-repair TEE exam. Review articles were also excluded.

Studies included were evaluated for selection bias (including attrition bias), confounding, measurement bias, and obvious outcome reporting bias. Retrospective studies have the potential risk of selective outcome reporting. Publication bias could also not be detected because data were not amenable to quantitative synthesis.

Results

We reviewed a total of 323 records, of which 21 were additional duplicates, and 302 records underwent title and abstract screening. Subsequently, 50 records were selected and underwent full-text screening. The final systematic review included 30 studies of intraoperative TEE post-MV repair and study characteristics are presented in Table 1.

Of the 30 studies included, 22 were prospective studies, and 8 were retrospective studies and a summary of the design and findings is presented in Table 2, including the intraoperative TEE approach and examination that was used in each study, the intraoperative TEE findings, and the significant results. Although most of the echocardiographers adhered to the intraoperative guidelines in evaluating the mitral valve, we noticed that no specific stepwise approach was utilized for the post-CPB assessment of the MV.

Clinical and methodological diversity

None of the studies included can be considered a Randomized Clinical Trial (RCT), once they are all observational, performed either retrospectively or prospectively. Although these studies share the assessment of the repaired MV using TEE, there are significant differences among them. Of the 30 studies included, 8 studies are non-comparative and describe findings in a series of cases, and the remaining 22 comparative studies investigate a broad spectrum of variables and parameters, using software analysis from different vendors.

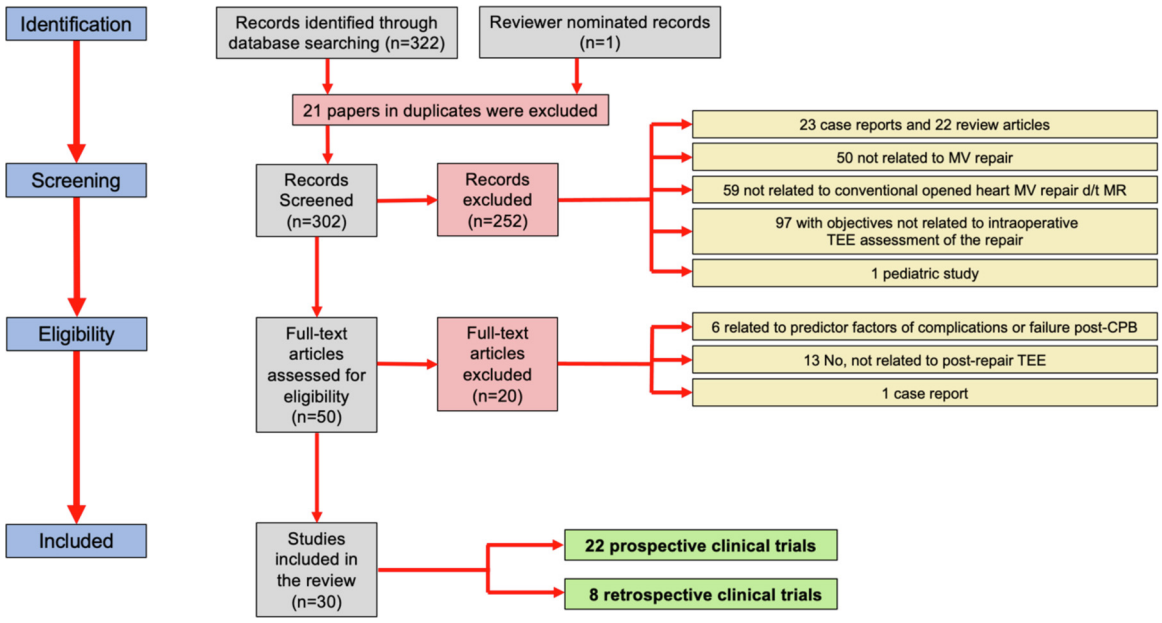

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Mitral valve pathology

All studies included patients with MR, however the baseline MV pathology for included patients is not homogeneous, with some studies including patients with degenerative disease only, others including patients with functional ischemic disease only, and others including both. We also found studies without documentation of the baseline MV pathology, and studies including any cause of MR (degenerative, ischemic, rheumatic, endocarditis, unknown).

Evidence synthesis

Most studies were non-comparative or descriptive in design rather than analytic, from which no estimates of effects could be generated. Furthermore, as presented above, we found clinical and methodological diversity across studies, and they included different baseline MV pathologies. Therefore, these studies are non-comparable and unfortunately data meta-analysis was not feasible. We adopted a qualitative approach to evidence synthesis and presented a narrative review of our findings.

Discussion

Intraoperative TEE provides an undisputed and important source of information for surgeons and anesthesiologists in mitral valve repair surgeries.[6,12,13] Guidelines on MR assessment and review articles on intraoperative TEE for MV repair surgery have been published, emphasizing the effect of afterload on the echocardiographic assessment of MR and the importance of assessing the valve under optimized hemodynamic conditions similar to patient's baseline vital signs. These studies also demonstrate excellent correlation between TEE and surgical findings in both simple[14] and complex pathologies,[15] providing a structured comprehensive approach on how to perform a post-CPB exam that addresses separation from CPB, MV assessment (competency, patency and restoration of leaflet coaptation), Left Ventricular (LV) global and regional function, Left Ventricular Outflow Tract (LVOT) assessment for MV systolic anterior motion, and presence of new aortic insufficiency.[6,16-21]

This systematic review aimed to examine the recent evidence and search for novel intraoperative TEE assessments post-repair that can impact short and long-term outcomes following the surgery. The search strategy used included all studies involving the utilization of TEE in the intraoperative period of surgeries in the MV, and we noticed heterogenicity amongst centers in the use of TEE post-CPB for decision-making Figure 2. presents a flowchart with a proposed stepwise approach for intraoperative assessment of MV repair post-CPB that can be used to evaluate the quality of the repair and guide decisions.

Technological advances

Of the 30 studies included in this review, 19 used novel 3D-TEE analytical software with different objective-derived measurements to assess[22-25] and investigate multiple geometric and dynamic changes of the repaired mitral valve[26-31] and mitral valve apparatus.[30,32-35] This technology was also used to compare geometric and dynamic changes using full versus partial annuloplasty rings[36,37] and full rings of different shapes[38] and different characteristics.[39,40] (Table 1) Although these studies used analytic software and offered objective evaluation of the MV post-repair, they are all descriptive in nature, and further randomized clinical trials are necessary to investigate the association between the objective-derived data and long-term outcomes.

Grapsa et al. used speckle tracking software analysis of the MV apparatus to calculate papillary muscles' strain and showed that patients with isolated posterior mitral leaflet prolapse are less likely to have any residual MR post-repair when the global papillary muscle strain of both papillary muscles is close or equal to zero.[41] Although promising, this

Table 1 Included studies characteristics.

Study	Country	MV Pathology	Design	Sample size	Analysis
Bartels et al. (2014)[24]	USA	Patients with no MV disease, degenerative and functional MR.	Cohort, retrospective case-control study	80	Comparative
Ben Zekry et al. (2016)[30]	USA	Patients with no MV disease and patients with degenerative MR.	Cohort, prospective observational study	30	Comparative
Grewal et al. (2009)[25]	USA	Patients with no MV disease, degenerative and functional MR.	Cohort, prospective observational study	57	Comparative
Ma et al. (2008)[20]	China	Patients with various MV pathologies	Case series, prospective observational study	24	Non-comparative
Ma et al. (2018)[34]	China	Patients with no MV disease and patients with degenerative MR.	Cohort, retrospective study	136	Comparative
Maffessanti et al. (2011)[21]	Italy	Patients with no MV disease and patients with degenerative MR.	Cohort, prospective observational study	74	Comparative
Mahmood et al. (2010)[36]	USA	Patients with degenerative and functional MV disease.	Cohort, prospective observational study	36	Comparative
Mahmood et al. (2008)[26]	USA	Patients with no MV disease and patients with MV disease of various pathologies	Case series, prospective observational study	102	Non-comparative
Mahmood et al. (2009)[35]	USA	Patients with degenerative and functional MV disease.	Case series, prospective observational study	75	Comparative
Maslow et al. (2014)[27]	USA	Patients with degenerative and functional MV disease.	Case series, prospective observational study	50	Comparative
Nishi et al. (2016)[37]	Japan	Patients with no MV disease and patients with degenerative MR.	Cohort, prospective observational study	44	Comparative
Owais et al. (2014)[38]	USA	Patients with no MV disease and patients with degenerative MR.	Cohort, prospective observational study	48	Comparative
Pan et al. (2008)[22]	China	Patients with degenerative MR.	Case series, prospective observational study	6	Comparative
Tautz et al. (2020)[23]	Germany, Swiss	Patients with normal and abnormal MV.	Case series, prospective observational study	10	Non-comparative
Veronesi et al. (2012)[31]	USA, Italy	Patients with no MV disease and patients with degenerative MR.	Cohort, prospective observational study	53	Comparative
Wang et al. (2011)[13]	China	Patients with degenerative MV disease.	Case series, prospective observational study	22	Comparative
Ender et al. (2010)[54]	Germany	Patients with MR, pathology not disclosed.	Case series, prospective observational study	110	Non-comparative
Grapsa et al. (2015)[39]	USA, UK	Patients with degenerative MV disease.	Case series, prospective observational study	64	Non-comparative
Guo et al. (2018)[52]	China	Patients with degenerative MV disease.	Case series, prospective observational study	48	Non-comparative
Kang et al. (2013)[44]	South Korea	Patients with MR (pathology not disclosed), Mitral Stenosis (MS) or combined MR + MS.	Case series, retrospective study	26	Comparative
Karamnov et al. (2020)[45]	USA	Patients with degenerative MV disease.	Case series, retrospective study	20	Comparative

Table 1 (*Continued*)

Study	Country	MV Pathology	Design	Sample size	Analysis
Maslow et al. (2011)[40]	USA	Patients with MR, pathologies not disclosed.	Case series, prospective observational study	25	Comparative
Riegel et al. (2011)[43]	USA, Germany	Patients with degenerative, functional and rheumatic MV disease.	Case series, retrospective study	552	Non-comparative
Vernick et al. (2013)[42]	USA	Patients with degenerative and functional MV disease.	Case series, prospective observational study	20	Comparative
Mabrouk-Zerguini et al. (2008)[53]	UK, France	Patients with degenerative, functional, and unknown MV disease.	Case series, prospective observational study	25	Comparative
Manabe et al. (2012)[32]	Japan	Patients with degenerative MV disease.	Case series, retrospective study	179	Comparative
Rosendal et al. (2012)[33]	Germany	Patients with no MV disease, degenerative and functional MR.	Cohort, retrospective study	50	Comparative
Vergnat et al. (2011)[29]	USA	Patients with degenerative MV disease.	Cohort, prospective observational study	16	Comparative
Vergnat et al. (2012)[28]	USA	Patients with functional MV disease	Case series, prospective observational study	21	Comparative
Wei et al. (2017)[51]	China	Patients with degenerative MV disease.	Case series, retrospective study	20	Non-comparative

is an isolated study and further trials are necessary to delineate the role of speckle tracking and determine the metrics of strain associated with quality or duration of the repair.

Iatrogenic mitral stenosis

A restrictive annuloplasty or extensive resection of leaflet tissue may decrease the effective Mitral Valve Area (MVA) during diastole, in turn leading to Mitral Stenosis (MS) following repair.[42] The influence of CPB on ventricular compliance immediately after surgery may be an important factor that limits the usefulness of Pressure-Half-Time (PHT) to assess MV patency post-repair,[43] and currently there is a call for guidelines to assess MS in a repaired MV, once there is conflicting data regarding which method should be used to determine the MVA immediately following repair (PHT, 2-dimension planimetry 2D-PLAN or 3-dimension planimetry 3D-PLAN).[44]

Our review found 5 studies on this specific topic. Vernick et al. showed that Doppler-derived trans-mitral gradients provide a simple, safe, and reliable measure of the true physiologic trans-mitral valve gradient.[45] Although a mean gradient of less than 5 mmHg across the valve is characteristic of an adequate repair,[19] Riegel et al. pointed out that higher mean gradients up to 7 mmHg immediately post-CPB might be present in situations of increased Left Atrial Pressure (LAP), namely high cardiac output, tachycardia and Atrial Fibrillation (AFib), and this may not cause clinical postoperative MS that needs to be addressed surgicaly.[46] Three observational studies attempted to compare different methods, and none of them showed strong evidence of a superior method[42,47,48] (Table 1).

Coaptation surface

A key objective of surgical valve repair is to restore the largest possible leaflet coaptation surface.[49-52] There is an association of CH > 8 mm post-repair with better outcomes although the normal Coaptation Height (CH) in a native MV ranges from 3 to 6 mm.[53] Wei et al. demonstrated that a taller coaptation height post-repair is associated with less residual MR in 12 months post-repair,[54] and Guo et al. showed that both 2D and 3D-TEE can be used to assess leaflet coaptation post-repair, with 2D been found to be a simpler and faster method.[55]

Left ventricular assessment

Predicting the risk of LV dysfunction post-MV repair is challenging because of the overestimation of LV ejection fraction in patients with severe MR. Mabrouk-Zerguini et al. showed that the Myocardial Performance Index (Tei-index) is not affected by MV repair. This index could be used to predict post-repair Fractional Area Change (FAC) and, consequently, predict patients at risk of post-CPB LV dysfunction.[56]

New LV lateral wall regional motion abnormality following repair should raise suspicion of injury to the circumflex artery.[6,15-18] Ender et al. proposed and validated a method to interrogate the circumflex artery with Color Flow Doppler (CFD) and Pulse Wave Doppler (PWD) at its proximal,

Table 2 Summary of study design and echocardiographic findings.

Study	Study objectives	Study design	Results	Author's conclusion
Bartels et al. (2014)[24]	Hypothesized that quantitative 3D analysis would reveal distinct differences among diseased, repaired, and normal MV.	Case-control observational clinical study. Retrospectively analyzed 80 patients who underwent intraoperative TEE: 20 patients with degenerative MR were evaluated before and after mitral valve repair, 20 patients had functional MR and 20 patients had no MV disease.	Annulus area was enlarged in degenerative and functional MR. Annular displacement distance was decreased in functional MR and repaired valves. Annular displacement velocity was decreased in functional MR. Annular area fraction was decreased in functional MR and repaired valves.	Normal, functional regurgitant, degenerative, and repaired MV have distinctly different dynamic signatures of anatomy and function as reliably determined by perioperative echocardiographic tracking.
Ben Zekry et al. (2016)[30]	The investigation was aimed at deriving novel intrinsic parameters of regional and global MA shape and function, namely, curvature and torsion.	Prospective observational study. Indices were evaluated in a group of 15 patients with normal MV and in a group of 15 patients with organic MR, prior to and after MV repair. Novel parameters of MA curvature and torsion were derived from 3D TEE.	Patients with organic MR presented the smallest global curvature and torsion; this decrease in curvature and torsion reflects a loss of tonicity of the MA tissue. These changes were largely corrected with MV repair surgery, to higher values, compared with normal individuals. The regional analysis revealed similar trends. The maximal MA curvature was found to be at the MA 'anterior horn', whereas the MA 'posterior horn' had the lowest curvature values.	Novel MA parameters of curvature and torsion can be computed from 3D echocardiography and provide quantitative characteristics of dynamic regional MA geometry. In patients with organic MR, the reduced regional and global curvatures improve following surgical MV repair. These quantitative parameters may help further refine the quantitative description of MA geometry in various mitral valve pathologies and after MV repairs.
Grewal et al. (2010)[25]	Investigated and compare mitral annular size, shape, and motion over the cardiac cycle using RT 3D-TEE in patients with myxomatous MV disease before and after repair, in normal control subjects and in patients with ischemic MR.	Prospective observational study. RT 3D-TEE of the mitral valve was acquired in 32 patients with MVD before and after repair, 15 normal control subjects, and 10 patients with IMR of identical body surface area.	RT 3D-TEE provides insights into normal, dynamic MA function with early-systolic area contraction and saddle-shape deepening contributing to mitral competency. MVD annulus is also dynamic but considerably different with loss of early-systolic area contraction and saddle-shape deepening despite similar magnitude of ventricular contraction, suggestive of ventricular-annular decoupling. Subsequent area enlargement may contribute to mitral incompetence. After mitral repair, MVD annulus remains dynamic without systolic saddle-shape accentuation.	RT 3D-TEE provides new insights that allow the refining of mitral pathophysiology concepts and repair strategies

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
Ma et al. (2008)[20]	Investigated the feasibility, imaging quality and accuracy of live 3D-TEE for assessing MV morphology to determine if live 3D-TEE has important value in MV surgery.	Prospective observational study. Twenty-four patients with MV disease underwent live 3D-TEE and 2D-TEE before and after MV surgery. Sensitivity, specificity, and total consistency rates of live 3D-TEE for diagnosing ruptured chordae were calculated and compared to surgeon's findings. We also compared the diagnostic accuracy of MV disease between live-3D-TEE and 2D TEE.	Live-3D-TEE allowed visualization of the anatomic structures of the heart online and clearly identified the valvular apparatus and their defects. Sensitivity and specificity for the detection of ruptured chordae by live 3D-TEE were 87.5% and 100% respectively, and the total consistency rate was 95.8%. Additional defects not diagnosed by 2D TEE were found in three cases (12.5%) preoperatively by live 3D-TEE. Live 3D-TEE could evaluate the function of prosthetic or native valves immediately after operation. One case was re-repaired (4.2%) using guidance by live 3D-TEE.	Live 3D-TEE enabled evaluation of MV function and provided adequate valuable information before and after MV surgery. We conclude that live 3D-TEE can play an important role in MV surgery.
Ma et al. (2018)[34]	Investigated the impact of full annuloplasty rings versus C-shape bands on mitral annular geometry in the presence of FED assessed by intraoperative 3D-TEE.	Retrospective study. 65 patients who underwent MV repair for severe MR caused by FED using full rings (the Ring group, n = 30) and C-shape bands (the Band group, n = 35). 71 controls without valvular heart disease were also included. Thorough 3D-TEE inspections were performed for the entire cohort to measure morphological parameters of MA before and after surgery. Mid-term repair durability and left atrial diameter were followed up.	The preoperative 3D-TEE parameters, including annular diameters, area, height and aorto—mitral angle, were significantly larger in the FED groups than normal, and were comparable between two groups using different annuloplasty devices. After repair, the anterior—posterior diameter, annulus circumference and area were significantly larger in the Band group than in the Ring group. The aorto—mitral angle became comparable with normal value in the Ring group, but not in the Band group. Follow-up echocardiographic data showed a significant correlation between postoperative aorto—mitral angle and reduced left atrial diameter at 50.3 months after surgery.	Compared with C-shape bands, full rings may impose less narrowing on aorto—mitral angle, which correlates well with mid-term left atrial reverse remodeling
Maffessanti et al. (2011)[21]	Quantified the effects induced by prolapse on MV anatomy in the presence of FED or Barlow's disease, assess the effect of surgery on the MV apparatus, and investigate the potential	Prospective observational study. 56 patients (29 with FED, 27 with Barlow's disease) undergoing MV repair and annuloplasty were studied immediately before and after surgery. Also, 18 age-matched	MV prolapse and regurgitation were associated with a markedly enlarged annulus and leaflets compared with controls, while annular height and the mitral aortic angle were similar. Patients with Barlow's disease showed	Intraoperative 3D-TEE allows quantitative evaluation of the MV apparatus in the presence of FED or Barlow's disease and could be useful for immediate

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
	role of 3D-TEE in surgical planning.	patients with normal MV anatomy, undergoing coronary artery bypass, were included as a control group. 3D-TEE data sets were acquired and analyzed to quantify several MV annulus and leaflet parameters using dedicated software.	greater values than those with FED. MV repair and annuloplasty led to a significant undersizing of leaflet and annular areas, diameters, and height compared with controls. CL remained in the normal range. Differences between Barlow's disease and FED were reduced but still present after surgery.	assessment of the surgical procedure.
Mahmood et al. (2010)[36]	Investigated if when compared to flat rings, saddle-shaped rings would decrease the NPA after MV repair for both ischemic and myxomatous MV disease.	Prospective observational study. Geometric analysis on 38 patients undergoing MV repair for myxomatous and ischemic MR with full flat rings (n = 18) and saddle rings (n = 18) were performed. The acquired 3D volumetric data were analyzed and the degree of change in the NPA was calculated and compared before and after repair for both types of rings.	Both types of annuloplasty rings resulted in significant changes in the geometric structure of the MV after repair. However, saddle rings lead to a decrease in the NPA, whereas flat rings increased the NPA.	Implantation of saddle-shaped rings during MV repair surgery is associated with augmentation of the nonplanar shape of the MA. This favorable change in the mitral annular geometry could possibly confer a structural advantage to MV repairs with the saddle rings.
Mahmood et al. (2008)[26]	Studied the feasibility of using 3D-TEE in the operating room for MV repair or replacement surgery. To perform geometric analysis of the mitral valve before and after repair.	Prospective observational study. Intraoperative reconstruction of 3D images of the mitral valve in 102 consecutive patients scheduled for MV surgery.	Successful image reconstruction was performed in 94 patients – 8 patients had arrhythmias or a dilated MV annulus resulting in significant artifacts. Time from acquisition to reconstruction and analysis was less than 5 minutes. Surgeon identification of MV anatomy was 100% accurate.	The study confirms the feasibility of performing intraoperative 3D reconstruction of the MV. The incorporation of CFD into these 3D images helps in identification of the commissural or perivalvular location of regurgitant orifice.
Mahmood et al. (2009)[35]	3D intraoperative TEE evaluation of the MV annulus before and immediately after repair	Prospective observational study. 3D geometric analysis on 75 patients undergoing MV repair during coronary artery bypass graft surgery for MR or myxomatous MV disease. Geometric analysis of the MV was performed before and immediately after valve repair with full rings and annuloplasty bands.	Complete echocardiographic assessment of the MV was feasible in 69 of 75 patients (92%) within 2 to 3 minutes of acquisition. Placement of full rings resulted in an increase in the NPA or a less saddle shape of the native MA. By contrast, the NPA did not change significantly after placement of partial rings.	Mitral annular nonplanarity can be assessed in the operating room. Application of full annuloplasty rings resulted in the MA becoming more planar. Partial annuloplasty bands did not significantly change the nonplanarity angle. Neither of the two types of rings restored the native annular planarity
Maslow et al. (2014)[27]	Examined the geometric changes of the MV after repair	Prospective observational study. 50 consecutive patients scheduled for elective repair of the MV for	Good correlations and agreement were seen between the MVA measured with 3D-Plan and PHT and were better	3D imaging provides caregivers with a unique ability to assess

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
	using conventional and 3D echocardiography.	regurgitant disease. Intraoperative TEE assessments of MVA were performed using 2D-PLAN, PHT, and 3D-PLAN. In addition, the direction of ventricular inflow was assessed from the 3D imaging.	than either one compared to 2D-Plan. MVAs were smaller after repair of functional disease repaired with an annuloplasty ring. After repair, ventricular inflow was directed toward the lateral ventricular wall. Subgroup analysis showed that the change in inflow angle was not different after repair of functional disease as compared to those presenting with degenerative disease.	changes in valve function after MV repair.
Nishi et al. (2016)[37]	Assessed the effects of different types of prosthetic rings on mitral annular dynamics using RT 3D-TEE.	Prospective observational study. 44 patients, including patients undergoing mitral annuloplasty using the Cosgrove—Edwards flexible band (Group A, n = 10), the semi-rigid Sorin Memo 3D ring (Group B, n = 17), the semi-rigid Edwards Physio II ring (Group C, n = 7) and ten control subjects. Various annular diameters were measured throughout the cardiac cycle.	Flexible anterior annulus motion in all of the groups except Group C. A flexible posterior annulus was only observed in Group B and the Control group. The MAA changed during the cardiac cycle by 8.4 ± 3.2, 6.3 ± 2.0, 3.2 ± 1.3, and 11.6 ± 5.0 % in Group A, Group B, Group C, and the Control group, respectively. The dynamic diastolic to systolic change in mitral annular diameters was lost in Group C, while it was maintained in Group A, and to a good degree in Group B. In comparison to the Control group, the MA shape was more ellipsoid in Group B and Group C, and more circular in Group A.	Although MR was well controlled by all of the types of rings that were utilized in the present study, we demonstrated that the annulus motion and annulus shape differed according to the type of prosthetic ring that was used, which might provide important information for the selection of an appropriate prosthetic ring.
Owais et al. (2014)[38]	Selectively flexible rings are used for annuloplasty during MV repair to facilitate dynamic annular motion while preventing annular dilation. This study assessed the extent and nature of the flexibility of 2 rings in vivo.	Prospective observational study. 3D-TEE was used intraoperatively to acquire data regarding dynamic motion of mitral annuli and annuloplasty rings in 33 patients undergoing mitral repair and in 15 control patients. Data were analyzed to assess the dynamic changes in annular geometry after implantation of selectively flexible rings.	After annuloplasty, there was an immediate and significant decrease in annular displacement and annular displacement velocity. Dynamic change in multiple variables including anteroposterior diameter and annular area was also significantly depressed. In comparison with normal MV, partially flexible rings allowed limited dynamic motion: percentage changes in anteroposterior diameter, AL diameter, PM diameter, and total circumference were significantly lower. Compared	Mitral annular dynamics were uniformly depressed after implantation of these rings. Selective flexibility could not be demonstrated in vivo using echocardiographic data.

