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Focused cardiac ultrasound

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Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Point-Of-Care Cardiac Ultrasound: is it time for anesthesiologists to embrace and achieve competence?

That will never come into clinical practice, and I am extremely doubtful because its clinical applications require much time and give a good bit of trouble both to the patient and practitioner.

J. Forbes — Preface for Laennec's Treatise, 1823

The statement above refers to the introduction of the stethoscope in clinical practice at the beginning of the 19th century. It shows that every new technology needs to overcome barriers before its acceptance. Point-Of-Care Ultrasound (POCUS) is a diagnostic modality adopted by several specialties to help in the clinical evaluation of the patient and the performance of several procedures. It has been familiar in anesthesiology for a long time due to its role in facilitating venous accesses and regional blocks.[1]

Given the inherent safety, portability, and relative cost-effectiveness of POCUS compared to other imaging modalities, it is unsurprising that this diagnostic tool is increasingly getting attention in modern medical practice. The advent of compact and versatile devices with enhanced image quality and sophisticated features[2] — such as color, pulsed, and continuous wave Doppler — has further advanced this trend. For the anesthesiologist, it is crucial to comprehend the wide range of POCUS applications,[3] covering cardiac, pulmonary, gastric, abdominal, neurological, and airway assessments. Such understanding facilitates the selection of the appropriate modality, thereby optimizing patient management and outcomes in the clinical scenario at hand.

Cardiac Point-Of-Care Ultrasound (C- POCUS) has the general characteristics of other POCUS modalities (qualitative assessment, simple execution) with the main objective of helping the diagnosis and assisting in situations of hemodynamic instability.[4] Based on a defined list of diagnoses, C-POCUS can reliably detect or exclude the presence of cardiac tamponade, myocardial ischemia, ventricular failure, hypovolemia, gross valvular pathologies, pulmonary embolism, and unexplained hypoxia. It can also be used in cases of circulatory arrest[5] to evaluate and guide cardiopulmonary resuscitation. It is essential to emphasize the enormous difference between C-POCUS and a formal transthoracic echocardiogram.[6] Although both use cardiac ultrasonography, a formal echocardiogram is a much more comprehensive and sophisticated diagnostic modality, requiring extensive training and following well-defined guidelines for acquiring, interpreting, and reporting exams[7] contrary to a focused qualitative assessment.

This issue of the *Brazilian Journal of Anesthesiology* discusses C-POCUS to assist hemodynamic monitoring, which is one of the pillars for indicating its clinical use. Souza et al.[8] used the suprasternal window to obtain the velocity time integral (VTI) of the descending thoracic aorta as a surrogate of cardiac output and compared it with the conventional method of measurement obtained through the apical window. Their findings not only suggest a good correlation between windows, but also that the proposed technique can be learned with relative ease to be applied in the daily anesthetic practice. Despite being a small study, it highlights the desired characteristics of the POCUS exam: quickness and reliability to assist in the clinical decision-making process. In other words, questions such as *"Is this low output state caused by hypovolemia (and a fluid challenge is warranted) or by ventricular failure (in which case a fluid challenge not only is the wrong answer but also potentially harmful)?"* can be answered swiftly and more accurately.

In another article, Roy et al.[9] discuss the variation of the inferior vena cava (IVC) diameter through the Collapsibility Index (CI) obtained by imaging it in the subcostal view trying to predict the occurrence of hypotension following spinal anesthesia. Despite the absence of correlation between the CI and the percentage decrease in the mean blood pressure (due to gaps in IVC ultrasound interpretation such as cardiac function, thoracic and abdominal pressure, blood volume, and vessel compliance),[10] the article also discusses and alerts the anesthesiologist about integrating several POCUS modalities (cardiac, vascular, and pulmonary) to obtain a complete assessment of the patient's hemodynamic status.[11] Such strategy seems to be especially useful when there is a multifactorial mechanism of hemodynamic

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instability, including multiple types of circulatory shock at the same time. POCUS may help providers to individualize each patient's pathophysiology and guide the most appropriate strategy in order to normalize tissue perfusion.

Even though it is widely used across various medical fields, the opportunities for POCUS training and the requirements for achieving proficiency and certification show considerable disparity between specialties. In anesthesiology, this variability is particularly pronounced. There is a pressing need for formal training curriculum within most medical residency programs, both in and outside Brazil. Additionally, rigorous evaluation and certification processes are essential to ensure appropriate proficiency in this critical skill.[12]

Regarding the general POCUS curriculum[1-6] and the specific domain of C-POCUS,[7-10] it is anticipated that anesthesiologists in training demonstrate the ability to:[13,14]

1) Recognize the clinical indication of the test: resuscitation, hemodynamic monitoring, and assistance in performing procedures.
2) Show basic knowledge of physics for image acquisition and what to do to optimize it.
3) Know the equipment, the different types of probes, and when and why use them.
4) Understand and perform probe movements (rotation, tilting, sweeping, angling, rocking) to acquire the best image for each evaluated structure.
5) Report the examination findings clearly and concisely to other professionals caring for the patient and document them in the medical record for possible follow-up.
6) Recognize the limitations of the exam and know when to request a comprehensive examination.
7) Know the basic anatomy of the heart, great vessels, coronary irrigation, and inferior vena cava.
8) Recognize and effectively obtain the most used windows for a focused cardiac examination: long and short parasternal, long and short subcostal, and apical four chambers.
9) Recognize and integrate the most common causes of hemodynamic instability in the perioperative period: size and function of the left and right ventricle (qualitative analysis), presence of pericardial effusion, gross valve alterations.
10) Integrate the findings with the ultrasonographic pulmonary examination and assessment of the inferior vena cava diameter.

The challenges of structuring learning opportunities in accordance with the requirements, associated with the evaluation and certification of anesthesiologists, have significant obstacles. These difficulties not only prevent a greater number of professionals from achieving proficiency, but also obstruct the integration of POCUS training into residency programs. The Brazilian Society of Anesthesiology (SBA) has been promoting workshops of C-POCUS for their members aiming to spread this knowledge among Brazilian anesthesiologists and residents.

Broadly, training programs proposed by societies both within and outside the field of Anesthesiology[14,15] are based on the following principles: formal didactic activities and use of simulators; creation of a minimal supervised exam portfolio (30—40 exams for C- POCUS); competency assessment (formative and summative feedback); and maintenance of competence acquired through a minimum number of exams performed annually at the end of the training.

Upon completion of the training, it is expected that the trainee holds the capability to acquire accurate and informative images, sufficient for proper interpretation. Furthermore, after reading these images, the physician should be able to make appropriate clinical decisions, avoiding both excessive interpretation and the oversight of crucial diagnoses.

Another important topic currently under discussion is when to start the POCUS training. The global tendency is to start it during medical school as a general competence before choosing a specialty. Still, this trend needs to be better evaluated due to the lack of guidelines and standards.[16]

There is no doubt that POCUS, in general, is a diagnostic modality that will be increasingly used and explored in our specialty. The concept of "whole body ultrasound" (WHOBUS), with the objective of increasing the speed and accuracy of the evaluation of critically ill patients, is already used postoperatively in several intensive care units where there is the integration of C- POCUS in the assessment of causes of hemodynamic instability and pulmonary US to diagnose causes of hypoxemia, besides abdominal US to assess causes of oliguria and optic nerve sheath diameter to evaluate intracranial pressure (ICP).[17]

It is essential that anesthesiologists, who deal with unstable patients during their routine, feel comfortable in recommending, performing, and interpreting this examination. Not only it provides real-time insights into the causes of the hemodynamic decompensation but allows for continuous monitoring of responses to the implemented therapeutic interventions. To achieve this, mechanisms must be created to offer an adequate training and evaluation curriculum for anesthesiologists already working in clinical practice and for future generations.

Conflicts of interest

The authors declare no conflicts of interest.

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EDITORIAL

Is the combination of oral midazolam and ketamine as preanesthetic medication a safe and effective practice?

Preoperative anxiety is very common in subjects who will undergo surgery, mainly children. Preoperative anxiety in children may manifest in different ways: some will verbalize what they are feeling, while others will have specific stress related behavior. In general, stress associated anxiety is related to fear of separation from parents, fear of experiencing pain, fear of not surviving the procedure, among other sources of worries.[1]

Anxiety may have two different manifestations: state and trait anxiety. While state anxiety is a transitory and emotional behavior that fluctuates over time, varies in intensity and includes feelings of tension, apprehension, nervousness, and worry; trait anxiety refers to a personality trait that remains stable over time.[2,3] Reducing anxiety in children undergoing surgery is important both for compassionate reasons as well as to increase their cooperation during anesthesia induction. However, it may also reduce the risk of postoperative emergence delirium and behavioral changes, as we will discuss further.[4,5] Interestingly, patients with high levels of preoperative state anxiety are particularly vulnerable to severe pain after surgery.[2]

Children with a higher degree of preoperative anxiety are also at greater risk of presenting maladaptive behavior in the postoperative period. Among these behaviors we may observe irritability, separation anxiety, nightmares, feeding problems, night crying, disobedience, and nocturnal enuresis. These behavioral changes may persist for up to one year, while negative memories of the perioperative period may persist into adulthood.[1,6]

The hypothalamic-pituitary-adrenal axis is activated by the stress caused by anxiety. This activation determines an increase in the glucocorticoid plasma level and may contribute to changes to the immune system with increased risk of infections.[1] Anesthetic premedication is one of the most helpful tools for reducing stress in children. Various drugs and dosage forms may be used as premedication, including oral midazolam and ketamine.[7] Midazolam is currently one the most used premedication drugs in pediatric practice.[8]

Midazolam is a water-soluble drug that can be administered orally, intranasally, sublingually, rectally, intramuscularly, or intravenously. It has fast onset, with duration of action of approximately 30 min, generally not interfering with vital signs in doses below 0.5 mg.kg^{-1}.[8,9] These characteristics make midazolam suitable as premedication, in special for children. The bioavailability of midazolam is on average 36%, with a very broad range (971%).[10] Its use as a premedication drug is associated with 60 to 80% of good responses, while in dental surgery the success rates are even lower.[9] For this reason, and to improve its success rate, other drugs may be associated to midazolam as premedication.

Ketamine has been studied as an adjuvant drug added to midazolam in the perioperative period. The rationale for the coadministration of these two drugs as premedication is the assumption that midazolam anxiolysis is added to the sedative and analgesic properties of ketamine, not increasing side effects.[11] Ketamine is a dissociative general anesthetic that, when used and in a lower dose, can be an analgesic. It is a racemic mixture, although more recently S-ketamine is commercially available. The latter may be associated with fewer side effects, although it is a two to four times more potent analgesic than the original compound. The bioavailability of oral S-ketamine is estimated to be 11%, suggesting that the first hepatic passage plays an important role, while the racemic compound has an oral bioavailability of 17 to 24%.[12]

Oliveira Filho et al published an interesting systematic review and meta-analysis in the BJAN on the use of oral midazolam alone and in combination with ketamine in the preoperative period for children. Their studied primary outcomes were anxiety and sedation levels, child's behavior during separation from parents, face mask acceptance, and venipuncture. Twenty studies were included in the meta-analysis, with a total of 1540 patients. Oral midazolam associated to ketamine was administered in 834 subjects, while 706 received only midazolam.[11]

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Unexpectedly, adding oral ketamine to midazolam did not improve anxiolysis. However, the probabilities of obtaining a better outcome was higher among patients who received the combination of both drugs for sedation, including behavior during parental separation, facial mask acceptance and venipuncture outcomes. Treatments did not differ regarding the probabilities of occurrence of adverse effects, including perioperative nausea and vomiting, hallucinations, excessive salivation, diplopia/nystagmus, or oxygen desaturation. Only one included study evaluated excessive sedation, headache, tachycardia, bradycardia, involuntary movements, hiccoughs, and delayed recovery, without observing differences among groups.

It is noteworthy that the association of these drugs can produce different (or more pronounced) anxiolysis and analgesia effects depending on the administered doses of each drug, the pharmaceutical presentation, and the characteristics of the studied population. According to Oliveira Filho et al, there is a great variation in the doses used for both drugs, from 0.2 to 0.75 mg.kg^{-1} for midazolam, and from 1 to 6 mg.kg^{-1} for ketamine, as well as the use of different pharmaceutical formulations.[11] The oral midazolam solution has adequate bioavailability for administration by this route, but when the parenteral presentation is used orally, changes in the solution's pH may occur, causing medication bioavailability and absorption changes interfering in the effectiveness of midazolam.[13]

The authors of the study concluded that, due to the small effect sizes, high within-study risk of bias, high methodological and statistical heterogeneity, and high risk of publication bias found in meta-analyses, a weak level of recommendation is provided for replacing oral midazolam alone with oral combinations of midazolam and ketamine for the preanesthetic medication of pediatric surgical patients.[11]

It is important to note that some groups of patients benefit from more powerful sedation and analgesia in the preanesthetic period, especially those with high levels of anxiety, changes in behavior and sociability, cognitive deficits, or the need for awake venopuncture. In this scope, in another study presented in the BJAN, Penna et al demonstrated that patients with autism spectrum disorder (ASD) are a group with special needs in terms of anesthetic care, requiring individualized care from the preoperative period to hospital discharge, with the aim of making the hospital experience less traumatic and as comfortable as possible.[14]

In the past 20 years, there has been a significant increase in the prevalence of ASD, mainly due to greater knowledge and better diagnostic methods for this condition. ASD is a neurodevelopmental disorder, present from birth and persistent throughout life, which causes impaired social interaction, communication and isolation problems, behavioral disturbances, disorders of the sensory sphere, as well as altered motor skills. Sensory disorders are represented by inadequate responses to tactile and proprioceptive stimuli and by altered pain perception.[15]

In the study by Penna et al, the need to use effective preanesthetic medication for dental treatment under general anesthesia in patients with ASD is evident, mainly justified by the difficulties in approaching these patients in the conventional way, both for dental treatment and preanesthetic management. In this parallel, double-blind, controlled, randomized clinical trial, the authors included 64 persons with ASD aged 2—59 years scheduled for dental care under general anesthesia. The primary objective was to compare the degree of sedation, and the secondary outcomes were the need for physical stabilization to obtain intravenous access, time to wake up, and the occurrence of adverse events. The sample was randomized to receive preanesthetic medication with an oral solution of midazolam alone 0.5 mg.kg (maximum 15 mg) or receive oral midazolam 0.5 mg.kg^{-1} (maximum 15 mg) associated with oral S-ketamine 3 mg.kg^{-1} (maximum 300 mg).[14]

The results are consistent with those observed in the systematic review and meta-analysis by Oliveira Filho et al.,[11] in which the level of sedation achieved by the oral association of S-ketamine and midazolam promoted better sedation, with an increase in the probability of Ramsay $\geq$ 3, compared to midazolam alone. The association was also useful from an analgesic point of view, facilitating venous access without requiring physical restraint. The association of midazolam and S-ketamine did not cause an increase in the time of awakening or the occurrence of adverse events when compared to midazolam alone.[14]

Based on these results, from both studies presented in this edition of BJAN, the association of ketamine and midazolam is an interesting alternative in preanesthetic medication, when a powerful sedative and anxiolytic effect is desired, especially in patients who are not very cooperative or with disorders related to socialization or sensory changes, in which the benefit of analgesia provided by ketamine is welcome. However, larger and new studies are needed comparing similar drug doses and presentations (formulations) in larger populations, in healthy individuals, in order to conclude that this association is superior from the point of view of sedation and anxiolysis, as well as, devoid of adverse events and prolonged awakening time in other clinical settings.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Comparative study between suprasternal and apical windows: a user-friendly cardiac output measurement for the anesthesiologist☆

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Doppler ultrasonography

Abstract
Introduction: Transthoracic echocardiography is a safe and readily available tool for noninvasive monitoring of Cardiac Output (CO). The use of the suprasternal window situated at the sternal notch can be an alternative approach for estimating blood flow. The present study aimed to compare two methods of CO calculation. We compared the descending aorta Velocity-Time Integral (VTI) measurement from the suprasternal window view with the standard technique to determine CO that uses VTI measurements from the LVOT (Left Ventricular Outflow Tract) view. We also aimed to find out whether after basic training a non-echocardiographer operator can obtain reproducible measurements of VTI using this approach.
Methods: In the first part of the study, 26 patients without known cardiovascular diseases were evaluated and VTI data were acquired from the suprasternal window by a non-echocardiographer and an echocardiographer. Next, 17 patients were evaluated by an echocardiographer only and VTI and CO measurements were obtained from suprasternal and apical windows. Data were analyzed using the Bland and Altman method (BA), correlation and regression.
Results: We found a strong correlation between measurements obtained by a non-expert and an expert echocardiographer and detected that an inexperienced trainee can acquire VTI measurements from the suprasternal window view. Regarding agreement between CO measurements, data obtained showed a positive correlation and the Bland and Altman analysis presented a total variation of 38.9%.

☆ Study conducted at the Hospital das Clínicas da Universidade Federal de Minas Gerais – HC/UFMG.

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Conclusion: Regarding accuracy, it is likely that TTE (Transthoracic Echocardiogram) measurements of CO from the suprasternal window view are comparable to other minimally invasive techniques currently available. Due to its user-friendliness and low cost, it can be a convenient technique for obtaining perioperative hemodynamic measurements, even by inexperienced operators.

Introduction

Cardiac Output (CO) is essential for oxygen supply to tissues and CO calculation has an important role in patient management during anesthesia and critical care.[1,2] CO measurements by thermodilution via Pulmonary Artery Catheter (PAC) is the most frequently used technique to obtain clinical reference and comparative values,[2,3] albeit randomized studies in critically ill patients assessing this method did not show improvements in mortality.[4–6] Furthermore, the risks related to the technique prompted a reduction in its use, and currently clinicians are inclined to use more accurate and less invasive methods to provide hemodynamic management for patients undergoing major surgeries.[3,7,8]

To date, there is no available gold standard method for obtaining noninvasive or minimally invasive measurements of CO due to the lack of accuracy and precision in measurements.[2,9] Among the methods and technologies available in recent years, Doppler echocardiography (Doppler-based) has been a valuable tool to assess and quantify CO. The method uses the principle that the blood flow velocity determined by Doppler sound waves is evenly distributed in the cross-sectional area of the vessel it passes through. Thus, the cross-sectional area times the mean flow velocity (Velocity-Time Integral – VTI) equals the volume of blood that passes through the vessel (Systolic Volume – SV).[3,10,11] When this volume is multiplied by the heart rate, the value of CO is obtained.

In clinically stable patients, Doppler-based CO measurements performed by an experienced cardiologist have reliable accuracy when compared with CO measurements using the PAC thermodilution method.[3,12–14] In 1984, studying patients without stenotic or regurgitant valve injury, Lewis et al validated the Doppler-based determination of the flow in the Left Ventricular Outflow Tract (LVOT) to calculate SV and CO.[10] In addition to providing noninvasive cardiac output determination, this tool is very useful for ER and ICU practitioners, as they can proficiently perform basic echocardiography exams to assess ventricular function and fluid status after fairly short training in the acquisition and interpretation of images.[15]

Perioperatively, the standard CO measurement using the LVOT cross-section area from the parasternal long axis view, multiplied by the VTI of the LVOT flow obtained from the 5-chamber apical window is not practical or feasible, because of patient position on the operating table and the presence of sterile drapes.[16] In this situation, calculating the VTI of the descending aorta from the suprasternal window can be an alternative for CO determination. Thus, the main objective of this study was to compare VTI measurements of blood flow by Doppler ultrasonography in the descending aorta from the suprasternal window of the transthoracic echocardiogram with VTI measurements of the LVOT flow, which is the standard approach for measuring CO. We believe there is a significant correlation between the measurements obtained from both windows by a specialized echocardiographer, and that a non-echocardiographer operator (3rdyear anesthesiology resident) will obtain satisfactory CO measurements from the suprasternal window, after basic training comprising a 12-h practice under professional guidance and performing at least 30 CO measurements on 15 different volunteers.

Methods

Selection of participants

The study was conducted after approval of the Ethics and Research Committee of Hospital das Clínicas, UFMG CAAE 05997118.9.0000.5149. Data were acquired at two different sessions, from May to June 2019. We included volunteers with over 18 years of age, from both sexes, able to understand and cooperate during all phases of measurements. We excluded subjects presenting history of cardiovascular disease and/or previous cardiac surgery and offering technical impediments to perform the measurements due to anatomical features (one participant was excluded due to silicone implanted prosthesis). Eventually we included 26 volunteers in the analysis in the first part of the study, in which VTI data were acquired from the suprasternal window by an inexperienced operator and by a specialist echocardiographer. In the second part of the study, 17 patients were examined only by the specialized echocardiographer with VTI and CO data acquisition from the suprasternal and apical windows. During all ultrasound measurements, Noninvasive Blood Pressure (NIBP) and pulse oximetry were monitored, and Heart Rate (HR) and mean arterial pressure were recorded by an Omni 612 monitor manufactured by Omnimed.