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
			with each other, the two rings resulted in similar changes in anterior annulus length, posterior annular length, and annular area.	
Pan et al. (2008)[22]	Investigated the value of RT-3D-TEE in MV repair.	Prospective observational study. RT-3D-TEE was performed in 6 patients with MV prolapse. Preoperative RT-3D-TEE studies were compared with surgical findings in patients undergoing surgical MV repair, and quantitative evaluation was performed before and after surgical MV repair.	RT-3DTEE could display dynamic morphology of MV, the location of prolapse, and spatial relation to the surrounding tissue. It could provide surgical views of the valves and the valvular apparatus. These results were consistent with surgical findings. The quantitative evaluation before and after surgical MV repair indicated that AL to PM diameter of annulus, anterior to posterior diameter of annulus, perimeter of annulus, and area of annulus in projection plane were significantly smaller after operation compared with those before operation. The length of posterior leaflet, the area of anterior and posterior leaflet, the maximal prolapse height, the volume of leaflet prolapse and the length of coaptation in projection plane were significantly reduced after operation.	RT-3DTEE is a unique new modality for rapid and accurate evaluation of MV prolapse and MV repair.
Tautz et al. (2020)[23]	Provided a new 4D segmentation method to enable a quantitative assessment of valve geometry and pathological properties in all heart phases, as well as the changes achieved through surgery.	Prospective observational study. Tracking-based approach combining GVF and PBD. An open-state surface model of the valve is propagated through time to the closed state, attracted by the GVF field of the leaflet area. The PBD method ensures topological consistency during deformation. For evaluation, one expert in cardiac surgery annotated the closed-state leaflets in 10 TEE sequences of patients with normal and abnormal MV and defined the corresponding open-state models.	The average point-to-surface distance between the manual annotations and the final tracked model was 1.00± 1.08 mm. Qualitatively, four cases were satisfactory, five passable and one unsatisfactory. Each sequence could be segmented in 2−6 min.	Our approach enables to segment the mitral valve in 4D-TEE image data with normal and pathological valve closing behavior. With this method, in addition to the quantification of the remaining orifice area, shape and dimensions of the coaptation zone can be analyzed and considered for planning and surgical result assessment.

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
Veronesi et al. (2012)[31]	Characterized MAC in 3D space before and after MV repair and to identify the untoward effects of annuloplasty rings on MAC compared with normal valvular function.	Prospective observational study. RT-3D-TEE was performed on 28 consecutive patients with degenerative MV disease and severe MR before and after MV repair and in 25 age-matched control subjects. Custom software was used to semi-automatically identify the mitral and aortic annuli throughout the cardiac cycle and to measure parameters describing valvular dynamics.	Patients with MR before MV repair were characterized by altered morphology and function of the MV but preserved MAC because of the maintained ability of the MA to change size and position. MV repair together with annuloplasty ring implantation forced the MA to be smaller and less pulsatile, with decreased displacement ability compared with normal mitral annuli. Because of this alteration in MAC, the "unaffected" aortic annulus became less pulsatile and less mobile.	This study shows unwanted and unexpected changes in aortic annular function secondary to MV repair with an annuloplasty ring due to altered MAC mechanisms. These changes may alter the dynamic mechanism of the aortic root that facilitates blood ejection, so MAC should be considered and evaluated from diagnosis to treatment in MV disease.
Wang et al. (2011)[13]	Delineated the utility of intraoperative TEE in robotic MV repair.	Prospective observational study. Intraoperative TEE was performed in 22 consecutive patients undergoing robotic MV repair for severe degenerative MR over a period of 2 years. Before CPB, TEE was used to define the lesions of degenerative MR and the localization of the prolapsed leaflets, and to evaluate the severity of MR. During establishment of peripheral CPB, TEE was used to guide placement of the cannula in the IVC, SVC, and AAO. After weaning from CPB, TEE was used to assess immediately the competency of the surgical repair.	Agreement between TEE and surgical findings was 92.3% for the lesions of degenerative MR, and 98.5% for the localization of the prolapsed leaflets. Under TEE guidance, all the cannulas in the SVC, IVC, and AAO were placed correctly. TEE demonstrated all the patients had successful robotic MV repairs.	Intraoperative TEE is a valuable adjunct in the assessment of robotic MV repair.
Ender et al. (2010)[54]	Evaluated an echocardiographic method to visualize the course and flow of the circumflex artery, to detect iatrogenic injury to this structure intraoperatively, as well as to predict the coronary dominance pattern in MV surgery patients.	Prospective study. 110 patients undergoing minimal invasive MV repair. Intraoperative TEE was used to visualize the circumflex artery using a combination of B-mode imaging and color Doppler with different Nyquist limits. The course of the circumflex artery and the coronary sinus and their corresponding diameters were documented at the proximal and distal ends of both vessels.	The course of the circumflex artery could be detected proximally in 109 patients (99%), to the point of intersection with the coronary sinus in 99 patients (90%), and distal to this intersection in 95 patients (86%). Three patients had evidence of iatrogenic aliasing (circumflex stenosis) or "no flow" (circumflex occlusion) on TEE examination after repair and therefore underwent surgical or percutaneous correction.	The early recognition of iatrogenic injury of the circumflex artery is feasible with intraoperative TEE examination and may lead to treatment before extensive myocardial infarction occurs.

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
		Preoperative angiographic data were used to determine the coronary dominance type.		
Grapsa et al. (2015)[39]	Assessed the papillary muscle strain as a contributor to recurrent MR after MV repair for FED.	Prospective study. 64 patients with isolated posterior MV prolapse and severe MR referred for surgery. 2D, 3D-TEE and speckle tracking were performed in all patients. The longitudinal strain of the AL and PM papillary muscles were individually calculated as well as the global longitudinal strain of both papillary muscles was measured before and after mitral repair and normalized to left ventricle end-diastolic volume.	Eight patients (12.5%) had at least moderate MR 6 months after mitral repair. The longitudinal strain of the AL and the PM papillary muscles as well as the global strain of both papillary muscles were all reduced after surgical repair. The longitudinal strain of the PM papillary muscle was the strongest predictor of recurrent MR. The global preoperative papillary muscle strain was also a determinant of recurrent MR when the global strain was greater than 29.05.	Patients with isolated posterior mitral leaflet prolapse are less likely having any residual MR post repair when the global papillary muscle strain of both papillary muscles is close or equal to zero. Strain of the papillary muscles may be an important determinant in predicting residual MR in patients who undergo mitral valve repair.
Guo et al. (2018)[52]	Evaluated the utility of 2D and 3D-TEE to assess MV coaptation before and after MV repair.	Prospective study. 48 patients undergoing MV repair for MR were studied. Assessed the utility of 2D and 3D-TEE to assess MV coaptation before and after MV repair. Complete conventional 2D and 3D-TEE studies were performed, and the degree of the MV coaptation defect before and after surgery was assessed by measuring the MV CL and CLI with 2D TEE, and the CA and CAI with 3D-TEE.	Compared with preoperatively, postoperative CL, CLI, CA, and CAI were significantly increased. Correlation analysis revealed that the CLI and CAI had a significant negative correlation with the degree of MR. Furthermore, correlation analysis revealed that the CLI was significantly correlated with the CAI both preoperatively and postoperatively.	The coaptation variables increased significantly in patients undergoing MV repair. The CLI and CAI significantly correlated with MR severity. The CL and CLI determined with 2D TEE are more feasible than the CA and CAI determined with 3D-TEE. Both 2D and 3D variables may complement each other for aiding MV repair. 2D CLI is an alternative to 3D CAI due to its simplicity.
Kang et al. (2013)[44]	Hypothesized that MVA with echocardiography, using 3D-PLAN technique (measured at one point at maximal opening of MV) versus PHT (measured during entire diastolic phase) in MV repair surgery would be different.	Retrospective study. 26 patients who had undergone MV repair were retrospectively reviewed, and two different observers measured the MVAs using PHT and 3D-PLAN technique. The MVAs derived from recorded medical data, using PHT and 3D-PLAN technique were abbreviated to MVA-PHT1 and MVA-3D1, and data from the PHT and 3D-PLAN	Intraclass correlation coefficients were 0.90 for the intra-operative PHT technique and 0.78 for the intra-operative 3D-PLAN technique. MVA-3D1, MVA-3D2 and MVA-3D3 were significantly larger than MVA-TTE, but intra-operative MVAs-PHT were not.	MVA measured by 3D-PLAN technique with TEE at the intra-operative post-MV repair period was seemed to be larger than that measured by the PHT technique with TTE at the post-operative period. However, it did not mean that the 3D-PLAN technique was inaccurate but needs cautions at

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
		techniques by observer A and observer B were determined as MVA-PHT2 and MVA-3D2, and MVA-PHT3 and MVA-3D3, respectively. The MVA derived by post-operative TTE using the PHT technique was determined as MVA-TTE.		determination of MVA using different techniques.
Karamnov et al. (2020)[45]	Compared repaired MVAs obtained with commonly used 2D and 3D echocardiographic methods to a 3DOA, which is a novel echocardiographic measurement and independent of geometric assumptions	Retrospective study. Intraoperative 2D and 3D TEE images from 20 patients who underwent MV repair for MR obtained immediately after repair were retrospectively reviewed. MVAs obtained by PHT, 2D-PLAN, and 3D-PLAN were compared to those derived by 3DOA.	MVAs obtained by the 3DOA method were significantly smaller compared to those obtained by PHT, 2DP, and 3DP. In addition, MVA defined as an area $\leq$1.5 cm^2 was identified by 3DOA in 2 patients and by 3DP in 1 patient.	Post-MV repair, MVAs obtained using the novel 3DOA method were significantly smaller than those obtained by conventional echocardiographic methods and may be consistent with a higher incidence of MVA reduction when compared to 2D techniques.
Maslow et al. (2011)[40]	3 different methods to measure MVA after MV repair were studied. Data obtained immediately after repair were compared with postoperative data. The objective was to determine the feasibility and correlation between intraoperative and postoperative MVA data.	Prospective study. 25 patients scheduled for MV repair surgery. Echocardiographic data included MVAs obtained using the PHT, 2D-PLAN, and the CE. These data were obtained immediately after CPB and were compared with data obtained before hospital discharge (transthoracic echocardiogram 1) and 6 to 12-months after surgery (transthoracic echocardiogram 2). Intraoperative care was guided by hemodynamic goals designed to optimize cardiac function.	The data show good agreement and correlation between MVA obtained with PHT and 2D-PLAN within and between each time period. MVA data obtained with the CE in the postoperative period were lower than and did not correlate or agree as well with other MVA data.	The MVA recorded immediately after valve repair, using PHT, correlated and agreed with MVA data obtained in the postoperative period.
Riegel et al. (2011)[43]	Hypothesized that intraoperative echocardiography can be utilized to diagnose iatrogenic MS immediately after MV repair.	Retrospective study. Data of 552 consecutive patients undergoing MV repair at a single institution were reviewed. Post-CPB peak and mean TMPG, and PHT were obtained from intraoperative TEE examinations in each patient.	Nine patients received a reoperation for primary MS, prior to hospital discharge. All of these patients already showed intraoperative post-CPB mean and peak TMPGs that were significantly higher compared to values for those who did not However, PHT varied considerably within the entire population, and only weakly predicted the requirement for reoperation	Intraoperative TEE diagnosis of a peak TMPG 17 mmHg or mean TMPG 7 mmHg immediately following CPB are suggestive of clinically relevant MS after MV repair.

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
			Receiver operating characteristic curves showed strong discriminating ability for mean gradients and peak gradients, but poor performance for PHT. A value of 7 mmHg for mean, and 17 mmHg for peak TMPG, best separated patients who required reoperation for MS from those who did not.	
Vernick et al. (2013)[42]	Evaluated the accuracy of Doppler-derived transmitral valve gradients immediately after MV repair by comparing them with near simultaneously obtained direct catheter gradients.	Prospective study. 20 patients presenting for MV repair surgery. After completion of the MV repair and subsequent cardiac de-airing, the patient was weaned from CPB. Immediately after separation, near simultaneous transmitral Doppler gradients were obtained with directly measured catheter gradients via the vent catheter.	While the mean peak gradient difference of 1.1 mmHg was small, the correlation between Doppler and catheter gradient measurements only approached statistical significance due to the large variance associated with the small sample size. In all patients with a peak gradient greater than 10 mmHg (4 of the 20 patients), overestimation of catheter gradients by Doppler occurred, with two showing a 62% to 73% discrepancy. In these two cases, there was also evidence for elevated LVEDP along with high transmitral blood flow velocities.	Doppler-derived transmitral gradients provide a simple, safe, and reliable measure of the true physiologic transmitral valve gradient. At the same time, it is important to recognize that significant Doppler over-estimation of catheter gradients may occur in patients with elevated Doppler transmitral velocities.
Mabrouk-Zerguini et al. (2008)[53]	Tested the hypothesis where the Tei-index could be useful in assessing the perioperative cardiac function in patients undergoing MV repair.	Prospective study. 25 patients were enrolled. TEE was performed perioperatively before and after the correction of MR. We compared the impact of the MV repair on the left ventricular FAC and the Tei-index. FAC was calculated from the transgastric short-axis view and Tei-index was determined from the four chambers and deep transgastric views.	FAC significantly decreased after MVR from 53% to 42%, while Tei index was unaffected. A significant relationship was found between the preoperative Tei index and the postoperative FAC. Moreover, a significant and clinically relevant relationship was determined between the predicted (using preoperative Tei-index) and the measured postoperative FAC.	FAC but not the Tei index is influenced by MVR. The preoperative determination of the Tei index allows predicting postoperative FAC and offers the opportunity to identify patients in whom a severe unsuspected systolic dysfunction could render difficult the weaning from CPB.
Manabe et al. (2012)[32]	Investigated SAM of the MV mechanism by analysing the change in MV morphology associated with operative procedures.	Retrospective study. Components of MV were measured before and after operative procedures by TEE in 179 patients who underwent MV repair. Comparisons were made between 15 patients with SAM (SAM group) and 164	Operative procedures shifted the coaptation point towards the LVOT by 6.9 mm and increased the extra portion of anterior leaflet that extended beyond the coaptation point by 5.4 mm. These changes were enhanced in the SAM group.	The results of this study show that operative procedures might modify the morphology of MV susceptible to developing SAM. Postoperative smaller annular diameter and anterior shift of coaptation point were

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
		patients without SAM (non-SAM group).	Intergroup comparison revealed that there were no differences in the preoperative MV morphologies between the two groups. After operative procedures, however, the SAM group showed smaller annular diameter and smaller coapted anterior/posterior length ratio compared with the non-SAM group.	considered to contribute to the development of SAM.
Rosendal et al. (2012)[33]	RT-3D-TEE permits excellent visualization of the LVOT and might improve standard 2D measurements. In this study, LVOT area and shape were assessed before and after MV surgery.	Retrospective study. 35 patients undergoing MV repair or replacement were compared with 15 patients undergoing coronary artery bypass grafting. LVOT area was measured by planimetry. Maximum possible methodologic errors by assuming a circular LVOT and an eccentricity index were calculated. LVOT diameter in a midesophageal long-axis view served to calculate the error for the circular LVOT determined in common intraoperative practice.	Common intraoperative 2D measurements underestimated actual LVOT area by 21%. MV surgery led to a significant reduction of LVOT area by 7%. Although LVOT height remained unchanged, width decreased, resulting in a more circular shape of the LVOT. This effect was more pronounced the smaller the size of the implanted annuloplasty ring or prosthesis. Coronary artery bypass grafting did not affect the LVOT. LVEF was significantly correlated with LVOT eccentricity. Impaired ventricular function and higher end-systolic volumes were associated with a rounder shape.	The eccentric LVOT shape leads to a distinct underestimation of its area with 2D measurements. LVOT eccentricity is less distinct in patients with low ejection fractions and higher end-systolic volumes. LVOT width is decreased through annuloplasty rings and prostheses, and the smaller the implanted device, the more profound the reduction.
Vergnat et al. (2011)[29]	Hypothesized that saddle-shaped annuloplasty would improve leaflet coaptation in cases of MV repair for flail posterior leaflet segments.	Prospective study. 16 with flail posterior segment and severe MR had MV repair using standard techniques. 8 patients received saddle-shaped annuloplasty and 8 patients received flat annuloplasty. RT-3D-TEE was performed before and after repair. Images were analyzed using custom software to calculate MAA, SLD, CW, TLA, and LCA.	Post-repair MAA and TLA were similar in both groups. Post-repair LCA was significantly greater in the saddle group than in the flat group.	When compared with flat annuloplasty, saddle-shaped annuloplasty improves LCA after MV repair for severe MR secondary to flail posterior leaflet segment. Use of saddle-shaped annuloplasty devices may increase repair durability.
Vergnat et al. (2012)[28]	Used RT-3D-TEE to assess the influence of the ring shape on leaflet curvature in patients with IMR.	Prospective study. RT-3D-TEE was performed in 21 patients with IMR after placement of either a flat or saddle shaped annuloplasty ring. A combination	Independently of the shape of the annuloplasty ring, all patients were subject to the same degree of annular undersizing. Patients who received saddle-shaped annuloplasty rings had	Saddle-shaped annuloplasty rings increase leaflet curvature compared with flat rings in patients with IMR. As a result, saddle-shaped annuloplasty

Table 2 (*Continued*)

Study	Study objectives	Study design	Results	Author's conclusion
		of commercially available and customized software was used to measure multiple leaflet curvature parameters across all regions of the MV.	greater leaflet curvature in all six MV leaflet regions compared with patients who received flat annuloplasty rings. These differences were statistically significant in all regions except the P1 region.	may decrease leaflet stress and potentially increases the durability of the repair in patients with IMR.
Wei et al. (2017)[51]	Investigated the association between the CH of MV and MR after MV repair.	Retrospective study with prospective follow-up. 20 patients that underwent MV valvuloplasty for MR were included. Ring annuloplasty was performed in all cases. MVd, CH, LVEF were measured by TEE before the operation in operation room and 3 months and 12 months after the operation by the TEE. A degree from 0 to 4 was used to measure the degree of MR.	There were 14 patients with 0, 3 patients with 1, 3 patients with 2 of MR 12 months after the operation. CH increased significantly at 3 months and 12 months after operation. MVd and LVEF were not significantly changed after MV repair. Furthermore, CH after resuscitation have a statistically significant negative correlation with the degree of MR 12 months after operation.	The MV repair with MV ring induces the morphologic change of the MV structure. The increase of CH after MV repair may be one of the main factors in regulation of MR.

2D, Two-Dimensional; 3D, Three-Dimensional; MV, Mitral Valves; TEE, Transesophageal Echocardiography; MR, Mitral Regurgitation; MA, Mitral Annulus; MVA, Mitral Valve Area; MVD, Myxomatous Valve Disease; FED, Fibroelastic Deficiency; NPA, Non-Planarity Angle; CFD, Color-Flow Doppler; 2D-PLAN, 2D Planimetry; PHT, Pressure Half-Time; 3D-PLAN, 3D Planimetry; RT, Real-Time; 4D, 4-Dimensional; GVF, Gradient Vector Flow; PBD, Position-Based Dynamics; MAC, Mitral-Aortic Coupling; CPB, Cardiopulmonary Bypass; IVC, Inferior Vena Cava; SVC, Superior Vena Cava; AAO, Ascending Aorta; AL, Anterolateral; PM, Posteromedial; CL, Coaptation Length; CLI, Coaptation Length Index; CA, Coaptation Area; CAI, Coaptation Area Index; 3DOA, 3D Orifice Area; CE, Continuity Equation; MS, Mitral Stenosis; TMPG, Transmitral Pressure Gradients; FAC, Fractional Area Change; LVEDP, Left Ventricular End-Diastolic Pressure; SAM, Systolic Anterior Motion; LVOT, Left Ventricular Outflow Tract; MAA, Mitral Annular Area; SLD, Septolateral Dimension; CW, Intercommissural Width; TLA, Total Leaflet Area; LCA, Leaflet Coaptation Area; IMR, Ischemic Mitral Regurgitation; MVd, MV short-axis dimension; CH, Coaptation Height; LVEF Left Ventricular Ejection Fraction; TTE, Transthoracic Echocardiography.