Echocardiographic Doppler measurements

Echocardiographic data were acquired using the US Philips Epiq 7 and Philips CX50 equipment (Philips Ultrasound Systems, Bothell, WA) and a 2–5 MHz sector transducer. In the first part of the study, measurements were performed by two operators in sequence, one specialized echocardiographer with extensive experience in the method (ECO) and one without experience (non-ECO). Both operators acquired VTI

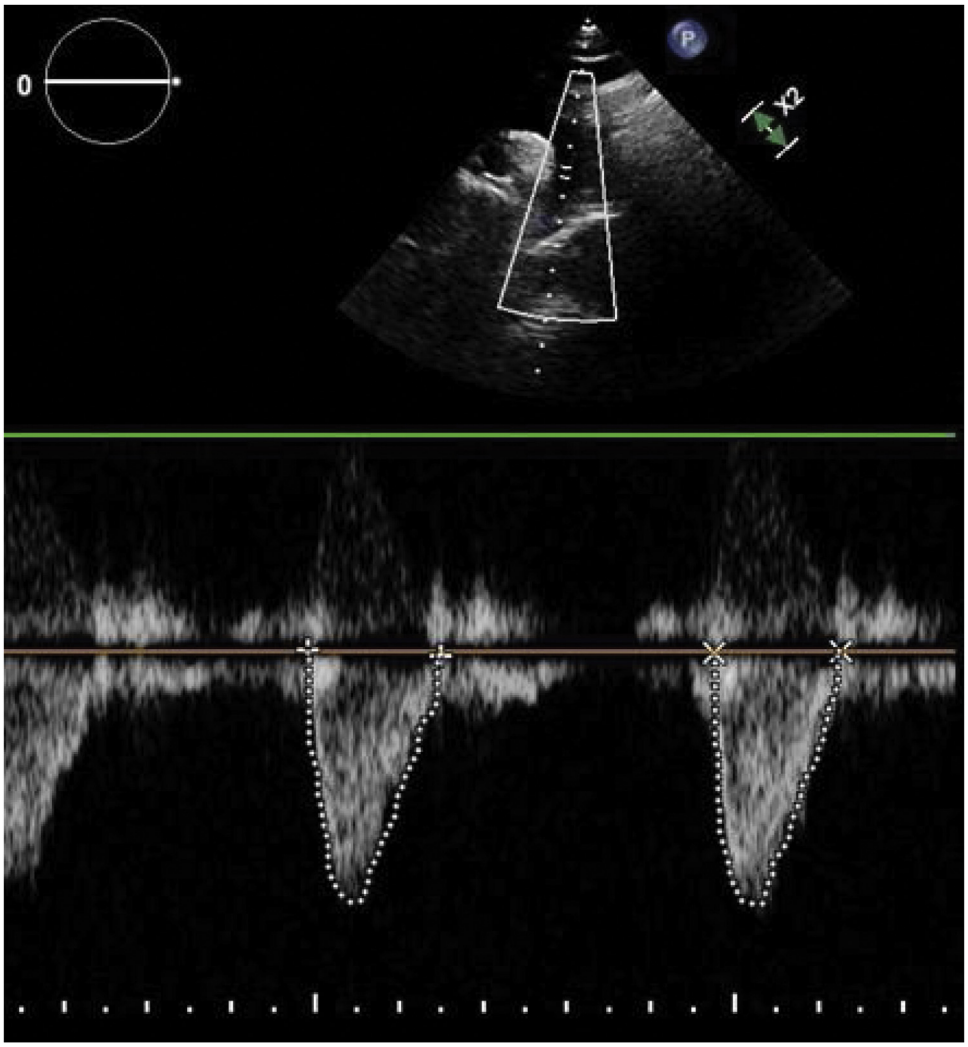

Figure 1 Echocardiographic image with the suprasternal window captured by an inexperienced operator. Measurements obtained from VTI after proper alignment.

measurements by Continuous-Wave Doppler (CW) from the suprasternal window. As the patient was in a supine position, this window was considered satisfactory when the aortic arch image was captured in its long axis, with the views of the takeoff of the innominate, left common carotid and left subclavian arteries. In the second part of the study, only the specialized echocardiographer performed measurements of VTI by continuous-wave Doppler from the suprasternal window and pulsed-wave Doppler in LVOT from the 5-chamber apical window, in addition to the measurement of the LVOT diameter (LVOTd) from the long axis parasternal window, with the volunteer in the left lateral position. The following equation was used to calculate the LVOT cross-section area: $A = 0.785 \times (LVOTd)$.[2] The cardiac output value was calculated in the classic way, that is, using the VTI obtained from LVOT times area of LVOT times heart rate at the time of the exam, as in the equation: $CO = VTI \times A \times HR$. In addition, cardiac output was calculated with the VTIs from the suprasternal window using the area value obtained from LVOT. The rationale for not using the descending aorta diameter was that the literature has documented well that the lateral resolution of the ultrasound is unfit to measure the diameter of the descending aorta.[17]

Data analysis

Data were analyzed using SPSS version 20 and MedCalc version 19.0.5. The normality of data distribution was confirmed using a Kolmogorov-Smirnov test. Data are reported as mean ± standard deviation.

Pearson's correlation coefficient was used to verify the association among variables. To analyze the agreement between the measurements of VTI obtained from the suprasternal window with the measurements of VTI of LVOT obtained from the 5-chamber apical view we used the Bland-Altman analysis, a scatter plot of the difference between the means of the methods in relation to their mean and standard deviation.[18] The cardiac output estimated with the measurement of VTI acquired from the suprasternal window was also submitted to linear regression analysis. The level of significance adopted was 5% ($p < 0.05$ was considered statistically significant). The significance of the sample was tested *a pos-*

Table 1 Characteristics of patients (mean ± standard deviation).

Patient Characteristics	n = 26	n = 17
Age (years)	29 ± 6	30.71 ± 7.1
Height (cm)	1.72 ± 0.09	1.72 ± 0.09
Weight (Kg)	67.56 ± 11.35	68.44 ± 10.52
Gender (F/M)	12 (46.2%) / 14 (53.8%)	7 (41.2%) / 10 (58.8%)

teriori by the GPower software, and satisfactory power was found (> 80%).

Results

Table 1 shows the characteristics of the volunteers evaluated in the two parts of the study. Column 1 shows the 26 participants evaluated by both researchers and column 2 shows the 17 participants evaluated from different windows by the same echocardiographer. Cardiac output was calculated using the formula: CO = VTI × A × FC (where VTI = Integral Velocity-Time; A = vessel cross-section area; HR = Heart Rate). Figure 1 shows an example of an image captured from the suprasternal window by an inexperienced operator during VTI measurements.

The *r* correlation between VTI measurements obtained by the two operators from the suprasternal window with the CW Doppler was 0.85. The analysis using the Bland Altman plot indicated an error percentage of 27.3% for the measurements made with the CW Doppler with a 95% limit of agreement, between 3.7 cm and 4.1 cm (Fig. 2).

Regarding agreement of the VTIs acquired from the apical and suprasternal windows, the sample with 17 evaluated participants showed satisfactory power. The *r* correlation between VTI at LVOT and VTI from the suprasternal window was 0.52. The Bland-Altman analysis showed a bias of 5.66 $cm.s^{-1}$, with 95% limit of agreement, between 0.79 cm and 12.11 cm and an error percentage of 52.6% (Fig. 3).

CO was calculated using the measurement of VTI from the suprasternal window with the CW Doppler and the cross-section area of LVOT. Then this CO value was compared to the standard determination of CO from LVOT. The *r* correlation between both determinations was 0.78 with adequate significance, and the regression equation obtained was: standard CO = 587.58 + 0.68 × CW suprasternal CO. The Bland-Altman analysis presented bias of 1459.3 mL with 95% limit of agreement, between 428.2 mL and 2490.4 mL and an error percentage was 38.9% (Fig. 4).

Discussion

When a new technique for measurement of a clinical variable is introduced, it is usually compared to an established reference technique. Usually, the implementation of the new technique depends on its degree of agreement with the reference technique and the potential benefits offered by the new method.[19] Our study revealed that that the limits of agreement (or proportion of the mean CO also described as error percentage) after the Bland Altman analysis was 38.9%

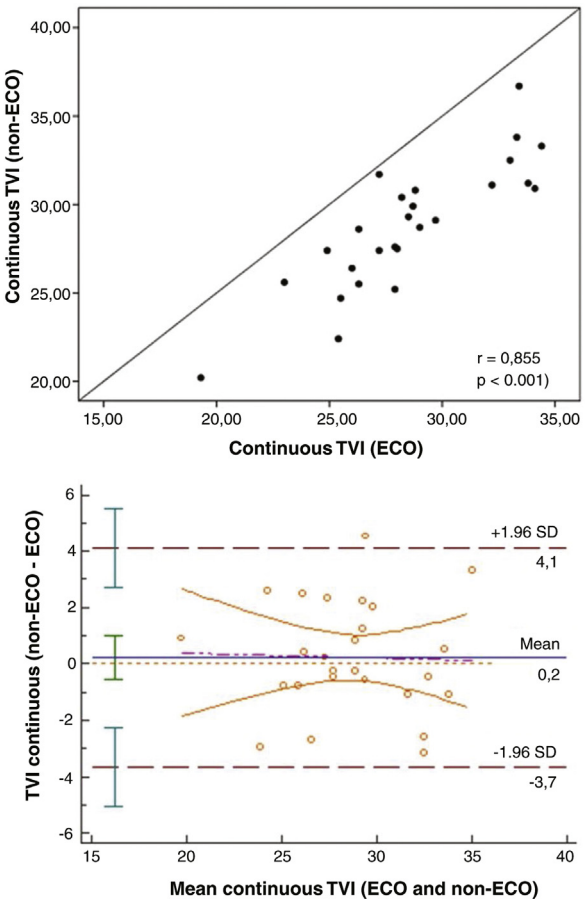

Figure 2 Correction plot between continuous VTI measurements performed by an experienced (ECO) and inexperienced (non-ECO) operator.