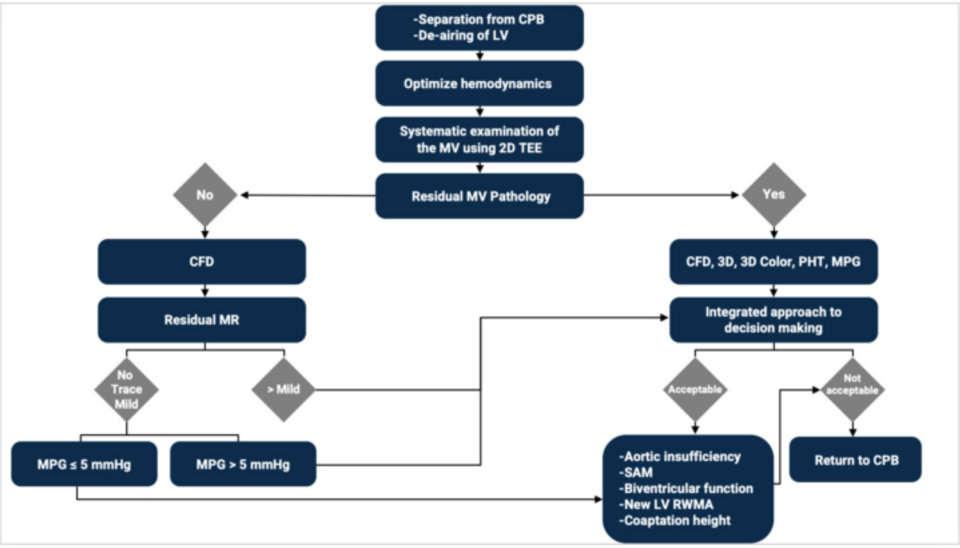

Figure 2 Flowchart representing an intraoperative stepwise approach to assess the Mitral Valve (MV) immediately after repair. Transesophageal Echocardiography (TEE) is used to guide the separation from Cardiopulmonary Bypass (CPB) and assure that the heart has no residual air; after hemodynamic optimization, a systematic examination of the MV using 2D TEE is used to identify if there is any residual mechanism of Mitral Valve Regurgitation (MR), and if this is not present, Color Flow Doppler (CFD) will confirm if there is residual MR. Any MR less or equal to mild is acceptable and further interrogation with Continuous Wave Doppler (CWD) calculating the Mean Pressure Gradient (MPG) will exclude significant Mitral Valve Stenosis (MS) post-repair. Residual MV pathology, any residual MR greater than mild and high MPG should undergo an integrated approach by the surgeon to decide if the repair is acceptable or not. If not acceptable, CPB is resumed, and further repair or replacement is performed. Once the outcome is acceptable, a comprehensive TEE examination is performed, including assessment of biventricular function, new Left Ventricle (LV) Regional Wall Motion Abnormalities (RWMA), new or worsening Aortic Valve Insufficiency, Systolic Anterior Motion of the MV and measurement of the MV Coaptation Height (CH).

intermediate, and distal segments, helpful to diagnose decreasedfloworocclusion.[57]

Limitations

Certain limitations can be appreciated in this study. Firstly, in chronological terms, our appraisal is limited to studies published from January 2008 until January 2021. However, most of the advanced technologies related to ultrasound and 3D-TEE were introduced to practice after 2008. Secondly, we did not find comparable studies and no data analysis was performed. A narrative description of the main findings was used as a feasible option. Thirdly, all studies included are observational in nature and ideally, adequately prospective randomized controlled trials are best suited to study outcomes with greater power of evidence. Finally, none of the studies included aimed to investigate the impact on the long-term outcomes, and no impact on duration of the repair or on patient's survival could be demonstrated.

Conclusion

This systematic review appraised the recent literature on intraoperative TEE for MV repair performed immediately after CPB. Although technological advances have allowed the objective assessment of geometric and dynamic alterations of the MV, the impact of the use of these technologies on short- or long-term outcomes has not been studied yet, and further prospective randomized trials are necessary to address this point. Moreover, we found uncertainty and conflicting evidence on the ideal method and metrics to evaluate MV patency post-repair, and few isolated studies validating methods to assess coaptation surface and LV function post-repair.

Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2022.03.002.

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SYSTEMATIC REVIEW

Effects of hypercapnia versus normocapnia during general anesthesia on outcomes: a systematic review and meta-analysis



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KEYWORDS
General anesthesia;
Hypercapnia;
Normocapnia;
Invasive ventilation;
Adverse events;
Time to extubation

Abstract
Background: The effect of mild changes in CO_2 levels to organ perfusion and tissue inflammation are well known, whereas an influence of hypercapnia under general anesthesia on adverse events as nausea and vomiting, or length of hospital stay is barely examined. The goal of our meta-analysis was to identify possibly positive effects of hypercapnia versus normocapnia in general anesthesia in adult patients.
Methods: We conducted a systematic review of parallel-arm randomised controlled trials comparing hypercapnia versus normocapnia in adult patients undergoing general anesthesia. In July 2018 and September 2019 we searched ''CENTRAL'', ''MEDLINE'', and ''Embase'', checked reference lists of all included studies and relevant systematic reviews for additional references to trials. Two review authors independently assessed trials for inclusion, extracted data, and completed a ''Risk of bias'' assessment for all included studies.
Results: Our search identified 297 records after abstract screening 30 full-text papers remained for further examination. Ten publications met our inclusion criteria and were used for narrative description of this systematic review. Three studies were eligible for the meta-analysis normocapnia versus hypercapnia with the outcomes: time to extubation and adverse events. On average, time to extubation was significantly reduced in the hypercapnia group with a mean difference 3.78 (95% CI 0.85 to 6.71). No difference was found regarding adverse events.
Conclusions: The findings of our study do not enable us to produce evidence of a positive influence of increased CO_2 partial pressure levels during general anesthesia. A well-planned, adequately powered randomized controlled trial would be desirable in the future.
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Introduction

Targeting physiological ranges of end-tidal carbon dioxide is a cornerstone of what is called good anesthesia practitioning. The level of carbon dioxide influences several physiological pathways, especially organ perfusion, and interacts with pulmonary vasoconstriction and modulates inflammation.[1] Especially in different comorbidities, even mild lower ranges of carbon dioxide are chosen to influence cerebral perfusion or cardiac output.[2,3] For practical reasons hypocapnia is often used to suppress the breathing reflex and possibly reduce the dose of anesthetics in general anesthesia.[4,5] Data from animal models investigating ventilator induced lung injury have demonstrated a protective effect of hypercapnia on the lung tissue and inflammation as well as in the diaphragm.[6] Data suggest that hypercapnia even during regular anesthesia may influence wound healing, possibly via perfusion changes.[7–9] The work of Wax and colleagues even pointed to a reduction in the hospital length of stay for patients after colon resection and open hysterectomy, which might be a profound influence for health care costs and morbidity by the simple measure of allowing hypercapnia to occur during general anesthesia.[10] Besides this study there is only nebulous evidence about the influence of hypercapnia during general anesthesia on adverse events, or anesthesia-related factors, as time to extubation.

This systematic review and meta-analysis seeks to identify possibly positive effects of hypercapnia versus normocapnia in general anesthesia in adult patients. Especially effects on the occurrence of adverse events like wound healing, time to extubation or admission to the ICU are investigated.

Methods

The protocol of this systematic review is registered at Prospero: CRD42018104506. The reporting of this systematic review is in line with the PRISMA statement for the reporting of systematic reviews.[11]

Eligibility criteria

We included parallel-arm randomised controlled trials (RCTs) reported as full-text, those published as abstract only, and unpublished data. We included trials comparing hypercapnia versus normocapnia in adult patients (≥ 18 years of age) undergoing general anesthesia. Hypercapnia was defined as a carbon dioxide partial pressure ($paCO_2$) > 45 mmHg and conditioned by this a respiratory acidosis with pH levels < 7.35.[12] Normocapnia was characterised by a $paCO_2$ between 35–45 mmHg. As no core outcome set for clinical studies investigating anesthetic care is available, the list of outcomes chosen is based on outcomes presumably most relevant to patients and measures from possible matching studies; we assessed time to extubation, hospital length of stay, incidence of wound healing complications, hospital mortality and adverse events (e.g. nausea, vomiting).

Systematic search

We identified trials through systematic searches of the following bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (Ovid, from 1946 onwards), Embase (Ovid, from 1980 onwards).

The preliminary search strategy for MEDLINE (Ovid) was adapted for use in the other databases. The search strategy was: hypercapnia[Title/Abstract] OR hypercarbia[Title/Abstract]) AND (anaesthesia[Title/Abstract] OR anesthesia[Title/Abstract]). Search results were limited to those that were randomised controlled trials and review. The Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) was applied to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL. We searched all databases from their inception to the present, and we imposed no restriction on language of publication or publication status. We also checked reference lists of all included studies and any relevant systematic reviews identified for additional references to trials.

Selection of studies

Two review authors (JP, CBr) independently screened titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as ''retrieve'' or ''do not retrieve''. We retrieved the full-text study reports/publication and two review authors (JP, CBr) independently screened the full-text and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report is the unit of interest in the review. In September 2019 we updated our search. We describe the selection process in sufficient detail to complete a PRISMA flow diagram and ''Characteristics of excluded studies'' table (Figure 1 and Table 1).

Data extraction process

We used a purposely pre-developed data collection form for study characteristics and outcome data, which we piloted on one study in the review. Three authors independently (JP, KA, CK) extracted the following study characteristics from the included studies (also compare Table 1). Methods (study design, number of study centres, total duration of study, date of study, withdrawals/drop-outs, inclusion criteria, exclusion criteria, experimental intervention, control, outcomes mentioned in ''methods'', funding for trial, and notable conflicts of interest of trial authors), patient characteristics (hypercapnia, normocapnia, sex, age, weight, BMI, American Society of Anesthesiologists (ASA) physical status, smoker, diabetes, diagnosis, operation method, $paCO_2$, paO_2, FiO_2, end-tidal carbon dioxide levels, and intraoperative concomitant medication), and outcome data (time to extubation, hospital length of stay, hospital mortality, other reported outcomes mentioned). We double-checked the correctness of the data extraction. We transferred data into the Cochrane statistical software Review Manager.[13] We contacted investigator or study sponsors in order to verify key

Table 1 Overview characteristics of included studies.

Study	Study design	Sex										Intervention	Control
		Patients(n)		Male (n)		Female (n)		Age (years)		Weight (kg)			
		HC	NC	HC	NC	HC	NC	HC	NC	HC	NC		
Acka 2013	Multicentre RCT	590	616	303	310	270	288	51	53	77	78	$PE'CO_2 \approx 50$ mmHg	$PE'CO_2 \approx 35$ mmHg
Baker 1976	Single centre RCT	42	16	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a	n.a.	$PaCO_2 > 60$ torr; > 60 mmHg	$PaCO_2 = 25–60$ torr; 25–60 mmHg
Enoki 2005	RCT	24	24	9	10	15	14	53	54	56	55	$etCO_2 = 45$ mmHg, expecting $PaCO_2 \approx 50$ mmHg	$etCO_2 = 35$ mmHg, expecting $PaCO_2 \approx 40$ mmHg
Gao 2015	Single centre RCT	25	25	14	12	11	13	48.7	47.6	64.6	63.9	$PaCO_2 = 60$ to 70 mmHg	$PaCO_2 = 35$ to 45 mmHg
Hager 2006	Single centre RCT	15	15	3	5	12	10	45	49	189	157	$etCO_2 = 50$ mmHg	$etCO_2 = 35$ mmHg
Katznelson 2013	RCT	22	19	n.a.	n.a.	n.a.	n.a.	51.8	57.7	n.a.	n.a.	6% CO_2 in O_2 through the inspiratory relief valve (hypercapnia induced after skin closure)	Continued to breathe on the semi-open anesthesia
Kwak 2017	Single centre RCT	20	20	13	10	7	10	50	53	69	64	$etCO_2 = 45$ mmHg	$etCO_2 = 35$ mmHg
Nakai 2013	Single centre RCT	15	15	8	7	7	8	57.2	55.6	64.8	62.3	$etCO_2 < 55$ mmHg	$etCO_2 = 33$ mmHg
Nekhendzy 2007	Single centre RCT	60	60	33	30	27	30	47	53	86	77	$etCO_2 > 60$ mmHg	$etCO_2 = 37$ mmHg
Son 2017	Single centre RCT	127	120	0	0	127	120	43	42	60	60	$PaCO_2 = 46–50$ mmHg	$PaCO_2 = 36–40$ mmHg

HC, hypercapnia; NC, normocapnia; RCT, randomized controlled trial; n.a., not applicable; $etCO_2$ or $pE'CO_2$, end tidal carbon dioxide level.

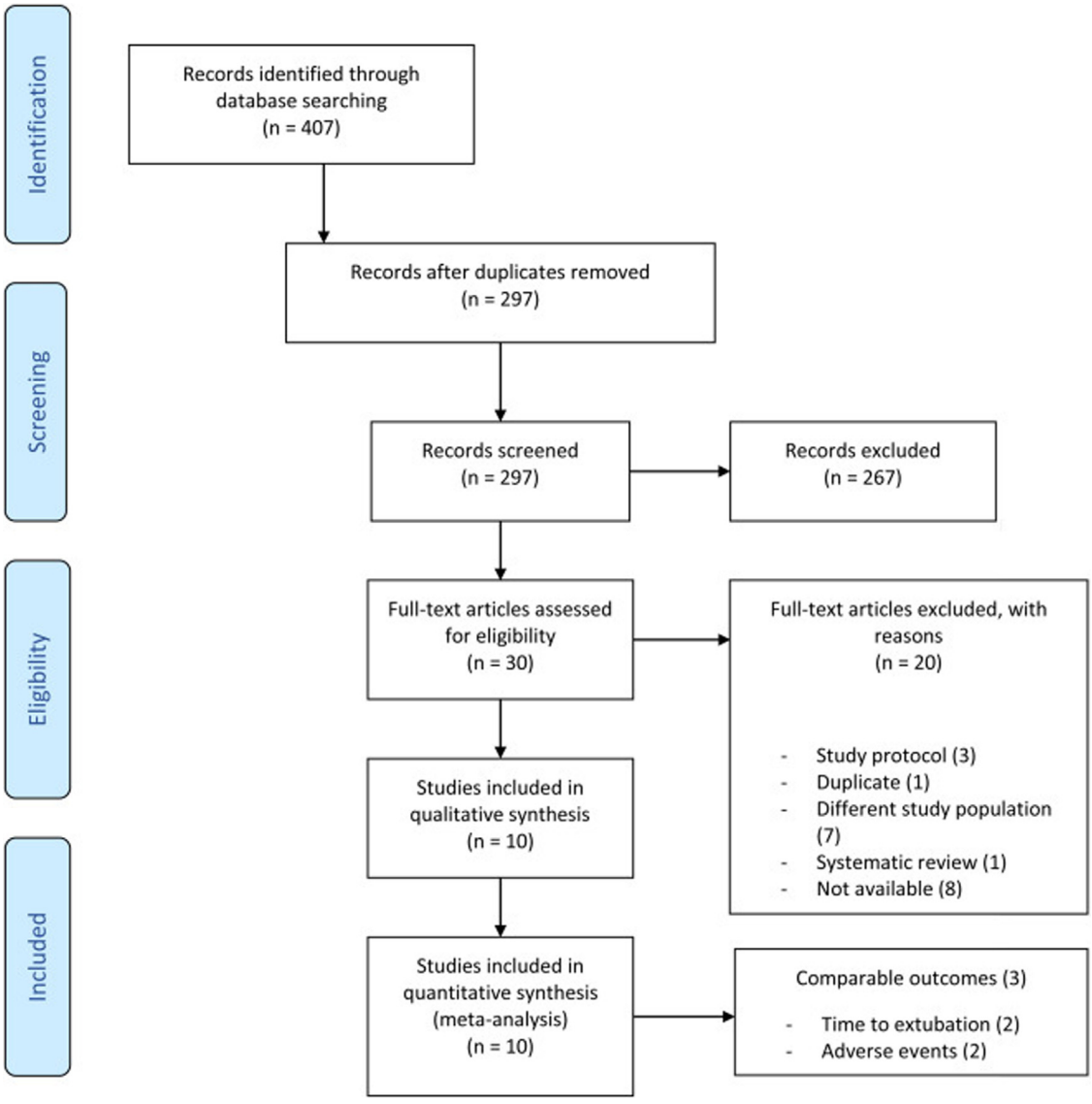

Figure 1 Flow diagram.

study characteristics and obtain missing numerical outcome data.

Assessment of risk of bias in included studies

Two authors (JP, CBe) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[14] We resolved any disagreements by discussion or by involving another author. We summarised the results of the ''Risk of bias'' assessment in both ''Risk of bias'' graph (Figure 2) and ''Risk of bias'' summary (Figure 3) for the following seven risk of bias domains: random sequence generation (checking for possible selection bias); blinding of participants and personnel (checking for possible performance bias); blinding of outcome assessment (checking for possible detection bias); allocation concealment (checking for possible selection bias); incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations); selective reporting (checking for reporting bias); and other bias (checking for other biases).

Measures of treatment effect

We analysed dichotomous data as risk ratios (RR) with 95% confidence intervals (CI). For continuous data, we used the mean difference with 95% CI for outcomes measured in the same way between trials. If pooling of data was not possible, we included a narrative summary of study results for the outcomes assessed in this systematic review.

Assessment of heterogeneity

Where we pooled data using meta-analysis, we assessed the presence heterogeneity by visual inspection of forest plots and by examining the X^2 (Chi^2) test for heterogeneity. We also assessed statistical heterogeneity in each meta-analysis using the Tau^2 (tau-squared), I^2 and Chi^2 statistics.

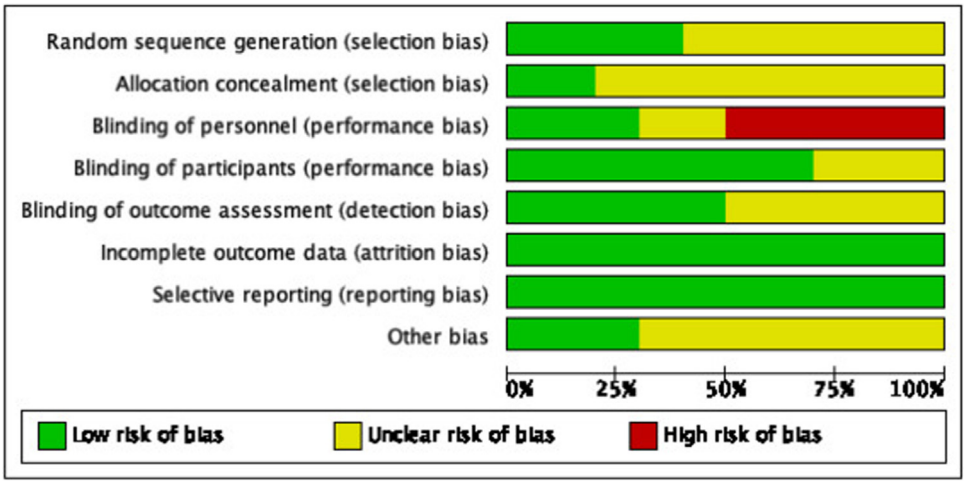

Figure 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

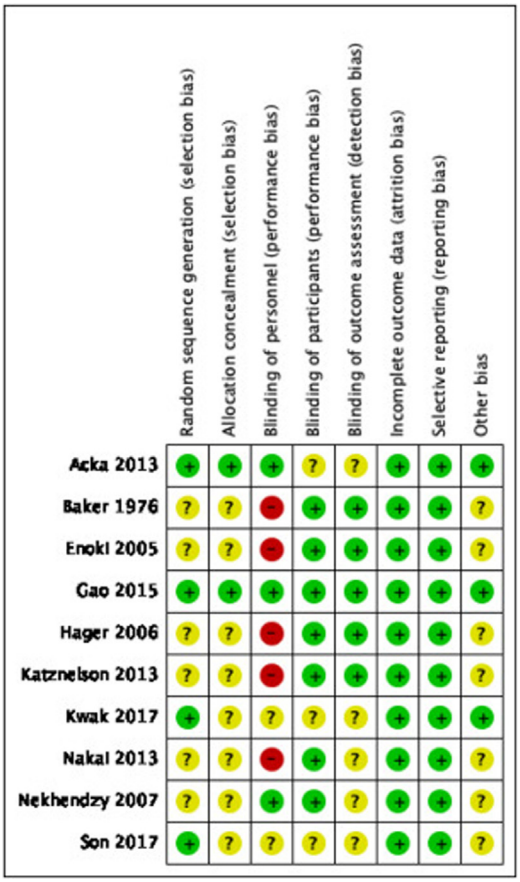

Figure 3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

We regarded heterogeneity as substantial, if the I^2 value was high (exceeding 30%); and either there is inconsistency between trials in the direction or magnitude of effects (judged visually) or there was a low *p*-value (<0.10) in the Chi^2 test for heterogeneity; or the estimate of between-study heterogeneity (Tau^2) was above zero.

Assessment of reporting biases

As we were not able to pool more than 10 trials, we did not create a funnel plot to explore possible small study biases.

Data synthesis

We undertook meta-analyses only where this was meaningful, i.e. the treatments, participants and the underlying clinical question were similar enough for pooling to make sense. Given the clinical heterogeneity in the setting of included studies (general anesthesia in a heterogenous patients), we used random-effects meta-analysis to produce an overall summary of average treatment effect across trials. We present results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Results

The search conducted on July 25, 2018 and on September 10, 2019 for an update identified 407 records. After duplicate removal, 297 records were screened during title-abstract screening of which 30 full-text papers were retrieved for further examination. Finally, 10 studies[7–9,15–21] met our inclusion criteria and were included in this systematic review. Katznelson and colleagues, Nakai and colleagues and Son and colleagues contributed data to the meta-analysis normocapnia vs. hypercapnia.[17,19,21] The study flow diagram is shown in Figure 1.

Study characteristics

The characteristics of included studies table shows full details of the included studies (Table 1).

Trial centres and design: Two studies performed multicentre trial, Akca and colleagues involved 6 hospitals and Enoki and colleagues involved 2 hospitals.[7,16] The other 8 studies performed single centre trials from which all were randomized controlled trials.[8,9,15,17–20]

Participants

A total number of 1,794 patients were included, comprising data on 969 female (54.0%), 767 male (42.8%) and 58 undefined (3.2%) patients (Baker and colleagues did not categorize its patients into male and female[15]). Akca and colleagues, Nekhenzy and colleagues, and Son and colleagues included minimal 60 participants per group. Baker and colleagues included 42 patients in the hypercapnia group but only 16 in the normocapnia group.[15]

Son included only women, the other studies included male and female patients.[21] In this systematic review we included the above mentioned studies comparing patients treated with hypercapnia or normocapnia. A total number of 901 patients were treated in a hypercapnia group (male 383; female 476; uncategorized 42) and 893 patients were treated in a normocapnia group (male 384; female 493; uncategorized 16).

Nakai and colleagues compared the influence of hypercapnia during surgery in elderly and middle-aged patients.[19] To avoid clinical heterogeneity in pooling of the studies we focussed on the data from middle-aged patients and excluded the data from elderly patients. There were 30 patients included in the hypercapnia group and 30 patients in the normocapnia group during the study of Nakai and colleagues.[19] From these 30 patients per group 15 patients were elderly people remaining 15 middle-aged participants in the hypercapnia and normocapnia group. The mean age of all patients was 50.6 (SD 4.5).