when the measurements of CO obtained with echo Doppler from the suprasternal technique was compared to the standard technique of measurement from the LVOT. Critchley and Critchley established that the variation between a new method of CO measurement and the reference method is acceptable if the limits of agreement between them are less than 30%.[20] However, although Bland Altman is a useful tool for describing the limits of agreement between two methods of measurement, conclusions about acceptability between the techniques are a matter of opinion and not just science. Analytical methods for comparing CO measurement tools need to go beyond that approach to provide insights into the role of technology in clinical practice and decision making.[21]

Several studies have revealed that the existing non-invasive techniques show an average variation of CO measurement of around 40%,[2,8,9,12] and consequently they do not meet the established value. Our data presented values comparable to those techniques. In addition, Peyton and Chong suggest that 45% could be the acceptable error percentage for CO measurement, which is a more realistic accuracy expectation in clinical practice. They also underscore that the effectiveness of a clinical monitor comprises several factors in addition to absolute accuracy, such as safety, convenience, adaptability, and cost.[8] Furthermore, during perioperative care, from the viewpoint

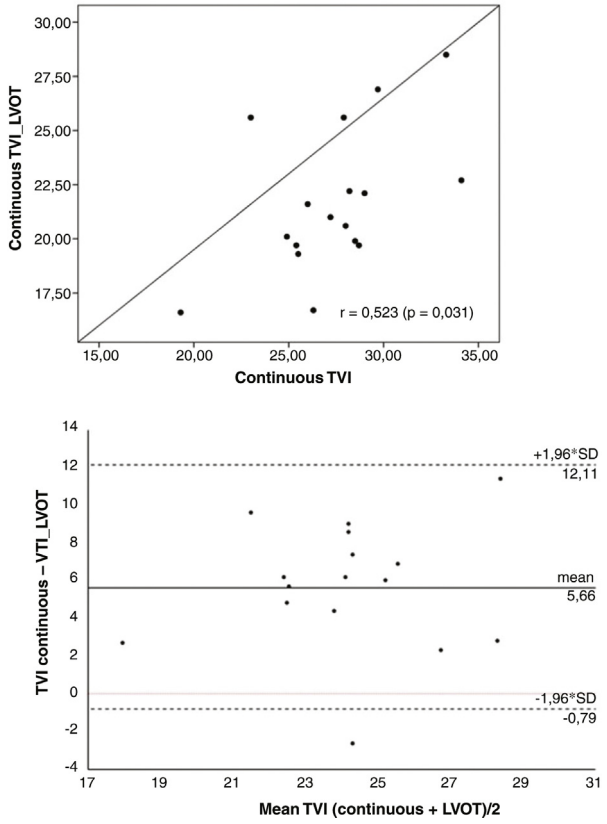

Figure 3 Correlation and Bland Altman between VTIs in LVOT and in the suprasternal window performed by an echocardiographic operator.

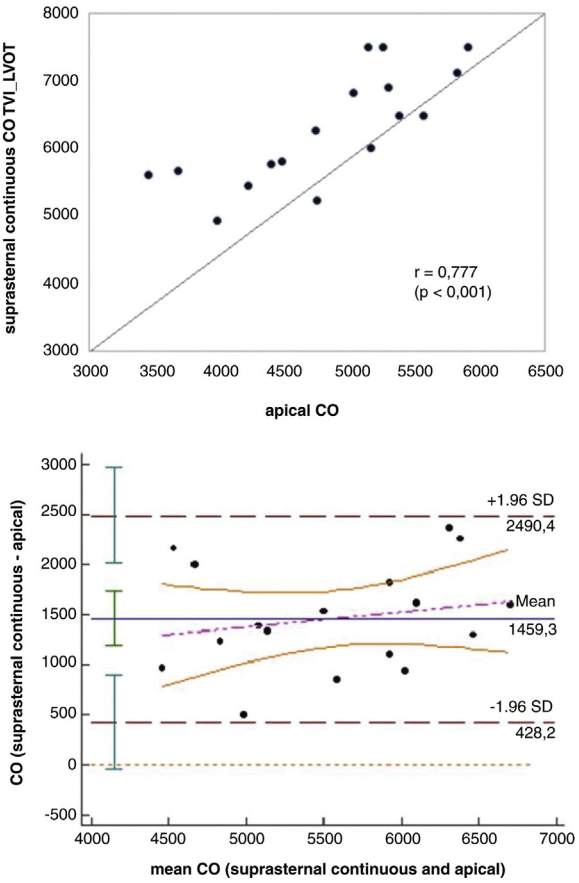

Figure 4 Correlation and Bland Altman between classic continuous CO and suprasternal window.

of decision making it is more important to have real-time access to the trend of the measurement, rather than a single isolated measurement. Real-time tracking of CO value oscillations using serial measurements is undoubtedly more important than the monitor's ability to provide a single, accurate measurement under stable conditions.[8] Analysis of the suprasternal VTI for CO calculation can be straightforward and can provide a sequence of CO measurements. Thus, even if we may be skeptical about one absolute value reading, this technique is still reliable as we can monitor the stroke volume trend and the effect of interventions during intermediate and major surgeries.

Standard echocardiography has evolved in recent years and with the development of compact, portable, and high-quality devices, it can now be performed at any site.[22] This monitoring is a new concept that has gained acceptance in several areas, comprising cardiology, emergency medicine, anesthesiology, obstetrics, and critical care. TTE (Transthoracic Echocardiogram) has been used in several steps of the decision-making process during patient management and, therefore, an increased number of anesthesiologists are getting TTE training and using it in their routine practice.[19,22,23] Sequential assessment of vital parameters perioperatively impacts anesthetic management. The more feasible and available the technique, the greater the ease and safety in managing critically ill patients. Bergamaschi et al revealed that physicians that were working at an ICU and were not cardiologists, after brief training on how to operate the echo Doppler device and determine VTI, were able to accurately calculate CO of ICU patients under mechanical ventilation.[15] Likewise, our data found that the inexperienced operator, after basic training, was able to estimate the value of VTI and CO quickly and accurately in patients without cardiovascular disorder. Thus, an anesthesiologist, after a relatively short standard TTE training, might be able to properly obtain measurements from the suprasternal window. On the other hand, as echocardiography is used to guide therapeutic decisions, one must consider the existence of inter-observer measurement variability and strive for technical excellence to provide accurate measurements.[24]

The thermodilution inference method, previously widely used as a standard technique for CO measurement, does not reflect the real CO, as there are inherent errors of accuracy and precision (10–20%) due to fluctuations in CO during the breath cycle, in addition to technique limitations.[19,25,26] Thus, the search for alternatives for less invasive hemodynamic monitoring intensifies every day and numerous monitors have already been developed. Nevertheless, when evaluating the role of new devices for calculating CO in clinical settings, the cornerstone question to be answered is whether the new device replacing the thermodilution CO determination can be used to provide guidance for clinical decisions. Despite the large number of studies evaluating new CO devices, few have answered this fundamental question.[21] In addition, another question to be considered is whether these CO monitors would positively change patient

clinical outcomes rather than only delivering measurements that would not modify patient management. The ideal monitor should be non-invasive or minimally invasive, provide accurate and reproducible readings, have favorable limits of agreement when compared to PAC, be dependable under different physiological conditions and be affordable. Finally, it should offer continuous measurements and have the ability to assess the impact of therapeutic interventions (e.g., hemodynamic response to administered fluids or vasoactive drugs). Thus far, no device has met all these criteria,[27] so it is necessary to keep studying patients in which CO monitoring is crucial to determine the range of values in which an intervention would or would not be well recommended. The impact of these decisions on patient outcome is the major issue and will require the development of further protocols based on studies involving larger patient populations.[21]

The limitations of our work are the small sample size, the determination from the window is investigator dependent as it requires basic and continuous training in the technique, and even though most studies used PAC measurements as a reference and assessed the method under anesthesia our study lacks PAC measurements because we evaluated only healthy and awake participants. In addition, although the measurement of the diameter in the descending aorta is not appropriate, the diameter measurement in the LVOT is not the ideal site to perform the calculation of CO when using VTI in the descending aorta from the suprasternal window.

In conclusion, our data indicate that measurements of CO by TTE from the suprasternal window are comparable to other minimally invasive techniques currently available. Due to its user-friendliness, low cost, capability to deliver reliable measurements enabling to monitor trends in stroke volume and the effect of interventions such as administration of fluids and inotropic and vasoactive drugs, it can be considered a suitable perioperative technique for acquiring hemodynamic parameters and calculating CO, including inexperienced operators. Additional investigations with larger samples should be carried out to complement and further validate our data.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Agreement analysis of stroke volume and cardiac output measurement between a oscillometric device and transthoracic echocardiogram in normotensive individuals: a preliminary report

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KEYWORDS
Stroke volume;
Cardiac output;
Noninvasive hemodynamics oscillometric method;
Mobil-O-Graph

Abstract
Introduction: The evaluation of stroke volume (SV) is useful in research and patient care. To accomplish this, an ideal device should be noninvasive, continuous, reliable, and reproducible. The Mobil-O-Graph (MOG) is a noninvasive oscillometric matrix validated for measuring aortic and peripheral blood pressure, which through conversion algorithms can estimate hemodynamic parameters.
Objectives: To compare the MOG measurement of stroke volume, cardiac output, and cardiac index with the transthoracic echocardiogram (TTE).
Methods: Healthy volunteers aged 18 years or older were included. Two-dimensional TTEs were performed by a single operator. Subsequently, the measurement of noninvasive hemodynamics with MOG was performed with the operator blind to the results of the echocardiogram. Correlation analyses between stroke volume, cardiac output, and cardiac index parameters were performed. The degree of agreement between the methods was verified using the Bland-Altman method.
Results: A total of 38 volunteers were enrolled with a mean age of 27.6 ± 3.8 years; 21 (55%) were male The SV by TTE was 76.8 ± 19.5 mL and 75.7 ± 19.3 mL by MOG, Rho = 0.726, $p < 0.0001$. The CO by TTE was 5.04 ± 0.8 mL.min^{-1} and 5.1 ± 0.8 mL.min^{-1} by MOG Rho = 0.510, $p = 0.001$. Bland-Altman plots showed a good concordance between the two techniques.

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Conclusions: Our study shows that the measurement of SV and CO by noninvasive hemodynamics with the MOG device offers a good concordance with the TTE with very few values beyond the confidence limits.

Introduction

The measurement of stroke volume and different hemodynamic parameters is useful in clinical scenarios such as surgical risk assessment, follow-up of patients taking cardiotoxic drugs, follow-up of patients with heart failure, and continuous monitoring in intensive care units.[1,2]

Traditionally, hemodynamic evaluation is performed through the use of invasive methods, such as thermodilution, which is considered the gold standard technique.[3] The disadvantage of these methods is the invasiveness, the associated risks, and the difficulty of repeating the measurements over time.

Recently, devices that study the functional dynamics of the cardiovascular system have been incorporated as an aid in the management of arterial hypertension and heart failure, optimizing pharmacological therapy and improving morbidity and mortality.[4,5]

Noninvasive methods commonly used in hemodynamic evaluation include impedance cardiography and echocardiography. Thoracic impedance cardiography (ICG) provides continuous beat-by-beat data using algorithms to derive stroke volume from thoracic volume changes.

Echocardiography is well-established clinically, providing a detailed and accurate evaluation of cardiac function and anatomy. However, its results are highly operator-dependent and sometimes limited by the position and physical structure of the patient.[1]

Recently, noninvasive pulse wave analysis methods that depend on personal data, such as age, height, and weight, have been incorporated into clinical practice.[6]

Within the systems that analyze the pulse wave, the Mobil-O-Graph (MOG) pulse wave analysis (PWA) monitoring system (I.E.M. GmbH, Stolberg, Germany) is a commercially available oscillometric matrix. Through the aortic waveform and by using PWA and wave separation, the central aortic augmentation index (AIx), increase pressure (AP), feed (Pf), and recoil (Pb) are obtained as components of the pulse wave and the reflection coefficient.[7]

MOG measures central pressures using brachial waveforms and the ARCSolver algorithm and estimates the cardiac index. Central systolic pressure, calculated with a transfer-function-like method (ARCSolver algorithm), using waveforms using brachial cuff-based waveform recordings, is suited to provide a realistic estimation of central systolic pressure.

This method is based on the arterial tree model in what receives a prescribed input aortic flow waveform or is coupled with a time-varying elastance model for the contractility of the left ventricle.

The arterial tree model is fully characterized by its geometry, the distensibility of all arterial segments, and the peripheral impedances (described by terminal compliances and resistances). Additionally, aortic flow is needed as a proximal boundary condition.

In clinical practice, MOG PWA is used to evaluate pulse wave velocity (PWV) and central aortic pressure (CAP), for which it has been validated against reference methods.[8]

Incorporating the noninvasive assessment of stroke volume (SV) and cardiac output (CO) in addition to CAP and PWV within a single measurement would be of value in the bedside evaluation and treatment of hypertensive and cardiac failure patients.

The objective of the present work is to compare a noninvasive, alternative MOG in the measurement of SV, CO, and cardiac index (CI) versus the measurements made by transthoracic echocardiogram (TTE) in normotensive healthy individuals.

Methods

A prospective, open, non-randomized study was conducted on healthy volunteers. Patients aged 18 years or older were included. At the time of the study, all the participants were in sinus rhythm and had no significant valvulopathies or stenosis of the upper limb arteries. Patients with trivial mitral regurgitation were not excluded.

Anthropometric parameters and risk factors for cardiovascular disease were reviewed. All the participants signed informed consent. This protocol was previously approved by the Institutional Committee for Health Research Ethics (CIEIS) of the Hospital Privado Universitario de Córdoba.

Transthoracic echocardiography was performed using a commercially available GE Vivid E9 (GE Medical Systems) with a 3.5-MHz transducer. Two-dimensional images and Doppler data were acquired according to current guidelines (Lang RM), ensuring the normality of the cardiac anatomy.

Stroke volume was calculated by multiplying the velocity-time integral of systolic flow velocities in the left ventricular outflow tract by the cross-sectional area of the outflow tract calculated from the diameter of the aortic annulus, assuming a circular geometry. All standard measurements were averaged from three beats.[9]

Left ventricular outflow tract (LVOT) velocity and velocity time integral (VTI) were acquired using pulsed-wave Doppler in the apical five-chamber view. The sample volume was positioned at valve level and then moved apically until valve noise was no longer detected. Pulsed-wave Doppler signals of LVOT systolic flow were manually traced on the modal curve. A sweep speed of 100 $mm.s^{-1}$ was used. Three cardiac cycles were averaged.

LVOT diameter was measured in a zoomed longitudinal parasternal long-axis view in a mid-systolic frame, using the inner edge-to-inner-edge technique from the point of

aortic cusp insertion into the interventricular septum to the point of aortic cusp insertion into the intervalvular fibrosa. LV SV was calculated using pulsed-wave Doppler as LV outflow tract area* LV outflow tract velocity-time integral.

For the performance of noninvasive hemodynamics, the MOG system, a blood pressure cuff was placed on the left arm. The device determines the brachial (peripheral) (PAS) and diastolic (DBP) systolic pressure and the waveform.

The data acquisition process for the algorithms is divided into two separate cycles. The first is used to calculate systolic and diastolic pressure by analyzing the oscillometric amplitudes recorded. The pulse wave is recorded during the second period. The algorithm for determining systolic and diastolic blood pressure is based on the analysis of the characteristics of the wavelengths of the oscillations.

The signal strength is recorded in the pressure sensor employing a 10-bit analog-digital converter, while the blood pressure cuff placed on the upper arm continuously deflates a super-systolic pressure level to zero.[6]

Depending on the blood pressure determined, the pulse wave is recorded and prepared for additional numerical treatment. By processing the signal by applying various filter techniques, the peripheral pressure wave is obtained.

Based on the generated aortic pulse wave, cardiovascular parameters are calculated using the idea that left ventricular ejection is subject to a principle of optimization.[10]

Statistical analysis

The quantitative variables were expressed as mean ± standard deviation and the median (range) where appropriate. The categorical variables were expressed as percentages. The normality in the distribution of the data was evaluated by the Shapiro-Wilk test.

Correlation analyses were performed between SV, CO, and CI parameters measured between TTE and MOG. For this analysis, the Spearman correlation coefficient was used. It was estimated that a good degree of correlation would be $r \geq 0.5$.

It was calculated that 35 individuals should be included in the study to account for an alpha error of 5% and a statistical power of 80%, and considering 20% of measurement errors or loss of measurements. The degree of agreement between the methods was calculated using the Bland-Altman plot.[11]

A value of $p < 0.05$ was considered statistically significant.

Statistical analysis was performed with IBM SPSS Statistics Base 22.0 and Med Calc® V10.2.0.0

Results

From April 1, 2018, to January 31, 2019, 38 healthy volunteers 18 years of age or older were enrolled in the study. The mean age of the participants was 27.6 ± 3.8 years, and 21(55%) were male. The baseline and clinical characteristics of the population are detailed in Table 1.

Table 1 Demographic and clinical characteristics of the population.

	n = 38	Mean ± SD
Male sex	21	
Age (years)		27.63 ± 3.8
Weight (kg)		69.16 ± 13.1
Height (cm)		169.76 ± 12.6
BMI ($kg.m^{-2}$)		23.8 ± 2.7
Body surface area (m^2)		1.8 ± 0.2
Smoking	2	
Arterial hypertension	0	
Diabetes	0	
Systolic blood pressure		118 ± 12.5
Diastolic blood pressure		73 ± 8
Central systolic blood pressure		108 ± 11
Central diastolic blood pressure		74 ± 8

BMI, body mass index.

Table 2 presents the mean and correlation values of SV, CO, and CI as measured by MOG and TTE. It was observed that the SV and CO values were very close as measured by both devices and that the correlation values were good and statistically significant. The agreement values presented by the Bland-Altman analysis in Figure 1 showed good values with very few cases beyond the 95% confidence interval range.

Conclusions

Our study shows that the measurement of SV, CO, and CI with MOG offers measurements with good agreement with the transthoracic echocardiogram. Concordance is good in both men and women (data not shown).

Previous studies that compared the ejection fraction measurement by impedance cardiography with echocardiography showed a poor correlation between both methods due to the difficulty of applying an algorithm based on the truncated cone model.[12,13]

Our hypothesis is based on Bauer et al., who demonstrated the validity of ejection duration measurement with the oscillometric MOG compared with the tonometric device SphygmoCor.[14] Previously, different mathematical algorithms were correctly validated for the calculation of SV, comparing the oscillometric methods to the value obtained by thermodilution as a reference instrument. The measurement of stroke volume with oscillometric devices may be affected by artifacts caused by patient movement, cardiovascular diseases, or vascular tree alterations. However, it offers a rapid measurement, with a good correlation with invasive devices that are available for medical use in outpatient practice.[15]

Critchley and Critchley[16] point out that any evaluation of cardiac output measurement devices must take into account the accuracy of the reference method. Previous studies categorize the echocardiogram validation as satisfactory against the gold standard of thermodilution, adding validity to the reference method used in this study.[17,18]

The measurement of cardiac output with magnetic resonance has been validated in previous studies presenting

Table 2 Spearman correlation of stroke volume, cardiac output, and cardiac index by echocardiogram and Mobil-O-Graph.

	MOG	TTE	Rho	95% CI	*p*
Stroke volume (mL)	75.7 ± 19.3	76.8 ± 19.5	0.73	0.530–0.849	<0.0001
Cardiac output (mL.min^{-1})	5.04 ± 0.8	5.1 ± 0.8	0.51	0.232–0.716	0.0018
Cardiac index (mL.min^{-1}.m^{-2})	2.80 ± 0.4	2.85 ± 0.4	0.368	0.055–0.615	0.0251

The values were expressed as mean ± SD.
TTE, transthoracic echocardiogram; MOG, Mobil-O-Graph.