The mean age of the hypercapnia group was 49.6 (SD 4.3) and the mean age of the normocapnia patients was 51.7 (SD 4.7). There was significant clinical heterogeneity with regard to type of surgery among included studies, which has impact on the baseline characteristics of patients within this systematic review. For instance, the mean weight of all the patients is 80.2 kg (SD 37.7). However, without the obese patients by Hager and colleagues[9] the mean weight is 67.0 (SD 9.2).

Risk of bias assessment

Table 1 provides details about the risk of bias in the included studies. Figure 2 shows a summary of our risk of bias judgements across studies and Figure 3 shows the risk of bias judgement more detailed per study.

Random sequence generation and allocation concealement (selection bias)

Random sequence generation was at low risk of bias in four trials[7,8,18,21] and unclear risk of bias in six trials.[9,15–17,19,20] Participants were randomised using computer-generated numbers[7,18,21] or sequentially blocking based on a random number table.[8] Allocation concealment was at low risk in two trials[7,8] and unclear risk of bias in eight studies[9,15–21] Acka and colleagues used sealed, sequentially numbered envelopes and Gao and colleagues divided the patients into two groups based on the blocking scheme.[7,8]

Blinding (performance and detection bias)

Blinding of personnel was at low risk of bias in three trials,[7,8,20] unclear risk of bias in two trials,[18,21] and high risk in five studies[9,15–17,19] In the study of Acka and colleagues the anesthesiologists were not blinded to group assignments, but gas monitors were shielded to prevent surgeons from determining randomized group assignment.[7] Attending surgeons, who were blinded to the randomized assignments, made hospital discharge decisions and wounds were evaluated daily throughout hospitalization by an investigator blinded to treatment. Gao and colleagues used two anesthesiologists, one with access to the randomization, and one anesthesiologist who did not have knowledge of the gas monitor and arterial blood gas analysis data, performed bronchoalveolar lavage.[8] All surgeons were blinded during the study of Nekhendzy and colleagues.[20] Blinding of participants was at low risk of bias in seven trials.[8,9,15–17,19,20] During these studies, patients were not blinded but participants could not influence the outcome. Unclear risk of bias was found in three studies[7,18,21] Blinding of outcome assessment was at low risk of bias in five trials[8,9,15–17] and unclear risk of bias in five studies.[7,18–21]

Incomplete outcome data (attrition bias)

All included trials were at low risk of bias for incomplete outcome data. There was no missing data or less than 20% missing data which could be neglected.

Selective reporting (reporting bias)

All included trials were at low risk of bias for reporting bias. All studies described the results they mentioned in the methods section.

Other potential sources of bias

Other sources of bias were at low risk in three trials[7,8,18] and unclear risk of bias in seven studies.[9,15–17,19–21] Acka and colleagues, Gao and colleagues and Kwak and colleagues provided information about the funding of the study.[7,8,18] Acka was supported in part by the Gheens Foundation (Louisville, KY, USA) and the Mater College for Postgraduate Research (Ireland).[7] Viasys Healthcare (Wheeling, IL, USA) provided the Hi-Ox Oxygen masks. All personnel financial interests have been disclosed. Gao was supported by a grant from the Medjaden Academy and Research Foundation for Young Scientists (Hong Kong, China).[8] All funding sources of Kwak were departmental and the authors declared to have no competing interests.[18]

Effects of interventions

Due to significant heterogeneity in outcome measurement and reporting, pooling of data for meta-analysis was only meaningful for two outcomes time to extubation and adverse events nausea/vomiting.

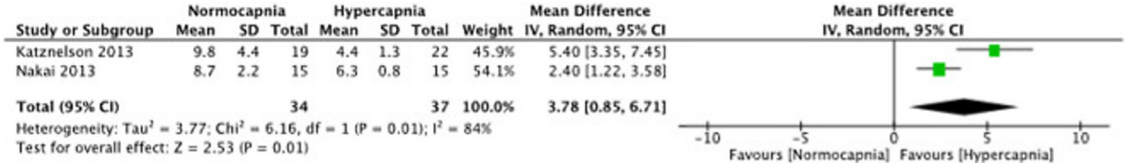

Figure 4 Forest plot of comparison: 1 Normocapnia versus hypercapnia, outcome: 1.1 Time to extubation.

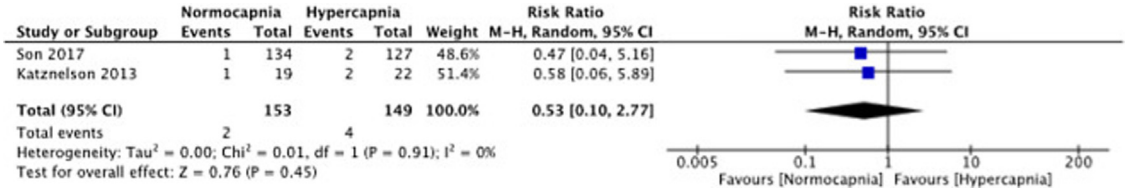

Figure 5 Forest plot of comparison: 1 Normocapnia versus hypercapnia, outcome: 1.2 Adverse events (nausea, vomiting).

Time to extubation

Among the 10 trials that met the inclusion criteria of the meta-analysis, only two (Katznelson; Nakai) trials measured time to extubation.[17,19] On average, we found that the time to extubation was significantly reduced in the hypercapnia group with a mean difference 3.78 (95% CI 0.85 to 6.71); 2 studies; 71 patients; $I^2 = 84\%$; Figure 4. Heterogeneity was substantial as I^2 was greater than 30%, the *p*-value for Chi^2 was 0.01 and Tau^2 was 3.77.

Adverse events (nausea, vomiting)

Two studies (Son and colleagues; Katznelson and colleagues) measured adverse events.[17,21] On average, no difference with regard to adverse events was reported among participants in the normocapnia or hypercapnia group with RR 0.52 (95%CI 0.10 to 2.76); 2 studies; 6 events; $I^2 = 0\%$; Figure 5. There was a low risk of heterogeneity as I^2 was 0% and the *p*-value for Chi^2 was 0.91.

Incidence of wound healing complications

The work of Akca and colleagues investigated the incidence of surgical site infections, but did not find a significant difference inbetween hypercapnic and normocapnic group.[7]

Hospital length of stay and hospital mortality

None of the included studies reported on hospital length of stay or mortality.

Discussion

Our systematic database research showed a very heterogenous set of studies. Following title and abstract screening we detected among the full-text articles assessed for eligibility a vast part with poor data according to our inclusion criteria. Due to that fact we were only able to pool a few studies helping to answer our research question, if hypercapnia during general anesthesia might have positive or negative effect on patient's outcome, morbidity and mortality.

Whereas physiological effects of mild changes in CO_2 levels on organ perfusion, hemodynamics, heart function and respiration are well examined; Wax and colleagues' study was the first to show an association of increased end-expiratory CO_2 levels during general anesthesia and length of hospital stay.[10] In our systematic review we found several studies examining intraoperative CO_2 levels connected to a mass of diverse physiological and clinical parameters. Unfortunately, we were not able to find another work beside Wax and colleagues that could produce profound evidence of an impact of hypercapnia during general anesthesia on hard criteria as length of hospital stay or admission to ICU.[10]

Regional effects of hypercapnia

Among those studies eligible for full text analysis and data extraction several authors investigated cellular processes such as tissue perfusion, inflammatory response, and wound healing.

Akca and colleagues focused on decreased wound infections depending on increased tissue pO_2 in hypercapnia.[7] Despite a trend towards a decreased rate of surgical site infections in the hypercapnia group (11.2% vs. 13.3%) the study was interrupted by the Executive Committee in interim analysis (n = 1206) because a significant difference after full sample size of n = 2000 patients was not to be expected.

Hager and colleagues worked on improvement of tissue oxygenation by increased CO_2 levels.[9] Whereas p_aO_2 was identical in hypercapnia and normocapnia group, subcutaneous tissue oxygenation was significantly greater in hypercapnia group ($p_{sq}O_2$ mean ± SD [mmHg], 78 ± 31 vs. 56 ± 13).

Gao and colleagues examined suppression of inflammatory response in accordance to hypercapnia in one lung ventilation during lobectomy (8). The hypercapnia group showed a lower expression of tumor necrosis factor (BALF and Interleukins) and required lower respiratory peak (mean ± SD [cmH_2O], 22.2 ± 2.9 vs. 29.8 ± 4.6) and plateau pressures (20.5 ± 2.4 vs. 27.1 ± 2.9) during operation resul-

ting in higher dynamic compliance (mean ± SD [ml.cm^{-1} H_2O], 46.6 ± 5.8 vs. 38.9 ± 6.5).

These data demonstrate a regional effect of hypercapnia on cellular pathways, tissue perfusion and local oxygenation, and suggest an influence on patient's recovery which is still to be subject of further investigations.

Hemodynamic effects

Another frequently investigated subject was the influence of mild hypercapnia on hemodynamics.

Enoki and colleagues observed arterial hypotension after induction of anesthesia.[16] They were able to show a significantly lower rate of hypotension 15 minutes after induction of anesthesia with Thiopental-Isoflurane in the hypercapnia group (mean systolic arterial pressure, 116 vs. 103, $p < 0.05$), which was absent in propofol anesthesia).

Kwak and colleagues observed oxygenation and changes in hemodynamics due to hypercapnia.[18] In sitting position during shoulder arthroscopy under general anesthesia the incidence of cerebral desaturation was significant lower in the hypercapnia group (0/20 vs. 5/20), regional cerebral oxygenation was significantly increased in the hypercapnia group ($p < 0.05$). Mean arterial pressure and heart rate were not influenced by hypercapnia.

In summary these data elaborate a CO_2 dependence of hemodynamics, especially mild hypercapnia seems play a role in avoidance of hypotension and cerebral desaturation under general anesthesia.

Effects of hypercapnia on outcome parameters

Unfortunately, most of these collected parameters were not able to be connected with either adverse events or positive effects on patient recovery nor were these data comparable to be pooled. The studies mentioned above did not investigate an effect of their findings to further course of hospital stay but focused on intra- and perioperative settings (see above). Questioning several authors of unpublished data concerning our point of investigation was denied.

Finally, we were only able to pool three studies that worked on hypercapnia related effects on general anesthesia and measured the same parameters as time to extubation and adverse events (nausea/vomiting). We were able to compare the outcomes of Katznelson and colleagues and Nakai and colleagues on time to extubation[17,19] and the data of Katznelson and colleagues and Son and colleagues concerning adverse events.[17,21] In our meta-analysis we found a significant decreased time to extubation in the hypercapnia group. In the work of Katznelson and colleagues time to extubation was less than half in the hypercapnia group (4.4 ± 1.3 to 9.8 ± 4.4 min).[17] It is well known that CO_2 partial pressure appears to be the strongest physiological trigger for respiration in glomus caroticum and central nervous system.[22] Patients with increased CO_2 levels under general anesthesia show a much shorter time to extubation – in the trial of Katznelson and colleagues even almost half compared to the normocapnia group – probably due to an increased respiration drive.[17] These findings could lead to a diminished overall time in the OR to sustain patients recovery and save clinical resources.

Whereas our meta-analysis of time to extubation consisted of an overall population of 71 patients, further trials with a larger set would be desirable in future.

The meta-analysis of adverse events contained a larger population of 302 patients. The pooled data of Katznelson and colleagues and Son and colleagues did not show a significant increased prevalence of adverse events as postoperative nausea and vomiting in the hypercapnia or normocapnia group.[17,21]

Limitations

Ten studies matched the inclusion criteria of our systematic review, however, due to significant heterogeneity in outcome definition, measurement and reporting, we were only able to include few studies in our meta-analysis focusing on the influence of intraoperative CO_2 partial pressure levels to patient's outcome. Also, patient population of the included studies consisted of relatively small sample sizes. However, based on the evidence that we have cited we are confident to have identified all studies in the field concerning this research question highlighting the need for a well planned and adequately powered randomized controlled trial.

Conclusion

These findings do not enable us to produce evidence of a positive influence of increased CO_2 partial pressure levels during general anesthesia on morbidity or mortality. However, it could be shown that increased CO_2 partial pressures leads to an earlier extubation in comparison to normal intraoperative CO_2 levels.

Since only a limited number of patients were included in well randomized studies, a large prospective randomized trial is warranted/desireable to define the value of high PCO_2-levels during surgery.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

We acknowledge the authors of the primary studies included in the meta-analyses, who have kindly provided additional data and information regarding their studies.

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CASE REPORT

General anesthesia for old Werner syndrome patient: a case report



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KEYWORDS
Aged;
Airway management;
Anesthesia, general;
Werner syndrome

Abstract Werner syndrome (WS) is a rare autosomal recessive, premature aging disorder whose clinical manifestations include short stature, bilateral cataracts, diabetes mellitus, hypertension, and atherosclerosis. WS first manifests during adolescence and patients usually die at 40–50 years of age. Only symptomatic treatment options available according to clinical manifestations. In anesthetic management, they need to be considered to elderly patients. Difficult intubation is expected and the patients are regarded as a high-risk group for anesthesia, owing to the concomitant cardiovascular and cerebrovascular disorders. The anesthetic management of WS requires a meticulous preoperative history taking, physical examination, and preparation for cardiovascular events.
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Introduction

Werner syndrome (WS) is a rare autosomal recessive, premature aging disorder affecting 1 in 1 to 10 million individuals of the population. The incidence of WS is significantly higher in Japan and North Sardinia. It occurs due to the mutation of the *WRN* gene that inactivates the function of helicase involved in DNA replication, repair, and telomere maintenance.[1]

The clinical features of WS include senile appearance, short status, muscle hypoplasia, progeroid changes in hair, bird-like facies, skin ulcers, and voice abnormalities. Progressive manifestations such as bilateral cataracts, osteoporosis, hypogonadism, diabetes mellitus, hypertension, atherosclerosis, and neoplasms lead to death.[2] The disease first manifests during adolescence and patients usually die at the age of 40–50 years. There are no disease-targeting treatments for WS, and only symptomatic treatments are available.

Atherosclerosis is one of the key features of WS. Peripheral arterial occlusive disease is common among patients, and intractable skin ulcers or gangrene of the lower limb may also occur.[2] We described a rare case of an old patient with WS who was administered general anesthesia for femoral popliteal bypass surgery.

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Case presentation

The patient provided written consent for the publication of this case report. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of Kyung Hee University Hospital (ethics code:2020-07-007, approval date: 2020.07.03).

A 65-year-old man diagnosed with WS was scheduled for femoral popliteal bypass surgery. The patient had an intractable skin ulcer with claudication due to peripheral arterial occlusive disease, and the vascular surgeon decided on surgical intervention.

The patient met all the cardinal signs and symptoms of WS.[2] He was 152 cm tall and weighed 38 kg. He had been prescribed aspirin, candesartan, trimetazidine, alogliptin, glimepiride, rosuvastatin, ezetimibe, sarpogrelate, limaprost, thioctic acid, and oxycodone for hypertension, stable angina, diabetes mellitus, cerebral infarction, and pain from calcific tendinitis of both Achilles tendon and right elbow. He underwent cataract surgery for both eyes under local anesthesia in his thirties, and completely lost his hair in his forties.

Physical examination revealed that the patient had a pinched face with small chin and sparse pubic hair. The patient's voice was high pitched and he stated that he had a ''feminine'' voice since childhood. The patient's American Society of Anesthesiologists (ASA) physical status was III.

We decided to administer general anesthesia after a cautious review of the patient. Regional anesthesia was excluded because his prothrombin time was prolonged (15.2 s) and activated partial thromboplastin time was 53.5 s. Intraoperative heparin use and possibility of a prolonged operation duration led us to select general anesthesia for the procedure.

We identified that the patient had severe limitations in flexion and extension of neck during the airway assessment. In addition to the poor dentation and relatively small chin, the thyromental distance was 5 cm, and his mouth opening was restricted to 2 fingers' distance (Fig. 1). The Mallampati grade was III. Right vocal cord paralysis was observed by an otolaryngologist (Fig. 2). We predicted difficulty in intubation and prepared a McGrath Mac videolaryngoscope (Covidien France SAS, Paris, France) with endotracheal tubes of various sizes. Moreover, an airway emergency cart was prepared, including a fiberoptic bronchoscope, before the patient was brought to the operating room.

Noninvasive blood pressure, heart rate, electrocardiography, oxygen saturation, bispectral index, and train-of-four (TOF) monitoring was performed during the entire duration of anesthesia. His blood pressure, heart rate, and peripheral oxygen saturation were 173/83 mmHg, 118 beats per min, and 100%, respectively, on arrival at the operating room. He was premedicated with glycopyrrolate 0.2 mg and preoxygenated with 100% oxygen for 5 minutes. We used propofol 60 mg and remifentanil 1 $\mu g.kg^{-1}.min^{-1}$ for anesthesia induction. TOF monitoring was performed at 15-seconds intervals by using the right ulnar nerve. After checking that the patient had attained a state of unconsciousness, manual ventilation was initiated with sevoflurane 2.5%, and rocuronium 40 mg was injected. The difficulty in mask ventilation was relieved by intraoral airway placement and the two-handed technique. Intubation was performed successfully with an endotracheal tube with an internal diameter of 7.0 mm using a videolaryngoscope, taking great care to avoid further damage to the already paralyzed vocal cord. Subsequently, continuous arterial pressure monitoring was performed through the left radial artery, and a central line was inserted into the right internal jugular vein under ultrasound guidance.

The heart rate decreased as the surgery progressed and was maintained within the range of 70 to 90 beats per min. The blood pressure was stabilized during the surgery using phenylephrine 0.5–1.51 $\mu g.kg^{-1}.min^{-1}$ and remifentanil 0.25–0.5 $\mu g.kg^{-1}.min^{-1}$. An infusion of 500 mL of volulyte and 1000 mL of plasma solution and transfusion of 2 units of red blood cells were performed. We maintained sevoflurane at a minimum alveolar concentration of 1.0, considering that the body is older than the chronological age. The depth of anesthesia was maintained properly between 35 and 50 bispectral index values during surgery, without significant changes on electroencephalography. The total anesthesia time was 5 hours and 15 minutes.

Concerned about respiratory depression, we did not use any other analgesics except fentanyl in intravenous patient-controlled analgesia (IV-PCA) for postoperative pain control. The IV-PCA regimen consisted of fentanyl 500 μg and ramosetron 0.6 mg and was programmed to deliver 2 $mL.h^{-1}$ as a background infusion, a demand volume of 0.5 mL, and a lock-out interval of 15 minutes with a total volume of 100 mL.

After surgery, post-tetanic count of 2 was checked, and muscle relaxation was reversed by sugammadex 150 mg (4 $mg.kg^{-1}$). Extubation was performed after confirming a TOF ratio of 0.9 and spontaneous ventilation. However, his drowsiness persisted. He did not respond to light stimuli but only to painful stimuli. The bispectral index remained between 70 and 80. He was transferred to the intensive care unit (ICU) for monitoring of consciousness and vital signs. He became alert within 12 hours and was transferred to the general ward in 2 days. As staying in ICU, only a single dose of meperidine 25 mg was administered intravenously except IV-PCA for postoperative pain, and the pain was managed under 3 points in numerical rating scale. The patient was referred to a physiatrist for rehabilitation due to the risk of aspiration due to vocal cord paralysis. He was discharged from the center 14 days after surgery without any complications.

Discussion

WS is a rare autosomal recessive disease caused by loss-of functions mutations in the *WRN* gene that impair DNA replication, repair, and telomere maintenance.[1] It is also known as adult progeria because the symptoms start in early adolescence, which is considerably late compared to Hutchinson-Gliford progeria syndrome. The average lifespan ranges from 30 to 54.3 years. The main causes of death include myocardial infarction and malignancy, and there are no specific treatments that target the syndrome itself.

Our patient was fairly old considering the average lifespan of patients with WS. Recently, treatment with HMG-CoA reductase inhibitors (statins) and peroxisome

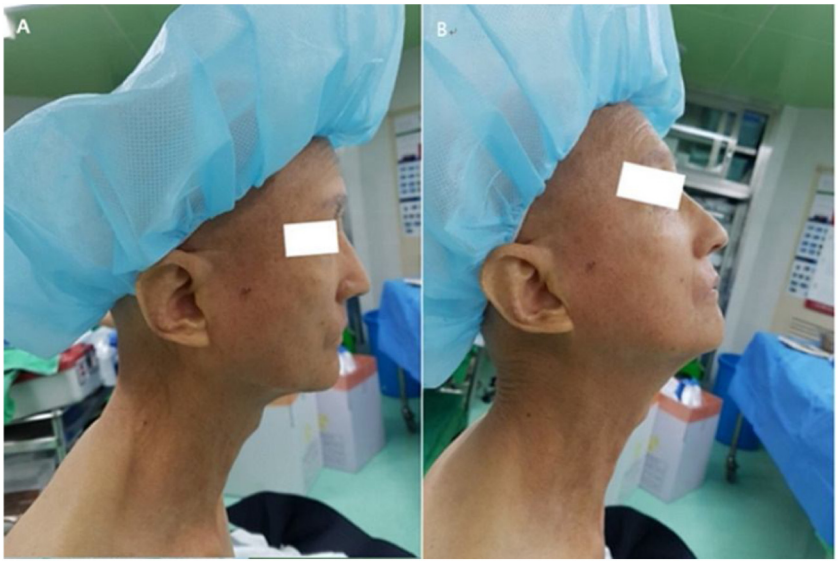

Fig. 1 Patient airway assessment before anesthesia in neutral position (A) and neck extension (B).

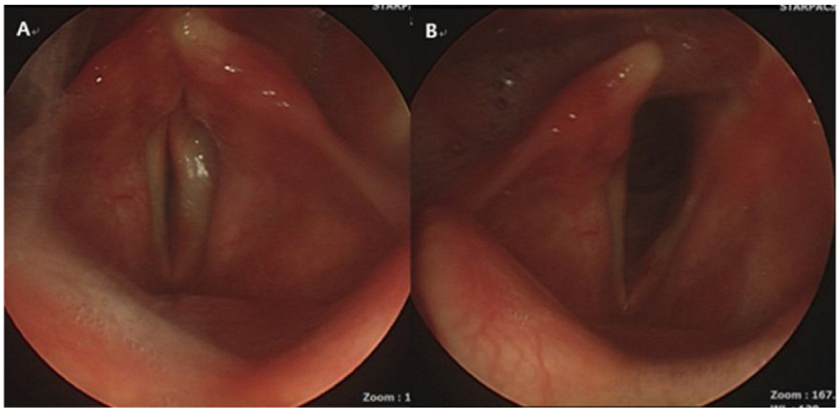

Fig. 2 Fiberoptic view of vocal cord before surgery. Closed (A) and open (B).

proliferator-activated receptor gamma agonists (pioglitazone) has prolonged the lifespan of these patients, by stabilizing the telomeres and preventing apoptosis.[3] These treatments prevent cellular dysfunction and delay fatal outcomes. Early diagnosis and administration of these drugs could aid in improving the quality of life and prolong the lifespan in patients with WS, despite the availability of only symptomatic treatment options according to the clinical manifestations.