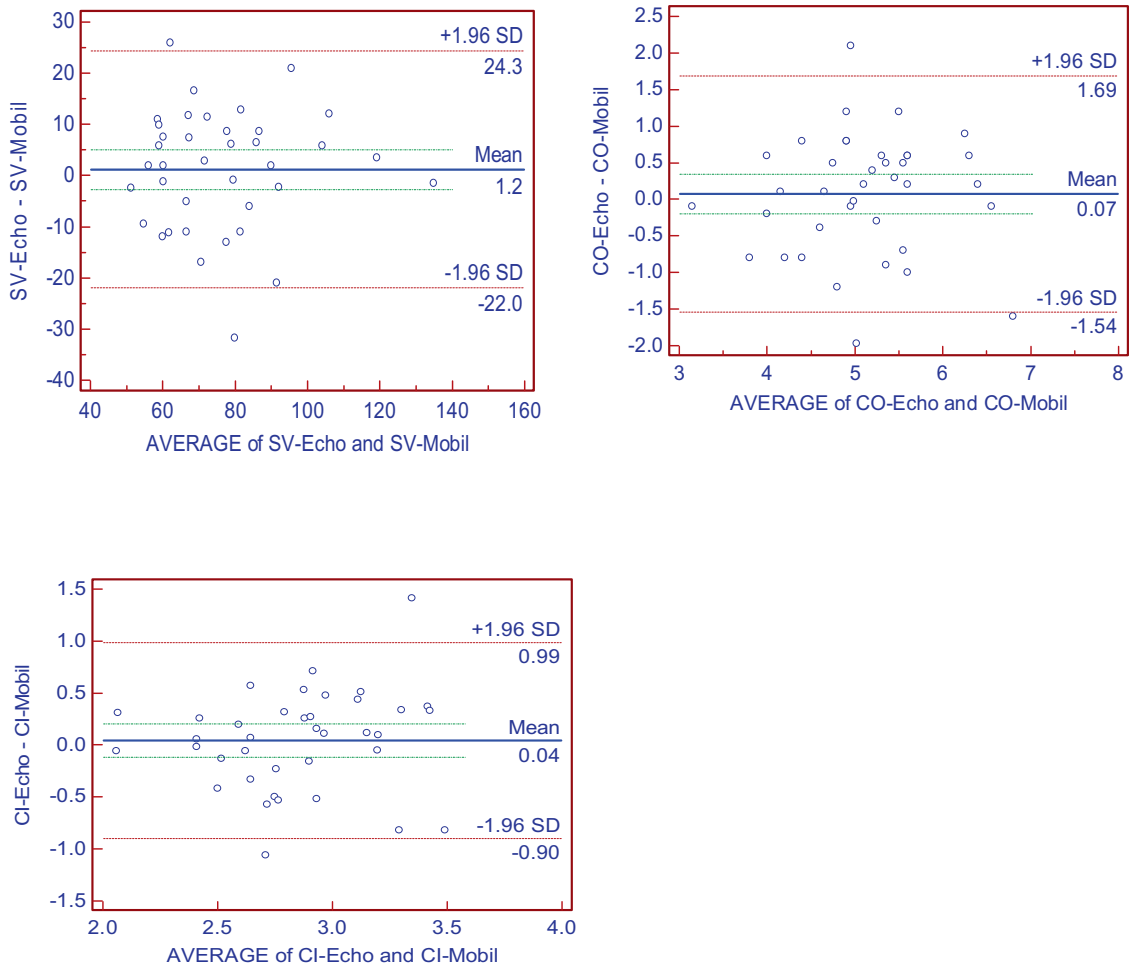

Figure 1 Bland-Altman plot showing the mean difference between the SV, CO, and CI by echocardiogram (Echo) and Mobil-O-Graph (Mobil). The black line is the mean of the differences; dotted lines show both lower and upper 95% confidence intervals (n = 38).

difficulties such as time management and processing of images, costs, and operator dependence.[19,20]

Our work has limitations. First, the study population comprises young people without proven heart disease, and therefore our results cannot be extrapolated to patients with impaired cardiac output, arrhythmias, valve abnormalities, or upper extremity arterial stenosis. Second, although the study conditions were standardized, the SV measurements were not simultaneous, which could have introduced differences in the values obtained.

Third, although the echocardiogram could be argued to be a reference standard in the calculation of SV, in clinical practice, the echocardiogram is the most commonly used noninvasive technique to evaluate the left ventricular ejection fraction since it is readily available in most institutions and can be performed at the bedside. Finally, even though the cohort of patients is small, it manages to demonstrate the usefulness of this method.

We conclude that the measurement of SV and CO by the oscillometric MOG offers results comparable to TTE in a population of healthy, young, normotensive adults.

If these data are confirmed in studies with a greater number of patients and with different alterations to left ventricular function, the measurement of SV by this noninvasive and inexpensive technique could be used in the follow-up and monitoring of patients with impaired left ventricular function.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Preoperative assessment of inferior vena cava collapsibility index by ultrasound is not a reliable predictor of post-spinal anesthesia hypotension

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IVCCI;
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Abstract
Background: Post-spinal anesthesia hypotension is of common occurrence, and it hampers tissue perfusion. Several preoperative factors determine patient susceptibility to hypotension. This study aimed to assess the effectiveness of the Inferior Vena Cava Collapsibility Index (IVCCI) for predicting intraoperative hypotension.
Methods: One hundred twenty-nine adult patients who were scheduled for elective surgical procedures after administration of spinal (intrathecal) anesthesia were included in the study. Ultrasound evaluation of the Inferior Vena Cava (IVC) was done in the preoperative area, and the patients were shifted to the Operating Room (OR) for spinal anesthesia. An independent observer recorded the change in blood pressure after spinal anesthesia inside the OR.
Results: Twenty-five patients developed hypotension (19.37%). Baseline systolic blood pressure and mean blood pressures were statistically higher in those patients who developed hypotension ($p = 0.001$). The logistic regression analysis for IVCCI and the incidence of hypotension showed r^2 of 0.025. Receiver Operating Characteristic (ROC) curve analysis demonstrated the Area Under the Curve (AUC) of 0.467 (95% Confidence Interval, 0.338 to 0.597; $p = 0.615$).
Conclusions: Preoperative evaluation of IVCCI is not a good predictor for the occurrence of hypotension after spinal anesthesia.

Introduction

Intraoperative hypotension has been the most frequent side effect after spinal anesthesia, with an incidence of 15.3% to 33%.[1] Hypotension can be severe (incidence 5.4%) and may cause systemic hypoperfusion and ischemic events. The

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magnitude of hypotension is determined by the preoperative volume status, which varies depending on ASA physical status, preoperative comorbidities, preoperative medications, and fasting. To prevent hypotension, neither crystalloid nor colloid (preloading or co-loading) was found to be superior.[1] Studies have shown the use of vasopressors like mephentermine, phenylephrine, or ephedrine to prevent or treat hypotension. Still, there is no accurate predictive tool to correctly evaluate the incidence of hypotension following spinal anesthesia in high-risk patients (old age/cardiac diseases/autonomic neuropathy) to avoid preemptive volume loading.[2] Hypotension occurs because of vasodilation due to preganglionic sympathetic fiber blockade resulting in peripheral vasodilatation. When spinal anesthesia reaches up to T4—T6 level, Systemic Vascular Resistance (SVR) decreases by 23—26%, Left Ventricular End-Diastolic Volume (LVEDV) by 20%, and Central Venous Pressure (CVP) by 2 —3 mmHg.[3]

In patients with pre-existing intravascular fluid deficit, the effects of hypotension are more pronounced, leading to many unwanted side effects like nausea, vomiting, aspiration, dizziness, syncope, cardiac arrhythmias. However, we cannot preload every patient prophylactically because there are side effects of volume overload like pulmonary edema, congestive cardiac failure, and renal dysfunction. That's why many new guidelines and recommendations are coming up which advocate only maintenance fluid administration in fasting patients preoperatively.[4-6] The goal should be to discover a new suitable predictive tool for hypotension to find at-risk patients in an easy, feasible, cost-effective, and non-invasive way.

Recently, ultrasound has come up as a new modality to predict the intravascular volume status of patients undergoing surgery. There are many methods for assessing intravascular volume preoperatively (CVP measurements, esophageal Doppler Ultrasound, pulmonary arterial catheterization, and transesophageal echocardiography). Still, most of them are invasive, time-consuming, or may require complex calculations. The ultrasound-guided measurement of the diameter of the Inferior Vena Cava (IVC) can indirectly assess the intravascular volume.

In this study, we hypothesized that preoperative Inferior Vena Cava Collapsibility Index (IVCCI) assessment is a good predictor of intraoperative hypotension within thirty minutes of giving spinal anesthesia in patients undergoing elective surgery.

Methods

The current prospective observational double-blinded study was conducted between the 8th of March 2018 to the 31st of December, 2019. Ethical approval was obtained from the Institute's Ethics Committee (AIIMS/IEC/2018/450) before enrolling the patients. This study adheres to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Potentially eligible participants aged between 18 and 75 years, with American Society of Anesthesiologists (ASA) physical status I or II were identified conveniently during the study period and scheduled for elective surgery under spinal anesthesia in the supine position. The written informed consent was taken from all the included patients. Exclusion Criteria were contraindications for spinal anesthesia (both absolute and relative), preoperative mean arterial blood pressure < 65 mmHg, preoperative heart rate < 45 beats.min^{-1}, preoperative dysrhythmia, psychiatric illness and pre-existing neurological deficits, patient with BMI > 30 kg.m^{-2}, and previous diaphragmatic surgery. After confirming fasting status in the preoperative room, the patient was instructed to relax in the supine position and breathe spontaneously for 5 minutes. An 18G peripheral intravenous (IV) line was secured, and maintenance crystalloid infusion (Ringer Lactate) was started at the rate of 2 mL.$^{-1}$.kg^{-1}.h^{-1}. Using a portable ultrasound machine (LOGIQ-e by GE health care) and a 3.5–5 MHz curvilinear probe, IVC was scanned in the subxiphoid region (paramedian long-axis view) just proximal to the drainage of the common hepatic vein to the IVC, according to the American Society of Echocardiography, by an independent observer who was trained in ultrasound (basic level I experience in echocardiography) and was supervised by an anesthesia faculty.[7] A 2D image was obtained where the IVC was joining the right atrium. IVC diameter variation was registered using M-mode imaging in both inspiration and expiration. It was done 2 to 3 cm distally from the junction of the IVC and the right atrium. The attending anesthetist registered the time from putting the probe on the patient and localizing the IVC. If the measurement time exceeded ≥ 15 minutes[8] and still the IVC could not be located due to any reason (like excess fat/bowel gas shadows), the case was excluded. Minimum ($IVCD_{Min}$) and Maximum Diameter ($IVCD_{Max}$) of IVC was assessed by the M mode of the ultrasound, and the IVC Collapsibility Index (IVCCI) was measured using the formula: ([Maximum IVCD - Minimum IVCD]/Maximum IVCD) × 100. Three such measurements were taken at one-minute interval, and the average was taken as IVCCI (Fig. 1). Each measurement was saved to be reviewed later by an expert radiologist.[8]

After arrival to the operation theatre, patients did not receive any fluid preloading. Standard noninvasive monitoring, including Noninvasive Blood Pressure (NIBP), Electrocardiography (ECG), and Pulse Oximetry (SpO2), was attached to the patients, and baseline parameters were recorded. All the patients received spinal anesthesia using a 25/27G Quincke needle (B. Braun Medical SA, Melsungen, Germany) with the needle orifice oriented cranially and the patient in the sitting position by the median approach at the level of the L3—L4 and L4—L5 intervertebral space with 25 mcg of fentanyl and 2.5 to 3 mL of 0.5% bupivacaine (hyperbaric) (considering the type of surgery and patient's constitution) to achieve spinal block height to the level of T9 to T10. The patient was made supine immediately after spinal drug administration and remained supine till the end of the study period (30 min). The pinprick test was used to determine the sensory level by an anesthetist who was not further involved in the study.[9] Then, serial heart rate and NIBP were recorded at 0, 5, 10, 15, 20, 25, and 30 minutes after spinal anesthesia by an independent observer who was not present at the time of IVCCI assessment. Clinically significant hypotension was defined as more than or an equal to 30% reduction in pre-induction baseline values. If the procedure was converted to GA or abandoned due to any reason before 30 min after giving spinal anesthesia, the case was excluded from the study.