The anesthetic management of patients with WS is challenging because of the possibility of a difficult airway and comorbidities that may cause complications during anesthesia and surgery. There are few studies and case reports on anesthesia in WS due to the rarity of the syndrome itself. Regional anesthesia or local anesthesia should be primarily considered if the patient does not have any coagulation disorders owing to the risk of managing a difficult airway.

However, the anesthesiologists chose general anesthesia for this patient after considering the preoperative medication, prolonged operation, intraoperative heparin use, and patient compliance. It is vital for the operators to be prepared for dealing with a difficult airway and cardiovascular compromise during anesthesia. The small mouth, poor dentition, mandibular hypoplasia, maxillary hypoplasia, and craniofacial abnormalities make intubation challenging, and it is essential to evaluate the patient's airway prior to surgery. Awake bronchoscopic intubation should be considered, and a difficult airway cart should be ready with the patient's arrival into the operating room. Small face masks and laryngeal mask airway might be required, because the patient's body is relatively small, and it is natural that a small endotracheal tube be used for intubation.

The accompanying comorbidities should be assessed meticulously before surgery. In addition to obtaining the medical history, a multidisciplinary approach, including a molecular biological assessment, is necessary. Patients with WS are considered to be at a high risk for myocardial infarction, cerebral infarction, and hemorrhage caused by atherosclerosis. Continuous arterial pressure monitoring is recommended along with preparation for extensive cardiovascular events.

Anesthesiologists are requested to consider residual effects of drugs because respiratory depression in WS patients can cause drastic outcome due to the patients' appearance. Extubation has to be performed after neuromuscular transmission confirmed complete recovery of muscle relaxation.

Also, pharmacodynamic and pharmacokinetic characteristics including drug interactions have to be reviewed in choosing anesthetics especially for opioids. Remifentanil was the only opioid used during anesthetic time in this case due to its very short life-time and not context-sensitive characteristic. Short-lived anesthetics are preferred for rapid emergence in general anesthesia of WS patients.

The volume of distribution of lipophilic drugs is increased, and most intravenous and inhalation agents used by anesthesiologists have a longer elimination phase, considering that the body age is far greater than the chronological age, and that the total body water decreases with aging.[4] The dose of anesthetics and other drugs should be adjusted in a manner similar to that for elderly patients.

Conclusion

Few studies have reported on general anesthesia in patients with WS. Preoperative evaluation including airway assessment is crucial, and preparation for a difficult airway and possible cardiovascular events are essential. All medications and anesthetic management should be provided according to the guidelines for the anesthetic management of elderly patients, considering that the body has aged more than the chronological age.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Transient unilateral lingual nerve injury following the use of laryngeal mask airway Supreme: a case report



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KEYWORDS
General anesthesia;
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Prednisolone;
Sensation disorders

Abstract Lingual nerve injury rarely occurs after using the laryngeal mask airway (LMA). A 40-year-old woman with no comorbidities visited the hospital for left breast-conserving surgery. Anesthesia was performed using LMA Supreme™. She complained of decreased sensation in the right front part of the tongue postoperatively. She received prednisolone and tongue sensation returned on postoperative day 28. The lingual nerve could be damaged by the LMA, particularly the lateral edge of the tongue base and inner part of the mandible around the third molar. When using the LMA, it is necessary to check the cuff pressure to prevent lingual nerve damage.
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Introduction

If the laryngeal mask airway (LMA) is properly mounted, the tip of the LMA is placed between cervical vertebrae 6 and 7, i.e., the side of the upper esophageal sphincter and lower boundary of the hypopharynx.[1] Although the LMA is associated with several complications, cranial nerve injury rarely occurs. Therefore, determining its incidence rate is difficult. Furthermore, the mechanism of damage is unclear. Here, we report a case of abnormal tongue sensation caused by temporary lingual nerve damage in a patient without any underlying disease who was administered general anesthesia using an LMA to undergo left breast-conserving surgery.

Case report

Informed consent to publish the case report was obtained from the patient. The institutional review board of our institute approved this study (IRB#: NCC2021-0037).

A 40-year-old woman (height 163.6 cm and weight 41.5 kg) with no specific medical history was diagnosed with invasive ductal carcinoma in the left breast. She was admitted to our hospital to undergo left breast-conserving surgery with axillary lymph node dissection. No metastasis to bones or other organs was observed on preoperative examination. Blood test, electrocardiography, and chest radiographic findings were normal. At the time of admission to the operating

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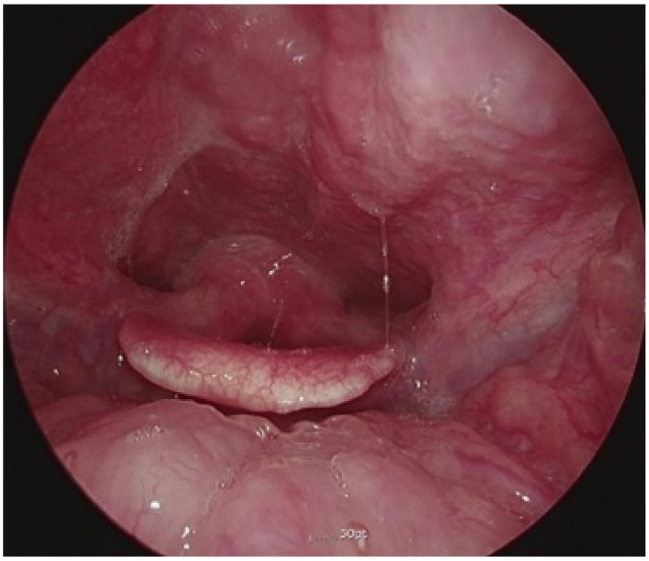

Figure 1 Normal laryngoscopic findings of the patient.

room, her blood pressure was 150/67 mmHg, pulse rate was 103 beats.min^{-1}, and percutaneous oxygen saturation was 99%. For anesthesia induction, total intravenous anesthesia was initiated by setting the target concentrations of propofol and remifentanil to 6 μg.mL^{-1} and 3 ng.mL^{-1}, respectively, using a target-controlled infusion pump under oxygen inhalation of 6 L.min^{-1}. After loss of consciousness and availability of manual bagging, vecuronium 3 mg was intravenously injected. After confirming that the muscle was relaxed, as Train of Four was 0, LMA Supreme™ No. 3 lubricated with normal saline was inserted and mounted without any resistance. After introducing the LMA, both lung sounds and chest movements were symmetrical without any sounds over the epigastrium and no audible leak. In addition, the curve of the end tidal carbon dioxide monitor on the ventilator was normal. There were no specific problems during the surgery, including the patient's blood pressure which was maintained at normal, and the LMA was removed after consciousness and spontaneous breathing returned. No signs of bleeding were noticed in the posterior region of the LMA at the time of removal. The total operative time was 1 h and 20 min and anesthesia time was 2 h and 5 min. There was almost no bleeding during the operation, and the total amount of crystalloid administered was 550 mL.

The patient recovered in the recovery room without any specific problems and was transferred to the general ward. At the time patient arrived to the general ward, there was no problem with tongue movements. However, the patient complained of numbness in the right front part of the tongue in addition to decreased sensation compared with the left part of the tongue. Nevertheless, tongue deviation or vocalization problems were not observed. The patient started eating porridge from the evening of the surgery and there was no problem with taste sensing and food swallowing at that time. On postoperative day 1, the aforementioned symptoms were checked by an otolaryngologist, and laryngoscopy did not reveal any damage to the structures in the oral cavity. Furthermore, there were no problems with larynx movement (Fig. 1).

Otolaryngological examination revealed that loss of sensation was a symptom caused by a temporary right lingual nerve injury, which could be improved. From postoperative day 1, prednisolone 40 mg was administered for 3 days based on the discretion of the doctor in charge; the dose was reduced by half (20 mg → 10 mg → 5 mg → stop) each day.

From postoperative day 2, the tongue sensation of the patient gradually started to return. On postoperative day 4, when the sensation was tested by stimulating the tongue with a toothpick and cotton swab, it was noted that the symptoms had improved. The sensation in the right front half of the tongue was approximately 40% of that in the left front half and felt similar on both sides of the posterior half. On postoperative day 6, the sensation in the one-third part of the right side of the tongue was approximately 60% of that in the left side, and there was no difference in the sensation between the right and left sides in the remaining part of the tongue. On postoperative day 28, all senses of the tongue had returned to normal.

Discussion

The lingual nerve branches off from the mandibular nerve, goes between the lateral pterygoid muscle and medial pterygoid muscle, and passes around the ramus of the mandible. It passes the inner side of the mandible around the third molar, and at the front, it passes the hypoglossus muscle and arrives at the tongue. Finally, this nerve forms a terminal branch at the bottom of the mucosa of the tongue. This nerve is responsible for sensation in the anterior two-third of the tongue. Around the ramus of the mandible, it meets the chorda tympani nerve, a branch of the facial nerve, which is responsible for taste in the anterior two-third of the tongue.

The lingual nerve could be damaged by LMA. In particular, the lingual nerve is known to be damaged at the lateral edge of the tongue base or inner mandible around the third molar.[1] As the chorda tympani nerve is present on the path of the lingual nerve, damage to the lingual nerve could result in changes in tongue sensation as well as in taste. In case of lingual nerve damage, abnormal tongue sensation occurs at the front of the tongue within a few minutes to at least 24 h after LMA insertion.

Use of nitrous oxide (N_2O), incorrect placement of LMA, LMA cuff pressure of >60 cmH_2O, or incorrect size of the LMA can result in lingual nerve damage.[1] Traumatic insertion by not inserting the LMA smoothly, secondary chemical nerve injury using the incorrect lubricant during LMA insertion, long surgical time, strong head turning during surgery, or postural problems, including the prone or lateral position, could also result in lingual nerve damage. Furthermore, patients with diabetes or peripheral vascular disease as an underlying disease may be affected.[1]

For most patients, lingual nerve damage naturally improved without treatment, generally within several hours to around 6 months.[1] Besides, psychotherapy, antidepressants, steroid, and anticonvulsants could be helpful, and nerve block or surgical repair can also be an option.[2]

In the present study, the patient had no underlying disease, her body mass index was 15.5 kg.m^{-2}, and N_2O was not used during anesthesia. Furthermore, tidal volume, peak

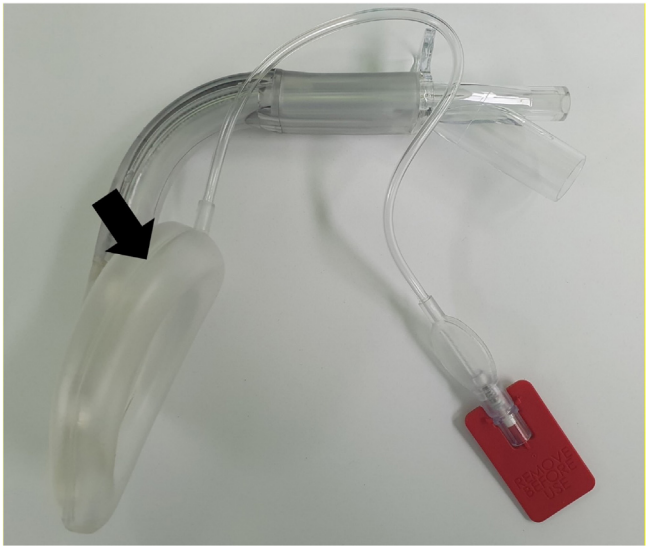

Figure 2 Laryngeal mask airway (LMA) Supreme No. 3. The black arrow indicates the possible region of the LMA responsible for the nerve damage.

inspiratory pressure, and plateau pressure were within normal ranges during surgery, confirming that there was no problem with the LMA placement. During LMA insertion, the LMA was lubricated with normal saline and smoothly inserted to ensure that there was no chemical damage or traumatic insertion. During surgery, the patient was maintained in the supine position, and the surgery duration was not long. Therefore, this temporary lingual nerve damage could have been due to overpressure to the cuff caused by not monitoring cuff pressure (Fig. 2).

Presently, LMA is classified and chosen based on the patient's weight. LMA Supreme™ No. 3, used in this case, is generally used for patients weighing 30–50 kg. The manufacturer recommends the injection of <30 mL of air in the cuff and the maintenance of cuff pressure at <60 cm H_2O. In our case, 20 mL of air was injected for proper airway seal. According to a study, although N_2O is not used, the cuff pressure can be higher than the recommended level as the anesthesia time elapses in three-fourth of the patients.[3] There are reports on nerve injuries caused by LMA ProSeal™ or LMA classic™, which could have ballooned the cuff, like LMA Supreme™ in this case; however, lingual nerve injury has also occurred due to i-gel™, which cannot balloon the cuff.[4] According to Brimacombe et al.,[5] even if the cuff volume suggested by the manufacturer is injected, perfusion decreases in the tissue to which the cuff touches, resulting in nerve or tissue damage. Therefore, even if the suggested cuff volume is well maintained, it is necessary to check the cuff pressure.

In conclusion, when considering this case to prevent lingual nerve damage during anesthesia, if LMA that can control the cuff volume is used, the cuff pressure needs to be checked using a manometer immediately after LMA insertion. Furthermore, additional checking is necessary in case of long surgeries. Although the incidence rate of lingual nerve injury is very low and usually is improved without leaving any complications, the most important thing to prevent injuries caused by anesthesia is to use the LMA correctly.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL IMAGES

A case report of ''pearl necklace'' in the abdomen: magnetic beads ingestion resulting in an anesthetic emergency

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Accidental ingestion of magnetic foreign bodies is a common pediatric problem attributed to the increasing availability of magnetic toys. A single magnet ingestion may be harmless; however, swallowing of numerous magnets can lead to catastrophic consequences.[1] The image from a 4-year-old boy following ingestion of 36 magnetic beads showed a tight intact beaded ''pearl necklace'' appearance located in the right abdomen (Fig. 1). The ingestion and possible magnetic beads interaction across the intestinal wall propose the risk of pressure-induced intestinal necrosis with forces up to 1,300 G, contributing to subsequent obstruction, fistulation, perforation, and even toxic shock.[1]

Urgent removal often requires the use of general anesthesia and is recommended in all cases of multiple magnet ingestion, unlike the expectant approach performed in the majority of foreign body ingestion. For the urgent removal, a rapid-sequence anesthesia induction and endotracheal tube should be preferred due to a possibility of a full stomach and the need to secure the airway.[2] Although magnetic beads are radio-opaque and abdominal radiography is the best choice for diagnosis, ultrasound-guided fast evaluation conducted by anesthesiologists may be more helpful in determining the location of magnets before skin incision in emergency laparoscopic surgery.[3] Considering the potential serious complications, including septic shock from intraperitoneal infection and significant intraprocedural hemorrhage owing to the erosion of mesenteric vessels between the magnets, large bore intravenous access for rapid infusion and an arterial line for monitoring real-time hemodynamics should be

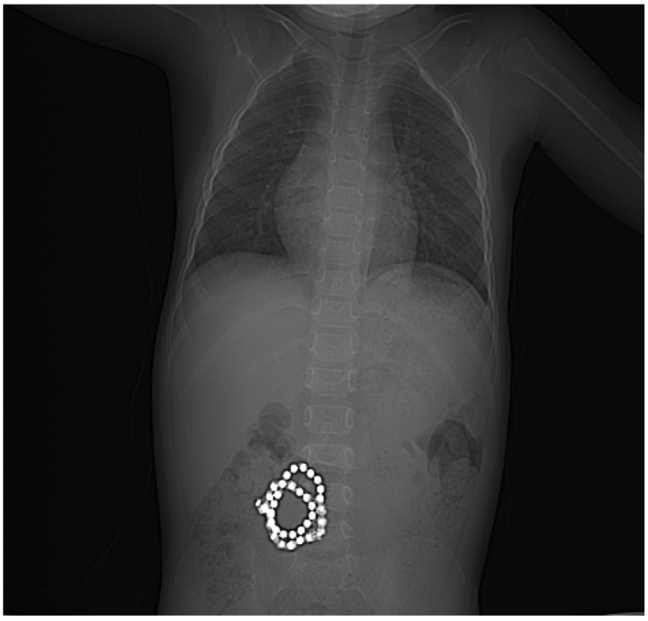

Figure 1 The figure showed a tight intact beaded ''pearl necklace'' appearance located in the right abdomen in a 4-year-old boy following ingestion of 36 magnetic beads.

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preoperatively obtained. Patients with complications may be appropriately transferred to the intensive care unit intubated and sedated for further treatment after surgery. The written informed consent was obtained from the patient's guardian.

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Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL IMAGES

A simple technique to maintain intraoperative head and neck neutrality



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During laparoscopic cholecystectomy, the left-tilt plus reverse Trendelenburg positioning required can result in the head and neck being turned to an extreme left and/or flexed position (Fig. 1A). In certain upper extremity surgeries, the patient is positioned at the edge of the table and the patient's head is at risk of drifting unnoticed off the edge (Fig. 1B).

Excessive head rotation is potentially harmful. Weintraub and Khoury have shown that major occlusion of the vertebral artery occurs in 56.4% and 13.3% of patients with (mean age 71 years) and without (mean age 66 years) vascular risk factors, respectively, upon maximum head rotation.[1] In adults, Burbridge et al have found that 80% of the internal jugular vein is occluded during head turn of ~55°, potentially raising intracranial pressure.[2] Carotid dissection has been reported in a 36-year-old healthy woman clutching her phone between her head and shoulder for 32 minutes.[3] One may speculate that carotid compression plus reverse Trendelenburg positioning could compromise cerebral perfusion. Patients with cervical spine pathology may not tolerate head flexion and tilt. Stretching of the contralateral ligaments, muscles, and nerves create strain.

Figure 1C shows how use of the anesthesia circuit holder can maintain the patient's head in a neutral position. Figure 1D shows the same arrangement reinforced to stabilize the head and neck. Finally, the anesthesia circuit holder is shown in Figure 1E.

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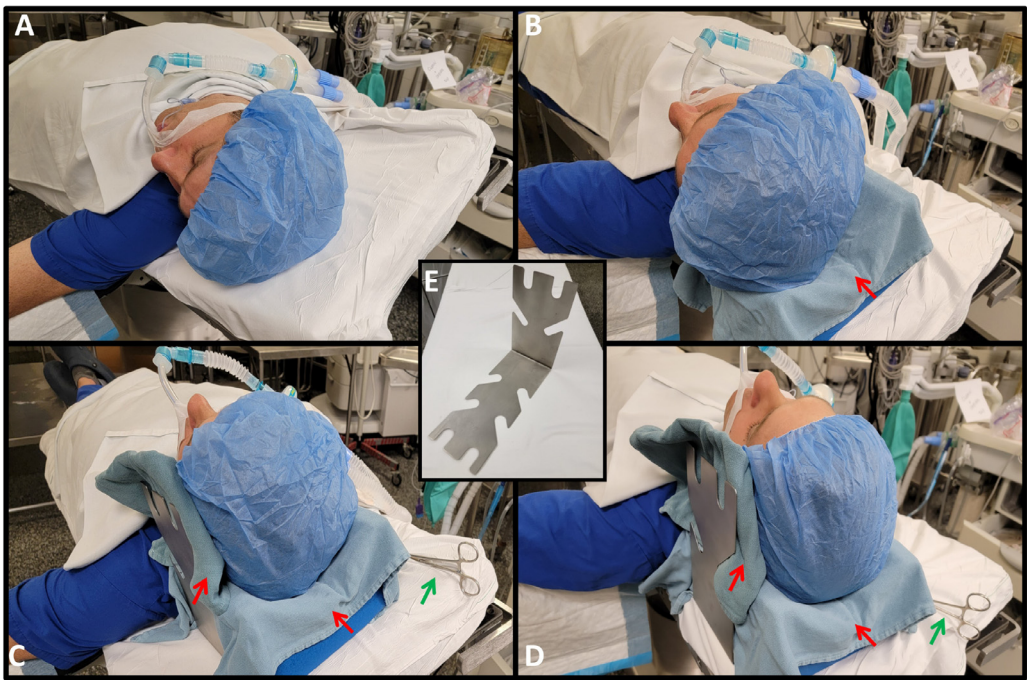

Figure 1 Typical head positions during surgery. (A) Significant flexion and left lateral neck/head tilt during typical patient positioning for laparoscopic cholecystectomy (i.e., reverse Trendelenburg with left lateral tilt of the surgical table). In this example, the (optional) pillow/cushion commonly used to support the patient's head is absent. (B) Patient positioned at the edge of the surgical table as commonly observed in upper extremity surgeries. Notably, the surgical table remains in neutral position, but the patient's head is at risk of falling off to the side of the surgical table (especially with surgical manipulation) despite the use of a pillow/cushion to support it. Finally, panels (C) and (D) depict the simple use of the anesthesia circuit holder (E) to maintain the patient's head/neck in neutral position during cholecystectomy (reverse Trendelenburg and steep left lateral tilt of the surgical table) and upper extremity surgery (surgical table in neutral position). Note the use of a clamp (green arrow) to secure the circuit holder against the mattress and/or its covering sheet to prevent it from slipping along with the patient's head, thereby further stabilizing the head/neck position. Also, a towel (red arrows) is used for providing comfort and to isolate the patient's face/head from the metallic holder to prevent against electrocautery-induced skin burns.

Conflicts of interest

The authors declare no conflicts of interest.

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SHORT COMMUNICATION

Use of software to guide the management of intraoperative hemodynamic instability

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Focused cardiac point-of-care ultrasound is a well-established tool for hemodynamic monitoring during the management of patients admitted to the emergency room, intensive care unit, and operating room.[1-5] The focused cardiac point-of-care ultrasound protocol[1,2,5] comprises the assessment of the preload and filling of the ventricle, the analysis of left ventricle systolic and diastolic function, and the evaluation of right ventricle function.[1-5] Therefore, the protocol assists the decision-making process during the management of hemodynamically unstable patients.

We developed a mobile application (app) for Android® platform aiming to facilitate and help anesthesiologists in training to learn how to make decisions during periods of intraoperative hemodynamic instability. The app, named iEcho®, is registered with the National Institute of Industrial Property (INPI) under the number: BR 512016001497-0. It is a software developed to facilitate the training of anesthesiologists in point-of-care cardiac ultrasound, as well as to assist the decision-making process during intraoperative hemodynamic instability.

The app was developed based on flowcharts covering echocardiographic assessments and their clinical interpretations, and it uses pulsed Doppler and tissue Doppler to evaluate left atrial pressure and the diastolic function; tissue Doppler to analyze left ventricle function; and the measurement of the left ventricle end-diastolic diameter to assess left ventricle end-diastolic volume. Therefore, it enables the analysis of the left ventricle volume, and its systolic and diastolic functions, and it also suggests treatment options for the hemodynamic unstable patient.

While using the iEcho®, the anesthesiologist must observe the following steps (Fig. 1A):

1. Register the patient on the app.
2. With Transthoracic Echocardiogram (TTE), capture the apical 4-chamber view;[1,5] or with Transesophageal Echocardiography (TEE), capture the mid esophageal 4-chamber view.[3] The pulsed Doppler should be positioned at the point of coaptation of the mitral valve leaflets to calculate the velocity of the E wave.[2-4]
3. With Transthoracic Echocardiogram (TTE), capture the apical 4-chamber view,[1,5] or with Transesophageal Echocardiography (TEE), acquire the mid esophageal 4-chamber view.[3] Then, the tissue Doppler is aligned to the lateral mitral annulus, and the velocity of both the lateral e' wave and the lateral s' wave is calculated.[2-4]
4. With the TTE on the parasternal short-axis view[1,5] or the TEE on the transgastric short-axis view,[3] calculate the Left Ventricle End-Diastolic Diameter (LVEDD).[2-4]

After acquiring E wave velocity, wave velocity, s' wave velocity and LVEDD, the data must be entered on the app (Fig. 1A). Alongside where each parameter is entered, there is a question mark icon (Fig. 1A). When the icon is clicked, a page opens with the technical information required for accurately acquiring the echocardiographic measurements.

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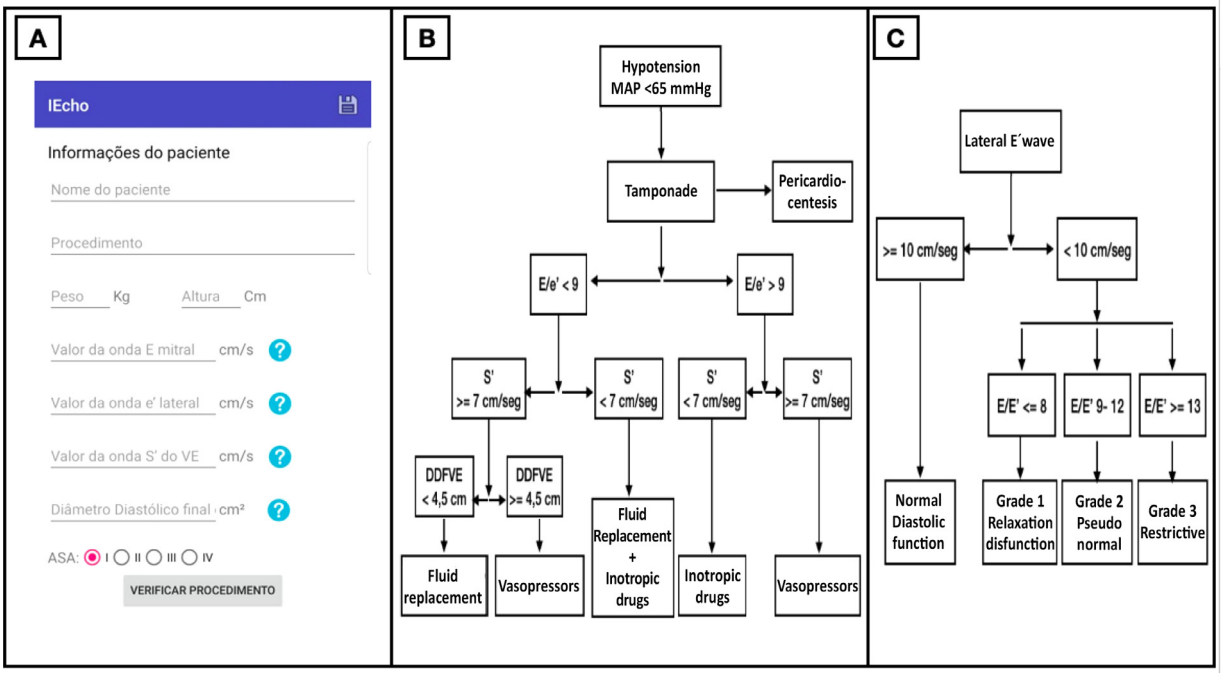

Figure 1 A, iEcho® app home page with patient demographics to be filled out and the measurement of mitral E wave velocity, lateral mitral annulus e' wave velocity, lateral mitral annulus s' wave velocity, and left ventricular end-diastolic diameter. (B and C) Flowchart depicting the analysis of the diagnosis of hypotension and suggesting treatment automatically delivered by the application software. MAP, Mean Arterial Pressure; E/e', Ratio between mitral E wave velocity and mitral lateral annulus e' wave velocity; s', Velocity of left ventricular contraction represented at the lateral mitral annulus; LVEDD, Left Ventricular End-Diastolic Diameter.

When this step is finished and all measurements entered, the app will automatically inform the user whether the left ventricle has normal or decreased contractility, the severity of diastolic dysfunction (normal, Grade 1, 2 or 3 diastolic dysfunction),[4] and will suggest the most appropriate therapy for the patient, depending on the data entered into the software (Figs. 1B and 1C).

The app aims to facilitate the learning process of anesthesiologists who are at the beginning of the learning curve of point-of-care cardiac ultrasound,[5] as well as to promote clinical interface between the echocardiographic data obtained and the patient's hemodynamic instability, assisting the decision-making process to attain better clinical outcomes.

Conflict of Interests

The authors declare no conflicts of interest.

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Brazilian Journal of ANESTHESIOLOGY

SHORT COMMUNICATION

Assessment of perioperative cognitive disorders in elderly patients undergoing elective surgery

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KEYWORDS
Cognitive disorder;
Perioperative;
Anesthesia

In recent years, the number of patients over 60 years of age undergoing surgery has increased significantly and several clinical studies have revealed cognitive function decline after anesthesia and surgery, even in the absence of symptoms. Studies have shown that cognitive decline is primarily associated with older age, lower preoperative intelligence quotient, lower level of schooling, or a combination of these factors.[1]

Perioperative Cognitive Disorder (POCD) is defined as a cognitive impairment in elderly patients that is triggered by surgery. It is considered a transient condition, but its progression resulting in cognitive impairment is reported in roughly 10—38% of patients in the first 2 to 3 months, and 3—24% in 6 to 12 months after major surgery.[2]

According to the new recommended nomenclature in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5), perioperative neurocognitive disorders can be classified as postoperative delirium or delayed neurocognitive recovery, when they develop up to 30 days after surgery. When recovery occurs from 30 days to 12 months after surgery the condition can be classified as mild or severe POCD.[1] Recent guidelines suggest that prompt detection of disability should not rely only on standard assessment, but mainly on structured screening tools.[3]

This study aimed to determine the prevalence of neurocognitive disfunction in elderly patients to be submitted to surgery at the Hospital Universitário Getúlio Vargas/Universidade Federal do Amazonas (HUGV/UFAM) and correlate the prevalence of neurocognitive disfunction with patients' level of schooling, presence of previous comorbidities, anesthesia technique, and surgery duration.

The study was approved by the Ethics Committee of the Universidade Federal do Amazonas/UFAM (CAAE: 20360319.3.0000.5020, opinion 3.683.997) on November 5, 2019. Informed consent was obtained from participants before the administration of the cognitive tests.

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A single-center, analytical, observational, and cross-sectional clinical study was carried out in patients that were scheduled for elective surgery under anesthesia from September 10, 2019 to January 30, 2020 at HUGV/UFAM, Manaus, AM (tertiary center).

The study included patients over 60 years of age, with complete independence and classified as ASA (American Society of Anesthesiologists) physical status I, II, or III. We excluded patients refusing to participate at any stage of the study; patients with special needs, and patients presenting neurological or psychiatric disorders precluding the administration of the cognitive test.

We assessed participants in the ward on two different occasions, on the day before surgery and on the first postoperative day. On both occasions, they answered the Portuguese version of the 10-Point Cognitive Screener (10-CS) questionnaire. Then we compared patient preoperative with postoperative scores. According to the score, a patient is classified as a normal cognitive test ($\geq$ 8 points), possible cognitive impairment (6—7 points), and probable cognitive impairment (0—5 points). The test was timed and comprised assessing the speed of processing and the execution of requested control processes, skills that are impaired at the onset of dementia.[3]

After test completion, when required, the score was adjusted according to the patient's level of schooling, adding 2 points for illiteracy, and 1 point for 1 to 3 years of schooling. The primary outcome of the study was to determine prevalence of early POCD and the secondary outcome was to assess the correlation of POCD with the level of schooling, pre-existing comorbidities, type of anesthesia technique, and duration of surgery.

Data analysis was carried out using Epi Info for Windows version 7.2.2.6. Sample size calculation was estimated considering the frequency of patients in the hospital, with a margin of error of 0.05 (α) and 95% power, with approximately 10% loss to follow-up and 5% loss due to non-follow-up or discontinued intervention. The Shapiro-Wilk test was used to assess normality of the variables. After the hypothesis of normality had been accepted at a significance level of 5% ($p > 0.05$), Student's *t*-test was used to compare means between paired samples and the Chi-Square test was performed to compare the differences between categorical variables, with a CI of 95%.

A total of 100 patients were initially recruited after hospital admission for elective surgery between September 2019 and January 2020. The study included 86 patients scheduled for surgery, that were comparable regarding demographic characteristics, level of schooling, physical status, and anesthesia technique performed. A total of 70 patients had pre-existing comorbidity, most frequently High Blood Pressure (HBP) and type II Diabetes Mellitus (DM II).

Regarding the results of the cognitive tests, no difference was found between pre- and postoperative test mean scores for 24 participants; the score was positive for 45 participants, and for 17 the score was negative and indicated cognitive impairment (19.76%). There was no statistical difference regarding level of schooling, pre-existing comorbidities, anesthesia technique used, and duration of surgery (Table 1).

As the population ages and medicine progresses, we can expect more elderly patients experiencing major surgery. The finding of 17 participants (19.8%) presenting POCD, revealed by the decrease in the postoperative score compared to the preoperative score, agrees with the results of previous studies in which the time of application of the intervention changed.[3] Regarding the distribution of participants according to the level of schooling, there was no difference in terms of cognitive impairment (p = 0.204), although a higher level of education may play a protective role in late POCD.[4]

As for the occurrence of POCD, no statistical difference was found between participants with HBP (p = 0.413) and DM

Table 1 Comparison of the postoperative score with the preoperative score considering the level of schooling, presence of comorbidities, type of anesthesia and surgery time in patients undergoing surgery at the HUGV, Manaus, AM.

	Postoperative score compared to preoperative							
	Decreased (n = 17)		No change (n = 24)		Increased (n = 45)			
Variable	f_i	%	f_i	%	f_i	%	Total	*p*
Schooling								0.204[a]
Elementary school	9	20.0	9	20.0	27	60.0	45	
High School/University	8	19.5	15	36.6	18	43.9	41	
HBP								0.413[a]
Yes	12	23.5	12	23.5	27	53.0	51	
No	5	14.3	12	34.3	18	51.4	35	
Diabetes mellitus								0.200[a]
Yes	1	5.6	5	27.8	12	66.7	18	
No	16	23.5	19	27.9	33	48.5	68	
Type of anesthesia								0.262[a]
Block/Spinal anesthesia	7	18.0	8	20.5	24	61.5	39	
General anesthesia	10	21.3	16	34.0	21	44.7	47	
Surgery duration (min)								0.680[b]
Median	150.0		137.5		140.0			
Q_1—Q_3	120—180		120—187.5		105.0—180.0			

f_i, Absolute frequency; HBP, High Blood Pressure.
[a] Pearson's Chi-square test.
[b] Kruskal-Wallis test.

II, (p = 0.200) compared to the participants that did not present these comorbidities. Concerning the anesthetic technique, 40.7% of participants underwent regional anesthesia and 39.5% general anesthesia, and it is not possible to associate the type of anesthesia with the onset of POCD (p = 0.262), and the same can be said for the duration of surgery (p = 0.680). These findings disagree with previous studies that described a higher incidence of POCD in major surgeries, generally associated with postoperative complications, higher stress response or longer hospital stays.[5]

Although no correlation was found with the extension and duration of surgery or with the type of anesthesia used, the prevention of POCD requires intervention on multiple factors that may not have been identified preoperatively, but still require concern during rehabilitation. The 10-CS questionnaire, based on empirical data, is considered a fast and user-friendly screening strategy, with higher accuracy and some practical advantages when compared to other commonly used tools. It is noteworthy to consider other existing postoperative factors that may contribute to mental decline, that request further research in this area of anesthesiology.

Conflicts of interest

The authors declare no conflicts of interest.

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Brazilian Journal of ANESTHESIOLOGY

SHORT COMMUNICATION

Quality, safety and efficacy in a communication protocol between the anesthesiologist and the allergist in perioperative hypersensitivity reactions

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Suspected hypersensitivity reactions in the perioperative period are unpredictable critical events with a potential risk of morbidity, such as neurological damage and mortality.[1] They pose a major challenge due to the various substances administered consecutively, hidden exposures, and associated clinical conditions that can make the clinical presentation difficult to recognize. Other clinical scenarios can mimic the presentation of hypersensitivity, whose confirmation is essential for safety in future exposures,[2] since it is impossible to determine clinically whether the reaction is immunological or not.[3] Correct investigation should guide appropriate management of future exposure of a patient.

Anesthesiologists are the professionals who most frequently witness hypersensitivity reactions during the perioperative period, diagnosing and treating the events, as well as collecting blood samples to measure mediators for diagnosis.

The interaction among anesthesiologists, allergists and immunologists, among others with extensive knowledge in drug allergy and perioperative anaphylaxis,[4] is warranted to identify triggering agents as well as the reaction mechanism, in order to reduce the occurrence of re-exposure to triggering agents and, consequently, reduce morbidity and mortality, and prevent perioperative anaphylaxis.

As in other organizations, the use of appropriate terminology among the teams involved is essential for successful management. Using a standardized vocabulary allows standardizing the data to be studied and minimizing missing information.

Thus, the proposal for a standardized instrument is presented in order to facilitate reporting of suspected perioperative allergy reactions, simplify communication among the professionals involved, help plan actions for diagnosis and guidance, and collect data for epidemiological studies.

An instrument for investigating perioperative hypersensitivity reaction was standardized (Fig. 1). The instrument consists of patient identification, admission data, place and time of reaction, substances used, description of the reaction, reaction management, outcome of the procedure, and test and investigation results.

The term hypersensitivity is comprehensive, as it encompasses reactions whose underlying mechanism may be allergic or non-allergic. It should be used to objectively describe reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal individuals.[3] This, therefore, is the appropriate term to describe a

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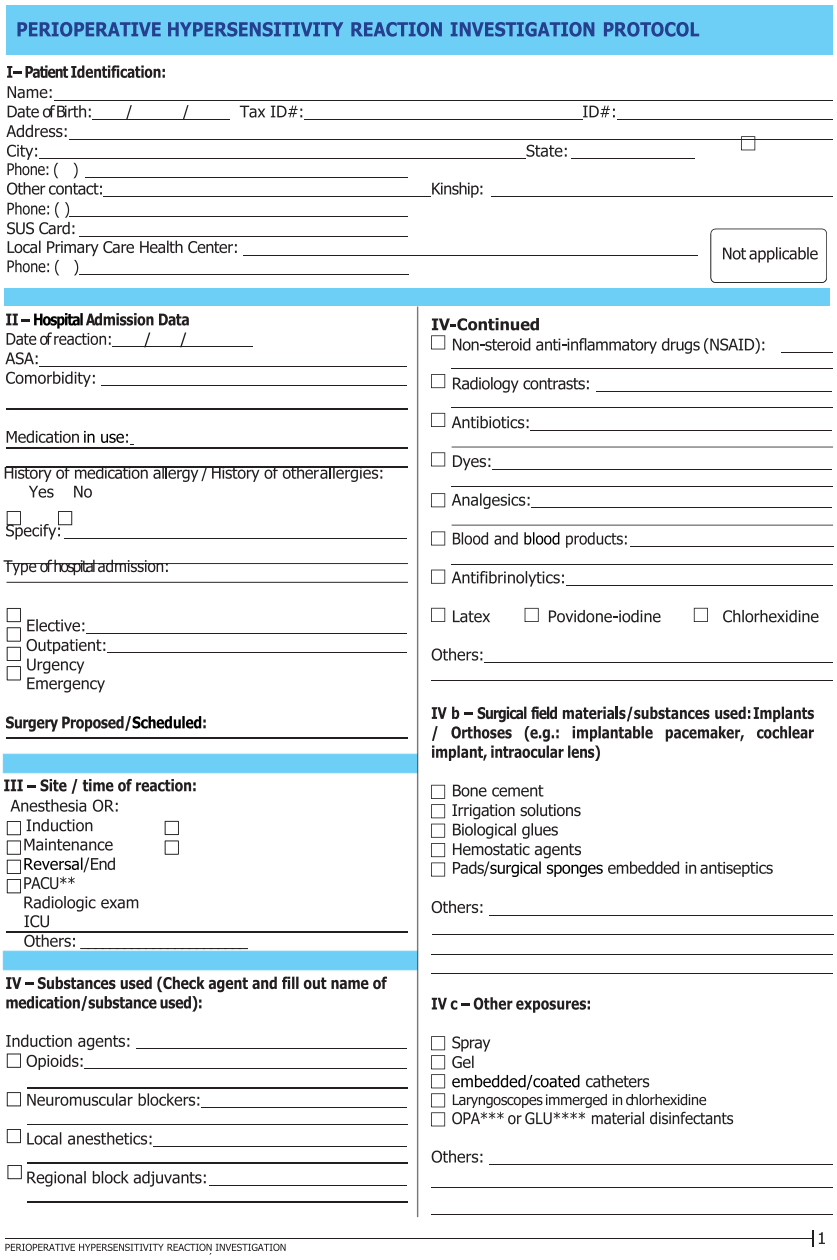


PERIOPERATIVE HYPERSENSITIVITY REACTION INVESTIGATION PROTOCOL

I– Patient Identification:
Name:
Date of Birth: / / Tax ID#: ID#:
Address:
City: State:
Phone: ( )
Other contact: Kinship:
Phone: ( )
SUS Card:
Local Primary Care Health Center:
Phone: ( )
Not applicable

II – Hospital Admission Data
Date of reaction: / /
ASA:
Comorbidity:
Medication in use:
History of medication allergy / History of other allergies:
Yes No
Specify:
Type of hospital admission:
Elective:
Outpatient:
Urgency
Emergency
Surgery Proposed/Scheduled:

III – Site / time of reaction:
Anesthesia OR:
Induction
Maintenance
Reversal/End
PACU**
Radiologic exam
ICU
Others:

IV – Substances used (Check agent and fill out name of medication/substance used):
Induction agents:
Opioids:
Neuromuscular blockers:
Local anesthetics:
Regional block adjuvants:

IV-Continued
Non-steroid anti-inflammatory drugs (NSAID):
Radiology contrasts:
Antibiotics:
Dyes:
Analgesics:
Blood and blood products:
Antifibrinolytics:
Latex Povidone-iodine Chlorhexidine
Others:

IV b – Surgical field materials/substances used: Implants / Orthoses (e.g.: implantable pacemaker, cochlear implant, intraocular lens)
Bone cement
Irrigation solutions
Biological glues
Hemostatic agents
Pads/surgical sponges embedded in antiseptics
Others:

IV c – Other exposures:
Spray
Gel
embedded/coated catheters
Laryngoscopes immerged in chlorhexidine
OPA*** or GLU**** material disinfectants
Others:

PERIOPERATIVE HYPERSENSITIVITY REACTION INVESTIGATION 1

Figure 1 Perioperative or periprocedural hypersensitivity reaction post-reaction assessment protocol.

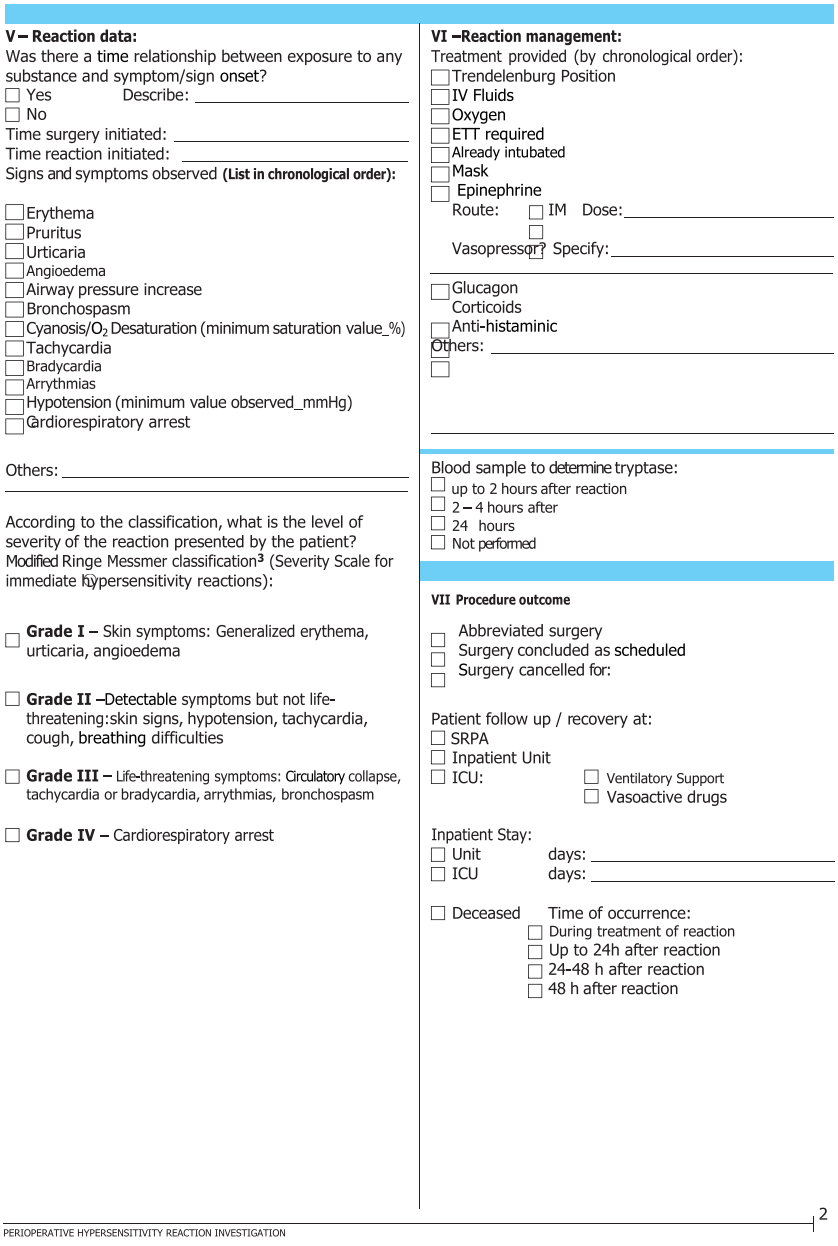
suspected clinical manifestation until the mechanism involved in the reaction is elucidated.[3] The World Allergy Organization (WAO), responsible for the revision of allergy nomenclature for global use, has recommended the standardization of terms.[5]

In convergence with the importance of nomenclature and correct classification of hypersensitivity events, not restricted to the perioperative period, the World Health Organization (WHO) introduced the subsection on hypersensitivity to drugs, in its International Classification of Diseases, WHO ICD-11, aiming at more accuracy in the registration of events and collection of epidemiological data, which support better quality care and action planning.[6]

According to the current nomenclature, allergy is any hypersensitivity reaction triggered by a specific immune mechanism. Anaphylaxis, in turn, is defined as immediate onset of a systemic reaction, with life-threatening respiratory and circulatory impairment. There is also non-allergic hypersensitivity, which defines the clinical presentation resulting from non-specific (direct) activation of cells of the immune system.[5] The modified Ring and Messmer scale is used to classify perioperative reactions clinically, according to the degree of intensity.[3]

In the investigation process of a perioperative reaction suspected of allergy, standardization in reporting can help minimize the risk of incomplete information and simplify communication among the professionals involved, helping to plan actions toward the correct diagnosis.