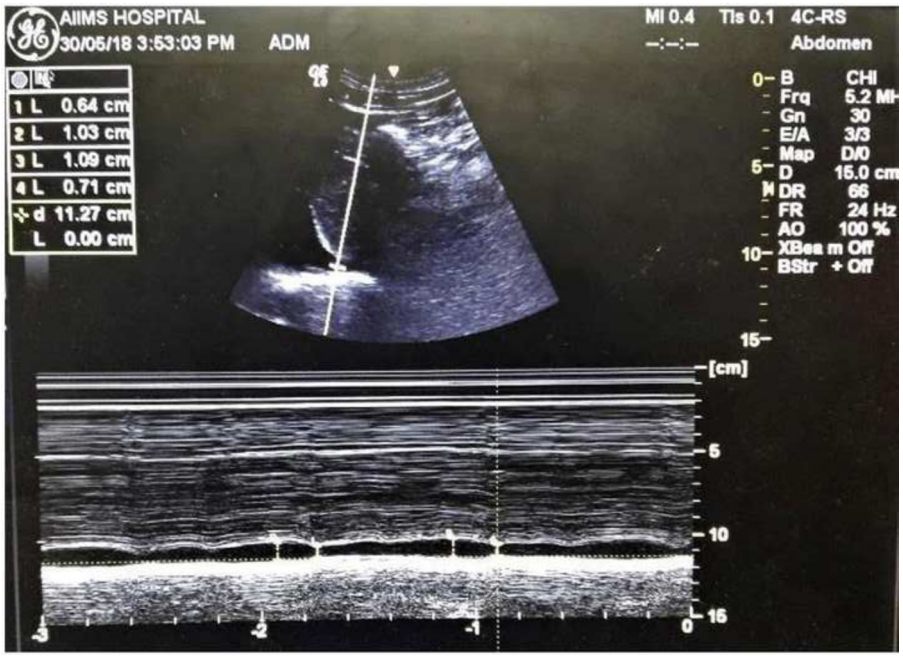

Figure 1 The Motion (M) mode of ultrasound scanning of the Inferior Vena Cava (IVC) showing minimum diameter 0.64 cm, maximum diameter of 1.09 cm, and thus Inferior Vena Cava Collapsibility Index (IVCCI) 41.3%.

Significant hypotension was managed with intravenous fluid administration and boluses of phenylephrine (100 μg) every 2 min to increase mean blood pressure > 70 mmHg or systolic blood pressure to 80% of the baseline.[10,11] Atropine 0.5 mg was used intravenously, when the heart rate was < 50 bpm. Nausea, vomiting, shivering, discomfort, allergic reaction, or any other complications were managed as per standard protocol. The patients were monitored after surgery in the recovery area in the immediate postoperative period, followed by observation in the ward. Data were collected on separate proforma sheets by the USG operator and the intraoperative attending anesthetist who performed the spinal anesthesia (unaware of the IVCCI of that patient) to overcome bias. The primary outcome was to assess whether IVCCI can predict hypotension and the secondary outcomes were to detect if there are other clinical predictors of hypotension.

The total number of patients who came to our institution during the study period were assessed as per our inclusion and exclusion criteria. Software SPSS version 21 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. A *p*-value of < 0.05 (two-tailed) was regarded as statistically significant. Excel spreadsheets (Microsoft, USA) were used to collect the data. The lowest Mean Blood Pressure (MBP) was documented after induction, and the percentage decrease in MBP was calculated as a fall from baseline in each patient. Kolmogorov-Smirnov one-sample test was used for checking normality. Data were expressed as mean ± Standard Deviation (SD) for continuous variables, and for categorical variables, percentages or absolute numbers were used.

Student's *t*-test or the $\chi 2$ test was applied to analyze patient characteristics, hemodynamic data, and IVC measurements, and the Pearson correlation coefficient (*r*) to examine the relationship between IVCCI and % fall of MBP. The Receiver Operator Characteristics (ROC) curve analysis was performed between IVCCI and % MBP reduction. Multivariate logistic regression was applied for the following confounders: age, ASA physical status, baseline Heart Rate (HR), and baseline Mean Blood Pressure (MBP).

Results

One hundred sixty-five patients were included in our study; in 18 patients, the vena cava was not seen on ultrasound, and we were unable to follow 18 patients. For the purpose of the study, 129 patients underwent statistical analysis. The flow diagram of the STROBE statement is shown in Figure 2. Among the 129 patients, 105 were male (81.4%), and 24 were female (18.6%). Ninety-eight patients were ASA I (76%), and 31 were ASA II (24%). The mean age was 43.15 years, with a standard deviation of 17.8. Thirty-seven patients (28.68%) had a history of hypertension, but it was controlled in every patient. The following surgical procedures were included: Orthopedic Surgery 38% (n = 49), General Surgery 26.4% (n = 34), Urology 19.4% (n = 25), Gynecology Surgery 8.5% (n = 11), and Plastic Surgery 7.8% (n = 10). Of the 129 patients studied, we observed significant hypotension in 25 (19.37%). Eleven patients received phenylephrine for severe hypotension, which lasted more than 2 min and/or severe hypotension persisting even after 500 mL of the fluid bolus. Three patients received atropine for bradycardia. After comparing the two groups (patients who developed hypotension vs. patients with no hypotension) (Table 1), no major differences were found in age, sex, IVCCI, and baseline HR after spinal anesthesia. However, patients with higher baseline SBP (p = 0.012), baseline DBP (p = 0.006), baseline MBP (p = 0.001) developed hypotension more often. ASA II patients developed hypotension more often than ASA I patients (p = 0.009). The scatter plot

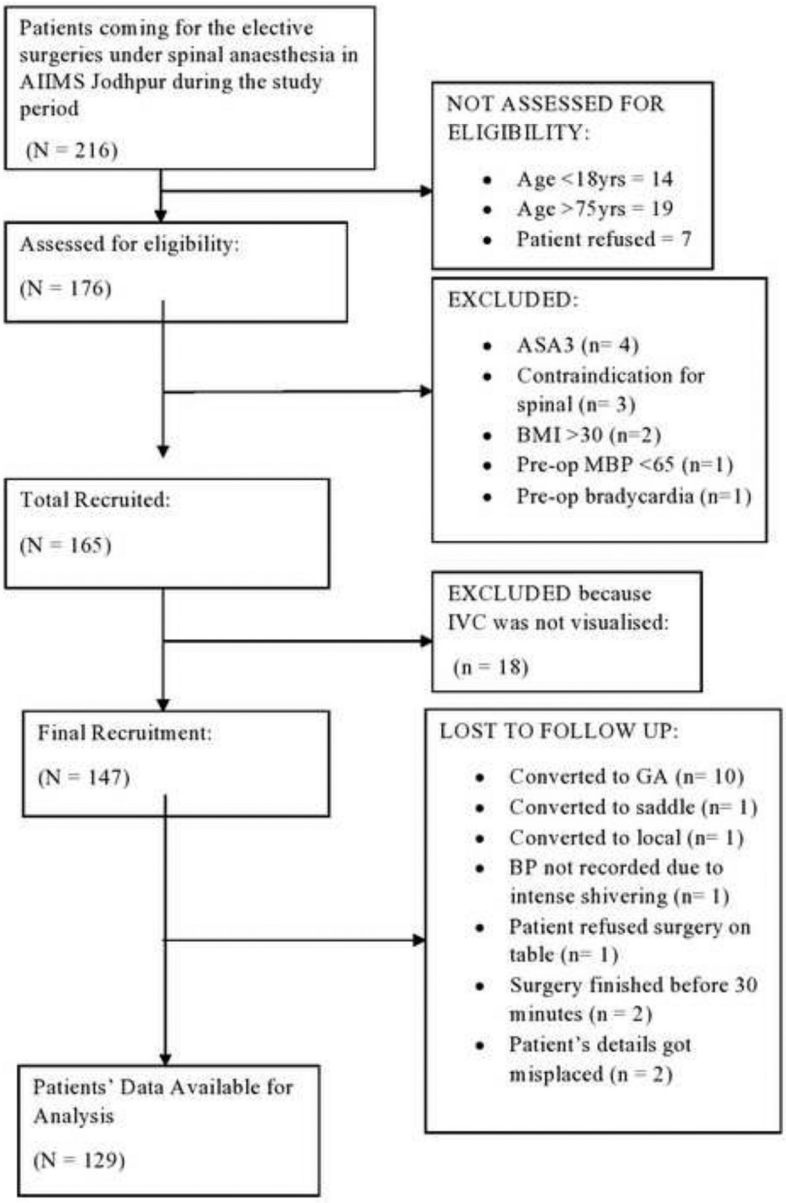

Figure 2 The flow diagram of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

(Fig. 3) suggests a linear relationship between the % decrease in MBP and IVCCI (r^2 = 0.025), which is not significant. That denotes that a progressive increase in IVCCI does not necessarily cause a more progressive fall in BP. The ROC curve analysis (Fig. 4) for predicting post-spinal hypotension did not demonstrate good diagnostic accuracy as the area under the curve was 0.467 (95% Confidence Interval, 0.338 to 0.597; p = 0.615). Multivariate logistic regression analysis demonstrated that neither IVCCI nor baseline MBP has good hypotension predicting capabilities (Table 2).