In a series of seventy patients assessed for perioperative hypersensitivity reaction, three of them had a new reaction on a subsequent exposure. In two of them, partial or



V – Reaction data:
Was there a time relationship between exposure to any substance and symptom/sign onset?
☐ Yes Describe: _____
☐ No
Time surgery initiated: _____
Time reaction initiated: _____
Signs and symptoms observed **(List in chronological order):**

☐ Erythema
☐ Pruritus
☐ Urticaria
☐ Angioedema
☐ Airway pressure increase
☐ Bronchospasm
☐ Cyanosis/O_2 Desaturation (minimum saturation value_%)
☐ Tachycardia
☐ Bradycardia
☐ Arrythmias
☐ Hypotension (minimum value observed_mmHg)
☐ Cardiorespiratory arrest

Others: _____

According to the classification, what is the level of severity of the reaction presented by the patient? Modified Ringe Messmer classification[3] (Severity Scale for immediate hypersensitivity reactions):

☐ **Grade I –** Skin symptoms: Generalized erythema, urticaria, angioedema

☐ **Grade II –**Detectable symptoms but not life-threatening:skin signs, hypotension, tachycardia, cough, breathing difficulties

☐ **Grade III –** Life-threatening symptoms: Circulatory collapse, tachycardia or bradycardia, arrythmias, bronchospasm

☐ **Grade IV –** Cardiorespiratory arrest

VI –Reaction management:
Treatment provided (by chronological order):
☐ Trendelenburg Position
☐ IV Fluids
☐ Oxygen
☐ ETT required
☐ Already intubated
☐ Mask
☐ Epinephrine
Route: ☐ IM Dose: _____
☐
Vasopressor? ☐ Specify: _____

☐ Glucagon
Corticoids
☐ Anti-histaminic
Others: _____
☐

Blood sample to determine tryptase:
☐ up to 2 hours after reaction
☐ 2 – 4 hours after
☐ 24 hours
☐ Not performed

VII Procedure outcome

☐ Abbreviated surgery
☐ Surgery concluded as scheduled
☐ Surgery cancelled for:
☐

Patient follow up / recovery at:
☐ SRPA
☐ Inpatient Unit
☐ ICU: ☐ Ventilatory Support ☐ Vasoactive drugs

Inpatient Stay:
☐ Unit days: _____
☐ ICU days: _____

☐ Deceased Time of occurrence:
☐ During treatment of reaction
☐ Up to 24h after reaction
☐ 24-48 h after reaction
☐ 48 h after reaction

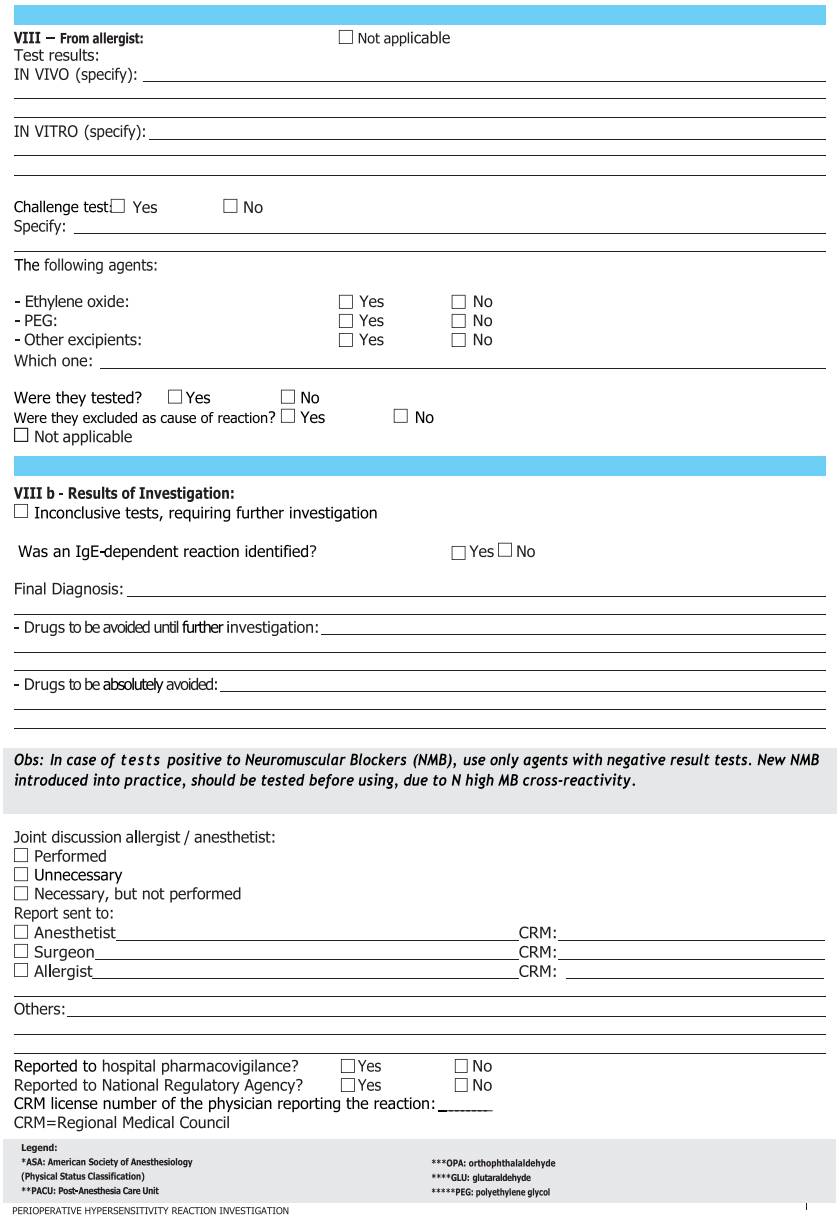
PERIOPERATIVE HYPERSENSITIVITY REACTION INVESTIGATION 2

Figure 1 Continued.

incomplete information was the cause of inadvertent re-exposure to the causative agent; in the third, the cause was mastocytosis.[1]

In the investigation of suspected allergic reactions, an emerging challenge is the search for hidden agents administered by other routes of exposure that are not as clear. Antibiotics delivered by bone cement or surgical cement, methylene blue added to blood derivatives for viral inactivation are a few mentioned.[7] Recently, polyethylene glycols, which are widely used as excipients in medicinal products, including sprays of local anesthetics, cosmetics, and household products, have been implicated as a suspected cause of anaphylaxis after the application of the mRNA COVID-19 vaccine.[8] Other possible agents rarely considered and that should deserve attention in the investigation are biological glues, hemostatic agents, irrigation fluids applied to the operative site, in addition to drug excipients and disinfectants.[7]

The less comprehensive version of the standardized instrument for investigating perioperative hypersensitivity reaction was presented at the World Allergy Conference.[9] It is a clinical practice-related protocol of the Núcleo de Avaliação de Reações do Tipo Alérgico a Drogas (NARTAD), in compliance with the recommendations established by services specializing in perioperative allergy investigation.[4] It corresponds to the norms established by the *Núcleo*, performing *in vivo* tests with neuromuscular blockers, antibiotics, opioids, Non-Steroid Analgesics (NSA), local anesthetics, latex and chlorhexidine. Skin tests are performed by prick test, and are intradermal; if indicated, challenge tests are also used. *In vitro* tests, such as specific measurement of



VIII – From allergist: ☐ Not applicable
Test results:
IN VIVO (specify): _____

IN VITRO (specify): _____

Challenge test: ☐ Yes ☐ No
Specify: _____

The following agents:

- Ethylene oxide: ☐ Yes ☐ No
- PEG: ☐ Yes ☐ No
- Other excipients: ☐ Yes ☐ No

Which one: _____

Were they tested? ☐ Yes ☐ No
Were they excluded as cause of reaction? ☐ Yes ☐ No
☐ Not applicable

VIII b - Results of Investigation:
☐ Inconclusive tests, requiring further investigation

Was an IgE-dependent reaction identified? ☐ Yes ☐ No

Final Diagnosis: _____

- Drugs to be avoided until further investigation: _____

- Drugs to be absolutely avoided: _____

Obs: In case of tests positive to Neuromuscular Blockers (NMB), use only agents with negative result tests. New NMB introduced into practice, should be tested before using, due to N high MB cross-reactivity.

Joint discussion allergist / anesthetist:
☐ Performed
☐ Unnecessary
☐ Necessary, but not performed

Report sent to:
☐ Anesthetist _____ CRM: _____
☐ Surgeon _____ CRM: _____
☐ Allergist _____ CRM: _____

Others: _____

Reported to hospital pharmacovigilance? ☐ Yes ☐ No
Reported to National Regulatory Agency? ☐ Yes ☐ No
CRM license number of the physician reporting the reaction: _____
CRM=Regional Medical Council

Legend:
*ASA: American Society of Anesthesiology (Physical Status Classification)
**PACU: Post-Anesthesia Care Unit
***OPA: orthophthalaldehyde
****GLU: glutaraldehyde
*****PEG: polyethylene glycol

PERIOPERATIVE HYPERSENSITIVITY REACTION INVESTIGATION

Figure 1 Continued.

IgE, tryptase, may also be requested as part of the investigation.

Anesthesiologists and allergists participated in the definition of information used to standardize perioperative hypersensitivity tests. The resulting final adjustments are presented in Figure 1.

The presentation of the instrument aims toward ample promotion and use among professionals involved in the investigation of suspected perioperative allergy events. Similar instruments are also used in other countries.[10]

Questions originated from the previously published standardized instrument[9] allowed the development of two questionnaires aimed at mapping events, their characteristics and diagnostic and therapeutic measures adopted. One questionnaire was distributed to Allergy specialists and another to Anesthesiology specialists, and answers are still to be evaluated. A third, more comprehensive and multicentric study, along with a national research network in Anesthesiology, is being prepared, and data collecting is anticipated for next year.

The communication protocol is expected to become simpler in order to report and send suspected perioperative hypersensitivity reactions for investigation, and, thus, move in the direction of the more widely recommended objective of preventing the risk event to occur. Moreover, "we aim to promote a warning sign related to anaphylaxis and strengthen patient safety culture".

Finally, we understand that employing a communication instrument between anesthesiologists and allergists to

assess suspected perioperative or periprocedural hypersensitivity reactions during a period is a major step, in the cumbersome process of acknowledging, treating, diagnosing and preventing future reactions.

Conflicts of interest

The authors declare no conflicts of interest.

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SHORT COMMUNICATION

Experimental model for local anesthetic spread in spinal anesthesia: application to medical education

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Medical education is student centered, and consolidated curricula have given way to new, more flexible and adaptive models, in which students' opinion and participation have gained importance.[1,2] The aim of the present study was to develop a low-cost experimental model (R$ 300.00) to demonstrate the spread of local anesthetics in spinal anesthesia, and to assess its impact on classroom teaching.[3]

This study was carried out at the Unicamp School of Medicine (Faculdade de Ciências Médicas/Unicamp) with approval of the Research Ethics Committee — CEP n° 3,556.842 Unicamp. The 110 3rd-year undergraduate students were invited, and 64 accepted to participate. They were separated into two groups, one control and the other intervention, with 32 students each, to evaluate the effectiveness of using the experimental teaching model. The groups were allocated based on simple randomization with sealed envelopes opened at the time of the lecture. After obtaining informed consent, the one-day study was performed by assessing one group after the other, so that the groups would not meet. The intervention was carried out in May 2019.

Both groups answered a quality-of-life questionnaire, then attended a lecture on spinal anesthesia. At the end, the control group answered a test on the topic (Table 1). In turn, the intervention group attended a demonstration on the spread of hyperbaric and isobaric bupivacaine using the experimental model, followed by an additional 15-minute period to use the model. Subsequently, they completed the test on spinal anesthesia.

The experimental model in the intervention group intended to demonstrate the anesthetic technique and the spinal spread of local anesthetics. Bupivacaine was used in two formulations: 0.5% hyperbaric and 0.5% isobaric. Dye (methylene blue) was added to bupivacaine in the proportion of 10 mL of local anesthetic to 0.5 mL of dye. Both formulations of bupivacaine differ in baricity and behavior after injection into the subarachnoid space: hyperbaric bupivacaine tends to sink and isobaric bupivacaine tends to remain static, without cranial or caudal spread in the cerebrospinal fluid. This effect results in clinical differences between the two formulations of bupivacaine.

The experimental model was placed in a wooden container with a lid, and measured 1.0 × 0.5 × 0.2 m. There was a drawing of the human spine on the back of the container, from the first cervical vertebra (C1) to the fourth sacral vertebra (S4). A hollow transparent glass cylinder with curves resembling the spine shape was developed to simulate the spinal canal. The glass structure was filled with a 0.9% saline solution and a hole was placed to inject the studied solution in the space between the third and fourth lumbar vertebra (L3—L4) (Fig. 1).

We used the Chi-Square test to compare categorical variables between groups, or when necessary, Fisher's exact test. As the numerical variables did not show normal distribution, we used the Mann-Whitney test to compare the two groups.

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Table 1 Spinal anesthesia test.

1. What is the key anatomical landmark for performing spinal anesthesia?
A) Posterosuperior iliac spine.
B) Projection of the L5 transverse process.
C) Point 3 cm lateral to the midline, at the L4 level.
D) Midpoint between the sacral hiatus and the posterosuperior iliac spine.

2. During the assessment of motor blockade in spinal anesthesia, inability to perform flexion of the hip or dorsiflexion of the foot indicates, respectively, spinal root blockade at:
A) L2 L3 and L4 L5
B) L1 L2 and L5 S1
C) L1 L2 and L4 L5
D) L3 L4 and L5 S1

3. Spinal anesthesia effect:
A) Gastric emptying time is abbreviated with T6 to L2 sympathetic blockade
B) Cardiovascular effects are independent of rostral spread of sympathetic blockade
C) Breathing is directly affected by the blockade of sympathetic autonomic fibers
D) Heating loss in every body region regardless of the level of spinal blockade

4. Main factor influencing the extent of lumbar epidural block:
A) Addition of epinephrine to the Local Anesthetic (LA)
B) Volume of the LA
C) Lower lumbar space capacity
D) Diffusion property of the LA

5. Regarding spinal anesthesia for outpatient procedures, it is correct to state:
A) When the Bromage scale decreases from 2 to 1, 90% of the patient's motor capacity is already recovered
B) Hospital discharge can be given after normalization of vital signs for at least 1-hour, postoperatively
C) The assessment of cognitive functions is the most important factor to determine hospital discharge

6. A 25-year-old patient, ASA IE, is diagnosed with appendicitis and scheduled for surgical treatment under spinal anesthesia. After thoracolumbar antisepsis, the spinal needle is inserted in the subarachnoid space and the CSF backflow stained with blood. In this scenario what is the next best recommended step?
A) Inject the local anesthetic
B) Immediately puncture another space
C) Keep the technique in case blood staining of the CSF disappears
D) Administer 10mg of vitamin K, intravenously, before repeating the puncture

7. Patient, 68 years old, 50 kg, 168 cm, has arterial hypertension and type I diabetes. He presents metastatic prostate cancer and is admitted to the intensive care unit due to bilateral pneumonia and peri malleolar abscess. He progresses with fever, tachycardia, increased insulin requirements, diabetic ketoacidosis, and respiratory failure. He has an orotracheal tube inserted, but adaptation to the mechanical ventilator is challenging, despite fentanyl sedation. Abscess drainage was performed under local anesthesia with 0.25% bupivacaine 30 mL, due to severe clinical condition of the patient. About 30 minutes after procedure onset, he showed greater ventilatory difficulty, followed by ventricular ectopias and QRS widening, which evolved to pulseless electrical activity. The most likely cause for the adverse outcome is:
A) Bupivacaine intoxication
B) Acute myocardial infarction
C) Septic shock
D) Barotrauma.

8. A 65-year-old patient, run over by a car, full stomach, with an open fracture of the proximal femur is scheduled for surgical fracture repair. On exam, patient shows anxiety and confusion, cold and sweaty skin, BP: 100 $\times$ 50 mmHg, HR: 140 bpm. Considering this hypothetical situation, which is contraindicated
A) Neuraxial block.
B) General anesthesia.
C) Use of colloids.
D) Total intravenous anesthesia.

9. The major determinant for sensory blockade duration of spinal anesthesia is:
A) Type of local anesthetic.
B) Addition of epinephrine.
C) Addition of clonidine.
D) Dose of local anesthetic

10. Regarding epidural anesthesia, it is correct to state that
A) Spinal anesthesia, unlike epidural anesthesia, can cause urinary retention.
B) Spinal anesthesia is associated with a very high risk of local anesthetic toxicity.
C) Spinal anesthesia is always a cause of arterial hypotension due to blockade of sympathetic nerves.

D) When performing spinal anesthesia for adult patients, the spinal puncture must be performed below the L1 vertebra, while for pediatric patients it must be performed below the L3 vertebra to avoid spinal cord injury.

11. The local anesthetic spread in spinal anesthesia:

A) Is inversely proportional to the injection speed.

B) Is directly proportional to the specific weight of hyperbaric solutions.

C) Is directly proportional to the pressure of the cerebrospinal fluid.

D) Is inversely proportional to the injected volume.

12. The likely diagnosis for a patient who experienced respiratory arrest after epidural anesthesia is:

A) Inadvertent intravascular injection.

B) Total spinal anesthesia

C) Acute myocardial infarction.

D) Pulmonary embolism.

13. In spinal anesthesia, the first sensation that disappears is:

A) Thermal.

B) Proprioceptive.

C) Painful.

D) Pressure.

14. In performing and evaluating spinal anesthesia, it is correct to affirm that:

A) The umbilicus corresponds to the T8 dermatome.

B) The medial malleolus and medial surface of the foot correspond to the L5 dermatome.

C) The imaginary line connecting the iliac crests corresponds to the L3—L4 interspace.

D) The xiphoid appendix corresponds to the T4 dermatome.

15. Which of the following is a delayed spinal anesthesia complication, more common in pregnant women?

A) Bradycardia.

B) Hypotension.

C) Respiratory failure.

D) Headache.

Spearman's correlation coefficient was used to verify the relationship between continuous and discrete variables. The coefficient ranges from -1 to 1. Values close to extremes indicate a negative or positive correlation, respectively, and values close to zero indicate no correlation. The significance level adopted for the statistical tests was 5%.

The groups were similar in relation to the domains and components of quality of life assessed by the SF-36 (Short Form 36), except for the functional capacity domain, in which the control group had better mean results of 95.3 (or median = 100) vs. the intervention group mean results of 91.4 (median = 95.0), $p = 0.0491$, Mann-Whitney test. In this domain, the control group showed better performance to execute physical activities. No correlation was observed between the number of correct answers in the spinal anesthesia test and the domains and components of quality of life found in the groups.

The groups presented similar performance results on the spinal anesthesia test based on the number of correct answers in each question, excluding question number 9. The percentage of correct answers for that question in the intervention group was 78.1%, significantly higher than the 37.5% found in the control group ($p = 0.0010$, Chi-Square test). No statistically significant difference between the groups was observed for the remaining questions ($p = 0.444$, Mann-Whitney test). The percentage distribution of correct answers for question 9 in the spinal anesthesia test showed a significant difference ($p = 0.0010$, Chi-Square test).

The total number of correct answers in the intervention group (median = 9.43) was higher than in the control group (median = 8.96), albeit the difference observed was not statistically significant.

A sample size calculation was performed for the study. Considering the final test score as the main variable of the study and a power of 80%, we estimated that each group would require 46 students. Given participation of students was non-mandatory, there were 32 students in each group, thus the estimated sample size was not reached, which is a limiting factor for more generalized conclusions.

The third-year students who participated in the study have access to new technologies that are intensely present in their routine. Of the total number of students, we reached 58% of voluntary participation.

Individually, the performance of both groups was similar for all test questions, except for the duration of spinal anesthesia that is associated with the dose of local anesthetic injected. Our findings suggest that using an experimental model enables visual observation of drug spreading and helps understand that drug distribution can impact spinal anesthesia, which may demonstrate the validity of the proposed model.

When correlating the quality-of-life questionnaire results with those of the spinal anesthesia questionnaire, no direct association was found between the performance in the two tests in both groups. Thus, as expected, the two samples were shown to be similar and that they would not interfere in the study. In the present study, no conflicting differences were observed between the groups.

Both groups showed a similar performance regarding the spinal anesthesia test. Only test question number 9 revealed a significant difference between the groups ($p = 0.0010$) with a higher rate of correct answers by the intervention group. Question 9 focused on the relationship between duration of spinal anesthesia and dose of local anesthetic (Question Answer D). Using the model that enabled visualization of drug dispersion allowed showing that drug spreading can affect spinal blockade duration.



Figure 1 Experimental model.

The intervention group had a higher total number of correct answers than the control group in the spinal anesthesia test, albeit not statistically significant. Small variations in results were not sufficient to support robust conclusions. Nonetheless, our findings suggest that using the model promoted a positive impact on the understanding of the spinal anesthesia technique and on the different properties of the anesthetics used, and that assessment of a larger sample[4] could have made the difference relevant.

One of the difficulties we faced during the study was the onset of the COVID-19 pandemic. After the intervention and statistical analysis, we concluded that a larger number of students would be required.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Perioperative management of immune-mediated necrotizing myositis



Dear Editor,

Patients with muscular disorders are at risk of both intra- and postoperative life-threatening complications.[1] Immune-mediated necrotizing myopathy is a rare autoimmune myopathy characterized by severe proximal weakness with infrequent extra-muscular involvement.[2] It is a disorder with a prevalence of 9—14 cases per 100,000 individuals.[2] There is no evidence regarding the anesthetic management of immune-mediated necrotizing myositis. We report a case in which a safe anesthesia management is described.

An 82-year-old male was scheduled to undergo a right hemicolectomy due to an adenocarcinoma. He had a history of immune-mediated necrotizing myositis diagnosed three years before, after presenting muscular weakness, dysphagia, and elevation of serum aldolase 56 $U.L^{-1}$ and Creatine Kinase (CK) 2341 $U.L^{-1}$. A muscle biopsy confirmed the diagnosis. At the time of surgery, his treatment regimen was prednisone 5 mg/ 24 h and azathioprine 150 mg/ 24 h, and his symptoms were muscular fatigue, slight dysphagia, and dysphonia. Aldolase and CK serum levels were normal in the previous controls. As per other comorbidities, the patient presented atrial fibrillation and chronic venous insufficiency. Physical examination revealed an elderly sarcopenic male (height 173 cm, weight 80 kg), moderately frail regarding the Clinical Frailty Scale.

Before the induction of general anesthesia, a blood sample was drawn in order to surveil CK levels, which were 143 $U.L^{-1}$. Standard monitoring, esophageal thermometer, processed EEG (BIS™, Medtronic, Minneapolis, MN, USA), and neuromuscular block monitoring (Tof-cuff™, RGB, Spain) were placed. The induction was performed intravenously with 80 mg lidocaine, 150 μg fentanyl, 150 mg propofol, and 50 mg rocuronium, and maintenance with desflurane to target a Bispectral index between 40—60, as well as with boluses of fentanyl. A Train-Of-Four (TOF) monitor guided the administration of rocuronium boluses to maintain adequate neuromuscular relaxation during laparoscopy (TOF count 0—1, post-tetanic count 6—10). At the end of the surgery, the Tof-cuff™ showed a moderate block (TOF count 2) and 160 mg sugammadex were administered to complete the reversal of neuromuscular block. Extubation was performed in the operating room uneventfully. The patient was transferred to the Intensive Care Unit (ICU) and did not present any complications, being transferred to the surgical ward in less than 24 hours. His CK levels at 5 hours after surgery were 125 $U.L^{-1}$, and 122 $U.L^{-1}$ 24 hours after. The patient was discharged on the third postoperative day without any further impairment on muscle fatigue, dysphagia, or dysphonia reported during hospitalization. Regarding his treatment regimen, prednisone was continued with a recommended increase in the dosage of 15 mg/ 24 h and azathioprine was restarted on the fifth postoperative day.

The conjunction of a muscular disorder and frailty, defined as a syndrome of decreased physiological reserve and resistance to stressors,[3] leads to vulnerability to adverse outcomes and potentially fatal complications, namely postoperative respiratory failure, respiratory infections, or wound dehiscence. This is the reason why a thorough preoperative assessment was performed, including routine blood tests with CK determination, electrocardiogram, and chest radiograph. A full-body CT scan performed as part of the tumor assessment was also available. Echocardiogram or cardiopulmonary exercise testing may be useful for risk stratification in selected patients.[1]

It is known that in other muscular disorders, such as dystrophies or myositis, volatile anesthetics and depolarizing neuromuscular blockers should be avoided due to the risk of triggering Malignant Hyperthermia (MH).[1] Even though only few muscular diseases carry a significant risk of triggering MH, due to a mutation of the ryanodine receptor, all patients with muscular diseases are at risk of presenting rhabdomyolysis.[4] Specifically, in immune-mediated necrotizing myopathy, which is characterized by myofiber necrosis, acute rhabdomyolysis can mimic a MH episode and can also be life-threatening. The action of non-depolarizing neuromuscular blockers seems to be prolonged in muscular disorders, therefore, the use of quantitative neuromuscular monitors should be considered mandatory.[1] Many authors state that the use of neuromuscular blocking agents should be avoided if possible.[4] However, since the surgery was laparoscopic, we decided to perform it under the best surgical conditions, by inducing a closely monitored moderate-deep neuromuscular block. Moreover, we decided to use desflurane because of its characteristics, such as rapid recovery and muscle relaxation, and the absence of robust evidence for being discarded in this condition. In order to diminish the risk of residual neuromuscular block, the administration of sugammadex

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has been reported as safe in patients with muscular diseases, even though this assertion has not been proven by randomized clinical trials.[5] Worth noting, patients with muscular disorders often present long-term steroid intake and can have pituitary-adrenal axis suppression; in such cases, corticosteroids have to be supplemented in the operating room.

Given that anesthetic drugs can alter postoperative muscle strength, ICU admission seems a reasonable option in order to carefully monitor the patient's respiratory function and provide respiratory support if necessary. Furthermore, patients suffering from immune-mediated necrotizing myopathy have the greatest muscle enzyme elevations among those with other forms of myositis and are consequently at risk of presenting a postoperative increase in CK levels which can induce acute kidney injury.[1]

As far as we know, this is the first case report describing the anesthetic implications of immune-mediated necrotizing myopathy. We describe the successful perioperative management of a frail patient with immune-mediated necrotizing myopathy who underwent major abdominal surgery under general anesthesia. There are no data to establish the safety of anesthetic drugs in this context and clinical trials are very unlikely to be performed, given that immune-mediated necrotizing myopathy is a rare disease. We illustrate how desflurane, rocuronium, and sugammadex may be an option for a safe anesthesia conduct if the patient is closely and carefully monitored. An appropriate perioperative care, having in mind each hospital's facilities, can almost make the risk of life-threatening complications in this rare muscular disorder vanish.

Declaration of Competing Interest

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LETTER TO THE EDITOR

Futility of end-of-life and emergency surgery in extreme high-risk patients: anesthetists' versus surgeons' perspective



Dear Editor,

In Europe, one third of surgical admissions are for emergency procedures that carry a risk of mortality up to 75% in high-risk patients.[1,2] Surgical procedures are also performed at the end of life. In the US, 25% of Medicare beneficiaries were operated within the last 3 months of life[3] which may increase family and patients' emotional distress, while little benefit is expected. It raises the issue of surgical futility in these patients.[4] It is a particularly relevant topic in the current context of the SARS-CoV-2 pandemic crisis with many hospitals being saturated.

Several patient- and family-related factors seem to guide surgeons in their decision to operate on a patient in end-of-life or emergency situations but less is known about determinants of anesthetists' attitudes.[5] The perception of futility and the appropriateness to proceed to surgery may differ between the two professions and may lead to inter professional conflicts. We performed a cross-sectional study in a large University-affiliated hospital in Switzerland, exploring professional differences in the definition of futility and factors leading to the decision to proceed or not to surgery.

Following a waiver of the Cantonal Ethics Committee of Human Research, all anesthetists and surgeons of specialties involved in emergency care were invited to answer a 60-item web-based anonymous questionnaire between March and April 2019. The questionnaire was developed following a formal literature review and pretested among hospital clinical experts in palliative care and emergency medicine. It included a clinical vignette describing a trauma patient (cervical trauma and bleeding pelvic fracture) with cardiac arrest and a recent diagnosis of lung cancer with a first cycle of chemotherapy already planned. Participants had to decide whether they would proceed with surgery or not and give the reason for their choice. The other parts of the questionnaire focused on physicians, hospital-related factors and assessed agreement with various definitions of futility and physicians' perception of autonomy. Answers were rated on a 4-point scale ranging from fully agree to fully disagree. Up to a maximum of 3 reminders were sent to all participants.

For descriptive analysis we used frequencies, proportions, and means with standard deviation. To compare decisions to proceed, definition of futility, and perception of autonomy between surgeons and anesthetists, univariate analysis was performed. Answers were dichotomized and Chi-Squared or Fisher exact test were used. Relative risk with 95% Confidence Interval (95% CI) was calculated. A p-value < 0.05 was considered statistically significant. Analyses were performed using Stata 15 statistical software (StataCorp LLC, College Station, Texas, USA).

A total of 109 (42%) participants — 62 anesthetists and 47 surgeons — answered the questionnaire. Amongst non-respondents, we found that 14% were unavailable or had no access to their e-mail during the survey period (confirmed by automatic out-of-office replies), and 2% were non eligible (medical students included by error in departmental mailing lists).

Most participants (71%) agreed to proceed to surgery for the trauma patient described in the vignette, with no significant difference between professional groups ($p = 0.87$). Amongst the 29% who answered they would not proceed to surgery, patient having a cardiac arrest (80.5%) and poor expected quality of life (89.7%) were the two most common reasons advocated.

There were several differences between professions regarding criteria defining futility of surgery (Table 1A). Compared to anesthetists, surgeons were more likely to proceed to surgery (79% vs. 60%), despite uncertain postoperative benefit ($p = 0.035$). They were also less likely than anesthetists (40% vs. 61%) to consider that a surgical procedure unable to offer a good postoperative quality of life was futile ($p = 0.031$).

These differences may be related to the professional culture of surgeons. Not offering surgery may be perceived as "giving up" and surgeons may feel compelled to "do everything possible to save the patient".[5] In contrast, more anesthetists than surgeons (74% vs. 53%), would agree to proceed to surgery in a patient with a "do not resuscitate order" ($p = 0.023$). The reason most often mentioned in free text answers was the provision of pain relief procedures particularly if it could be done with the use of noninvasive anesthesia techniques.

The overall feeling of decisional autonomy was lower amongst anesthetists than surgeons (Table 1B). They felt less free than surgeons (69% vs. 79%, $p < 0.001$) to decide

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Table 1 Futility perception and feeling of autonomy.

A. Questions related to futility	Anesthetists (n = 62)		Surgeons (n = 47)		RR (95% CI) surgeons vs anesthetists	*p*-value
	Disagree (partly/ fully)	Agree (partly/ fully)	Disagree (partly/ fully)	Agree (partly/ fully)		
Have you at one stage or another considered that operating the patient described in the vignette could be futile	12 (20%)	50 (80%)	9 (19%)	88 (81%)	1.01 (0.38–2.65)	0.978
A surgery bringing no physiological benefit must be considered futile.	15 (24%)	47 (76%)	8 (17%)	39 (83%)	1.55 (0.59–4.05)	0.363
A surgery bringing uncertain benefit must not be considered futile.	25 (40%)	37 (60%)	10 (21%)	37 (79%)	2.50 (1.05–5.92)	0.035
A surgery unable to offer a good postoperative quality of life is futile.	24 (39%)	38 (61%)	28 (60%)	19 (40%)	0.42 (0.19–0.93)	0.031
A surgery is always futile when the patient is very old.	57 (92%)	5 (8%)	46 (98%)	1 (2%)	0.24 (0.02–2.19)	0.178
A surgery is always futile when the patient has severe dementia.	38 (61%)	24 (39%)	36 (77%)	11 (23%)	0.48 (0.20–1.12)	0.090
A surgery is futile if the patient has a life expectancy of one month (and the surgery doesn't affect the prognosis).	19 (31%)	43 (69%)	8 (17%)	39 (83%)	2.15 (0.84–5.47)	0.103
A futile surgery is acceptable if the patient asks for it.	48 (77%)	14 (23%)	41 (87%)	6 (13%)	0.50 (0.17–1.42)	0.190
A surgery is futile if the patient has a life expectancy of one week.	8 (13%)	54 (87%)	4 (9%)	43 (91%)	1.59 (0.44–5.64)	0.468
A surgery can be futile even for a young patient.	4 (6%)	58 (94%)	4 (9%)	43 (91%)	0.74 (0.17–3.13)	0.683
A futile surgery is acceptable if the family asks for it.	54 (87%)	8 (13%)	45 (96%)	2 (4%)	0.30 (0.06–1.48)	0.121
A surgery isn't futile only if it brings benefit to the patient.	18 (29%)	44 (71%)	13 (28%)	34 (72%)	1.07 (0.46–2.48)	0.875
B. Questions related to autonomy						
You agree to take care of a patient with a "DNR order" in the emergency OR.	16 (26%)	46 (74%)	22 (47%)	25 (53%)	0.39 (0.17–0.88)	0.023
Before taking care of a patient with a "DNR order", you discuss again the limits of the order with the patient and his family.	10 (16%)	52 (84%)	4 (9%)	43 (91%)	2.06 (0.60–7.05)	0.239
You explain all the implications and possible complications of the anesthetic/surgical care.	10 (16%)	52 (84%)	0	47 (100%)	1.90 (1.57–2.29)	0.004
You feel free to decide whether to take care of a patient in the OR or not.	43 (69%)	19 (31%)	10 (21%)	37 (79%)	8.37 (3.46–20.24)	< 0.001
Your opinion whether to take care of a patient in the OR or not is respected.	33 (53%)	29 (47%)	8 (17%)	39 (83%)	5.54 (2.23–13.77)	< 0.001
You are involved during all the phases of the patient's evaluation before the OR.	34 (55%)	28 (45%)	13 (22%)	34 (78%)	3.17 (1.41–7.15)	0.005
Your evaluation can modify the care of the patient in the OR.	25 (40%)	37 (60%)	17 (36%)	25 (64%)	1.19 (0.54–2.60)	0.659
You feel pressure when deciding to take care for a patient in the OR.	33 (53%)	29 (47%)	43 (92%)	4 (8%)	0.10 (0.03–0.33)	<0.001
You are the only one who can decide if the patient must be operated.	59 (95%)	3 (5%)	36 (83%)	11 (17%)	6.00 (1.57–23.00)	0.004

Results are expressed in numbers (percents). DNR, Do Not Resuscitate, OR, Operating Room.

whether to proceed to surgery or not. They more often felt that their opinion was not taken into consideration and that they felt hierarchical pressure to proceed to surgery. Another finding was that anesthetists informed patients to a lesser extent than surgeons (84% vs. 100%) about all possible complications of an emergency intervention ($p < 0.005$).

This study has limitations. The cross-sectional design of the study does not allow causal inferences to be made but only speculations to be generated. It was a single center

study and generalizability of findings is limited to hospitals and working environment similar to the study setting. Thirdly, we approached all anesthetists and surgeons of specialties connected to the emergency unit. But only those that had substantial experience in the emergency setting answered, limiting response rate and generalizability of study results. However, since both surgical and anesthesia professional groups were well represented, the study has good internal validity.

Despite limitations, our study showed that anesthetists felt more concerned than surgeons by the benefit of surgery and postoperative quality of life. In contrast they were more likely to proceed with surgery in patients with "do not resuscitate orders" and informed patients to a lesser extent about all possible postoperative complications.

This highlights the ambiguity of the role that anesthetists play in emergency high-risk procedures because they are concerned by the importance of providing benefits to the patient but also exposed to external pressure to perform surgery in any circumstances, without fully informing patients about postoperative complications.

These study findings may contribute to improve mutual understanding when disagreement occurs between the two specialties. It may help to solve conflicts in the current context of overwhelmed hospitals

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Cardiac point-of-care ultrasound curriculum for anesthesia residents: the time is now

Dear Editor,

As an ultrasound (US) point-of-care modality, Focused Cardiac US (FOCUS) is defined as the use of US at the bedside to evaluate the unstable patient and, within a specific list of diagnoses, individualizing the clinical treatment for a given situation based on the findings using binary and qualitative questions.

However, in terms of training, there is no current consensus on what perioperative FOCUS comprises of, and no national curriculum in Brazil. To date, the only published national US curriculum is from the Association of Anaesthetists of Great Britain and Ireland and the Intensive Care Society,[1] however these curricula were developed without any distinctions for trainees in anesthesia or intensive care streams respectively.

In order to acquire the skills required to perform the FOCUS technique, there is a distinct need to develop a training curriculum that considers the different training phases (handling of the device and acquisition of images, interpretation of images, and correlation with the clinical situation). To successfully progress from one phase to the next, the student would need to clearly demonstrate proficiency in the previous stage. Additionally, there should be considerations made for the different phases of training, development, and experience within the anesthesia residency program, and what is the best time (if any) within the program for the introduction of the curriculum.

To learn the FOCUS technique, there should be an integration of two essential factors: the technical skills (acquisition, image optimization), and the interpretation of US findings in the context of the patients' clinical status.

Adult Learning Theory, or ''Andragogy'', was described by Malcolm Knowles[2] and is defined as the ''art and science of helping adults learn''. It is based on five assumptions about how adults learn and their motivation and attitude towards this process:

1 Adults are independent in their learning process.
2 They bring broad experience to the new learning process.
3 They value learning with practical results.
4 They are more interested in problem-centered approaches.
5 They bring an internal motivation to learn something new.

Constructivism[3] is one of those learning theories based on the idea that learners actively construct or make their knowledge using previous experience as a foundation and build on it with new things that they learn. The application of Constructivism to develop a new model of FOCUS training is based on some of the principles that make it the ideal theory for the development of a training model for anesthesia residents: 1. Learners ''construct'' their knowledge based on what they already know; 2. The teacher is viewed not as a transmitter of knowledge but rather as a guide who facilitates learning.

Acquisition of practical skills is an essential element in health professions education, and traditionally, procedures were taught using a s̈ee one – do oneäpproach, meaning that a teacher demonstrates and describes a procedure. Afterward, the students are asked to practice the same task. Although this approach has been prevalent and is still used in some situations, it is an unsystematic and unstructured approach that does not follow the current principles of adult learning and can sometimes put the patient at risk.[4] A more recent method described by Walker and Peyton describes a stepwise teaching approach consisting of four different steps: demonstration, deconstruction, comprehension, and performance.[5]

The creation of a training model based on the Constructivism Theory considers the basic knowledge of the anesthesia resident regarding the use of US for central venous access and regional nerve blocks. This base would then be extrapolated with the goal of diagnosis and management of many common causes of hemodynamic changes in the perioperative period using a point-of-care approach.

Based on all concepts exposed above, the curriculum for training anesthesia residents in FOCUS modality should be based on a horizontal program to be applied to all anesthesia residents, respecting the different training stages, and composed of the phases below.

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Phase 1

Program of formal classes with topics related to image acquisition, optimization, handling the device, choice of the probe, and most common clinical scenarios found in the operating room. Progression to the second training stage is granted after the student participates in the entire class program and is theoretically assessed using multiple-choice questions (MCQ) with a satisfactory result.

Phase 2

Acquisition and interpretation of images performed using simulation to familiarize the student with the handling of the device and what to expect from the technique. After training in the simulator with their proficiency assessed, progress to phase 3 is achieved.

Phase 3

The final part of the training would consist of examinations performed on actual, low risk, or stable patients undergoing elective surgical procedures while being under the direct supervision of the instructor. When proficiency of the technique is demonstrated likely after a logbook of 30 exams, as suggested in the literature,[6] there would be further practical progression. This evolution would include exam performance in unstable patients with a correlation of the exam findings and decision making.

The development of a training program aimed at the anesthesia resident must consider the particularities of the specialty (routine within the operating room) and the type of situations that can be encountered in daily clinical practice (e.g., hemodynamic instability that requires diagnosis and immediate treatment). Despite any difficulties, learning and being proficient in the US point-of-care modality is a fundamental skill to optimize the care for hemodynamically unstable patients, and the new generations of anesthesiologists should acquire this skill.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

A not so rosy picture: accidental intravenous injection of rose-tinted pourable chlorhexidine solution

Dear Editor,

Chlorhexidine is a routinely-used broad spectrum antiseptic for hand disinfection and surgical site preparation. Although perioperative allergic reactions to chlorhexidine preparations are frequently discussed, toxicity due to its accidental intravenous injection is sparsely reported. We recently encountered a case of accidental intravenous injection of chlorhexidine gluconate in a patient posted for coronary artery bypass surgery when after uneventful induction of anesthesia, the surgeon started preparing the right groin for IABP insertion, simultaneously with central line insertion by the anesthetist and accidentally kept the gallipot containing almost colorless chlorhexidine solution for surgical site preparation on the sterile tray meant for central venous catheter insertion (Fig. 1A). The anesthetist, mistaking the same as heparin–saline solution, inadvertently injected undiluted 2 mL (40 mg) of chlorhexidine gluconate solution intravenously while flushing a central venous catheter port, without any adverse consequences to the patient. Though no perioperative adverse event was reported, it led us to perform a literature search for accidental intravenous injection of chlorhexidine gluconate.

Using ''intravenous/intravascular chlorhexidine'', ''accidental intravenous chlorhexidine injection'' as key words in PubMed/Medline, Scopus, EMBASE, and Google, we identified four papers describing the same. We would like to brief the readers about possible circumstances of error, complications, and management of accidental intravenous chlorhexidine injection. Ishigami et al.[1] described a patient in whom 800 mg chlorhexidine gluconate (4 mL of 20% solution) was accidentally injected instead of a muscle relaxant. The patient developed acute respiratory distress syndrome (ARDS) despite plasma exchange therapy and subsequently required venoarterial extracorporeal membrane oxygenator (ECMO) support for recovery. Ploner et al.[2] accidentally injected 10–15 mL of 0.1% chlorhexidine gluconate mouthwash (10–15 mg) meant for dipping transesophageal echocardiography (TEE) probe, into central line when a wrong syringe was loaded in infusion pump, with uneventful recovery. Johner et al.[3] inadvertently injected chlorhexidine gluconate solution into radial artery catheter, resulting in necrosis of the thumb requiring surgical debridement and arthrodesis of the thumb phalanges. Kudo et al.[4] identified accidental intravenous injection of 10 mL of 20% chlorhexidine gluconate in central line port postoperatively as the cause of death of a 58-years-old woman who underwent synovectomy of her left middle finger. Apparently the on-duty nurse presumed the 20% chlorhexidine solution prepared for another patient with diabetic gangrene to be heparin saline solution used for routine central line flush while injecting the same.

Clinical features of accidental chlorhexidine intravenous injection may vary from mild urticaria with topical exposure to systemic anaphylaxis with parenteral exposure in central venous catheters. The commercially available specific diagnostic IgE analysis for chlorhexidine (ImmunoCAP Allergen C8, Sweden) has a cutoff value of 0.35 kUA/L.[5] Management is essentially supportive with volume resuscitation, steroids, antihistaminic, inotropes/vasopressors, ventilatory support, plasma exchange, and lastly ECMO.

In all the cases including ours, the incident could be attributed to faintly tinted/colorless pourable chlorhexidine solution, which was indistinguishable from heparin saline/normal saline solution intended for use on visual inspection (Fig. 1B). In the case reported by Ishigami et al.,[1] however, the unintentional administration occurred because the name of the muscle relaxant used was similar to the commercial name of chlorhexidine gluconate and the two containers were in close proximity. The present research report highlights a potentially lethal preventable toxicity in clinical practice which can improve patient safety. The take home message is: open systems as use of gallipots for injectable drugs should be discarded, only highly tinted/colored skin antiseptic preparation solutions of chlorhexidine should be available within the sterile surgical field, ISO labelled syringes should be available for parenteral use, and sterile labelling should be used in surgical field.

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Figure 1 A, two gallipots placed side by side, one with indistinct pourable 2% chlorhexidine gluconate with alcohol solution (with needle), the other with heparin saline solution with 2 mL of solution drawn from the corresponding gallipot in each syringe below it. B, normal saline (extreme left), 0.5%, 2%, and 4% (extreme right). Chlorhexidine gluconate solutions (3M, Avagard, with each solution poured in an open gallipot, and 2 mL of it drawn in the syringe placed directly below it).

Conflicts of interest

The authors declare no conflicts of interest.

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