Discussion

Intraoperative hypotension is a frequent complication after intrathecal local anesthetic administration. In this study, a fall in mean BP ≥ 30% from the baseline was taken as the cut-off for significant hypotension because this definition is included in most of these studies[3,11,12] and because mean BP is a better indicator for tissue perfusion than SBP or DBP. As only one cut-off of hypotension was taken, the incidence of clinically significant hypotension found in our study (19.37%) was much lower than what was found in other studies.[3,11] The study period was from intrathecal drug administration to 30-min after spinal anaesthesia,[11] during which no significant hemodynamic changes were expected due to the external factors. Female patients developed hypotension more often (33.3%) than males (16.19%) (p-value = 0.05). Many studies have tried to demonstrate the IVCCI as a fluid-responsiveness-predicting tool for guiding fluid therapy in resuscitation and intensive care settings.[13-17] In anesthesia, volume status optimization is the primary concern. Fluid

Table 1 Patient characteristics, hemodynamic data, and preoperative Inferior Vena Cava (IVC) ultrasound measurements of the study participants.

Variable	Developed hypotension (n = 25)	No hypotension (n = 104)	*t*-value	*p*-value
Age (years)	48.0 ± 18.2	41.4 ± 18.0	−1.636	0.104
Sex (male/female)	17/08	88/16	NA	0.055[b]
ASA (I/II)	14/11	84/20	NA	0.009[a,b]
IVCCI (%)	37.6 ± 23.9	39.7 ± 22.9	0.427	0.670
Baseline HR (beats.min^{-1})	79.2 ± 17.2	83.2 ± 16.3	1.087	0.279
Baseline SBP (mmHg)	142.3 ± 15.1	133.2 ± 16.2	−2.542	0.012[a]
Baseline DBP (mmHg)	86.9 ± 11.2	80.5 ± 10.2	−2.777	0.006[a]
Baseline MBP (mmHg)	111.1 ± 11.8	101.6 ± 13.2	−3.257	0.001[a]

Data are presented as absolute (n) and mean ± SD. SD, standard deviation; ASA, American Society of Anesthesiologists physical status; IVCCI, Inferior Vena Cava Collapsibility Index; HR, Heart Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MBP, Mean Blood Pressure.

[a] Significant difference between groups ($p < 0.05$).

[b] Chi-Square test.

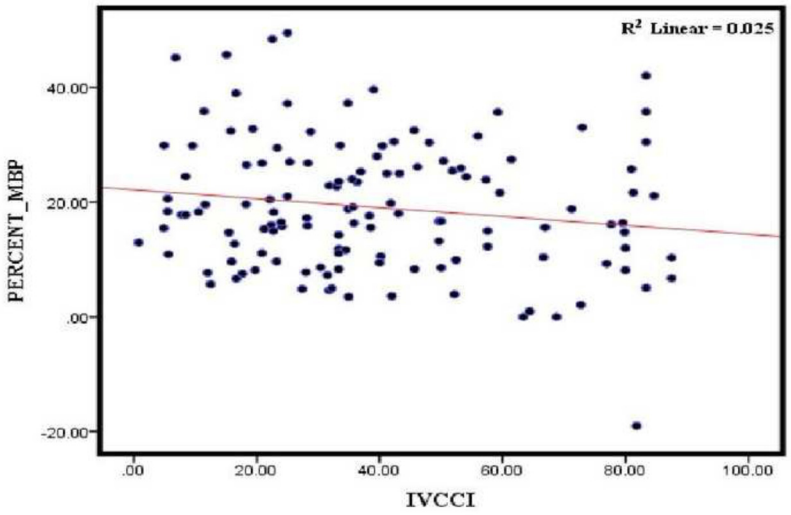

Figure 3 Scatter plot showing relationships of preoperative Inferior Vena Cava Collapsibility Index (IVCCI) with percentage decrease in Mean Blood Pressure (MBP) from baseline after induction of spinal anesthesia. The trend line is presented as the percent line.

responsiveness is a 10% to 15% increment in the cardiac output after a fluid bolus.[10] But very few anesthesiologists use cardiac output monitoring regularly.[18,19] So, most anesthesiologists use basic monitoring like blood pressure and HR as their main hemodynamic monitoring tool, and that's why we can include bedside IVC ultrasound to identify volume-depleted patients who need fluid optimization.

As a part of POCUS (point of care ultrasound), IVC ultrasound examination before spinal anesthesia to screen high-risk patients, the elderly, and suspected hypovolemic patients, is desirable. A significantly large IVCCI denotes truncated volume status, increasing the predicting value when the IVC diameter is smaller.[20] IVCCI was influenced by the sampling location[21] and that's why the measurement point was limited to 3 cm inferior to the right atrium.

The IVC scan failure rate was 10.9%, which was better than the study done by Dust et al.[22] The time taken to locate IVC was very variable from 5 up to 660 seconds, but was within the normal limits of 10 minutes as described by another study.[9]

In this study, we have failed to demonstrate the usefulness of IVC ultrasonography to anticipate blood pressure fluctuations after spinal anesthesia in spontaneously breathing patients like the study conducted by Ceruti et al.[3] and Ayyanagouda et al.[23] The ROC curve analysis showed an area under the curve of 0.467 (95% CI 0.338 to 0.597; $p = 0.615$). When the scatter plot was drawn between the percentage decrease in MBP and the IVVCI, it failed to demonstrate any correlation ($R^2 = 0.025$). But baseline SBP, DBP, and MBP were found to be higher in those patients who developed hypotension ($p < 0.05$). Logistic regression found that IVCCI was not a good predictor of post-induction hypotension (Odds Ratio = 0.988 with 95% CI 0.967 to 1.010; $p = 0.302$). There was no association between post-spinal hypotension and baseline MBP (OR = 1.041 with 95% CI 0.948 to 1.143; *p*-value = 0.402). In this study, 2.5 to 3 mL of local anesthetic

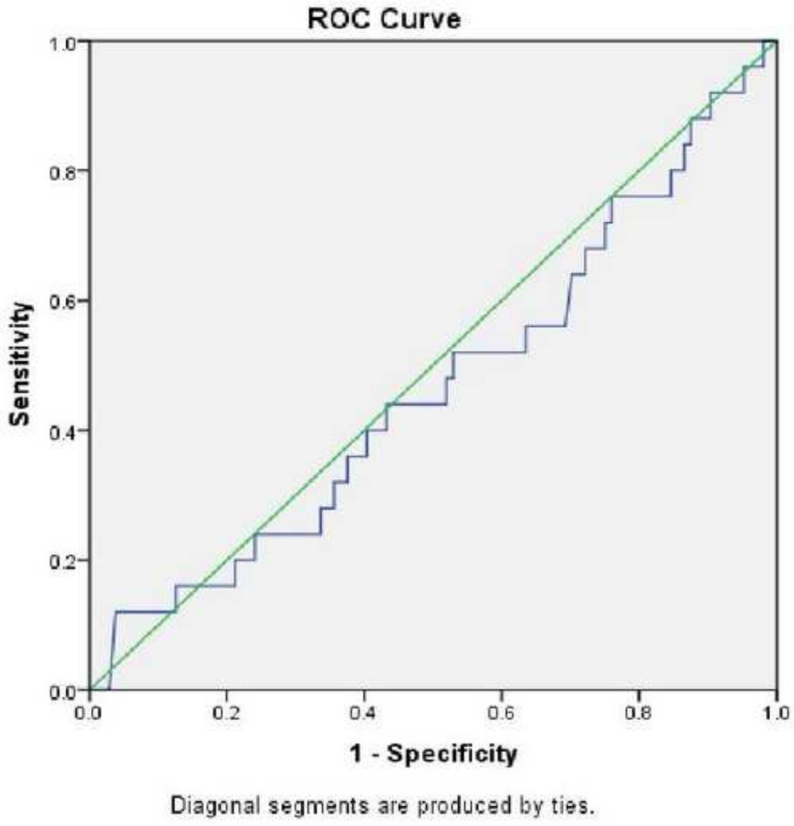

Figure 4 Receiver Operator Characteristic (ROC) curve for predicting post-spinal hypotension showing area under the curve of 0.467 (95% CI 0.338—0.597; $p = 0.615$).

was used for spinal block, depending on the type of surgery and patient constitution, to achieve spinal block height to the level of T9 to T10. There was no correlation between the amount of drug used and post-spinal hypotension though there was a 20% difference in local anesthetic mass.

Our findings can be explained by the fact that IVC is a high-capacity vessel and its diameter vary significantly from person to person. It also depends on age, body surface area, and BMI.[24,25] Intrathoracic and intra-abdominal pressures alter its diameter, and it is modified by various diseases like pneumonia or chronic obstructive diseases. The Inferior Vena Cava (IVC) diameter changes during the respiratory cycles because of the intrathoracic pressure changes.

Most of the previous data were from ICU settings, where IVC diameter changes were used to find out volume-responsive patients in circulatory shock. Our approach has this new aspect of finding its utility in the spinal anesthesiology setting. Some studies claim that it is controversial to use IVCCI after spinal anesthesia because it causes sympathetic denervation and reveals insufficient fluid reserve. One study could not detect the predictive role of the IVCCI in patients undergoing knee surgery,[26] while another found it as a useful tool to decrease the magnitude of hypotension by giving ultrasound-guided fluid therapy.[3] In a more recent study,[11] e caval-aorta index was found to be a stronger predictor than IVCCI. So, further investigations should focus on this aspect.

There were many limitations in the present study. USG observer experience was variable in some measurements. We included ASA I and II patients, because ASA III and IV patients might have more chances of hemodynamic instability in the post-spinal period. It could be either due to the depleted intravascular status or due to the poor

Table 2 Multivariate Logistic Regression of patients for hypotension after Induction (n = 129).

Predictors	Regression coefficient	Odds ratio	95% confidence interval of odds ratio	*p*-value
Constant	−4.468	0.011	NA	NA
Age	0.002	1.002	0.969 to 1.035	1.035
IVCCI	−0.012	0.988	0.967 to 1.010	0.302
Baseline HR	−0.026	0.975	0.943 to 1.008	0.131
Baseline MBP	0.040	1.041	0.948 to 1.143	0.402

IVCCI, Inferior Vena Cava Collapsibility Index; HR, Heart Rate; SBP, MBP, Mean Blood Pressure.

optimization of the actual disease process. It was a single-center study. Furthermore, a multicenter study is recommended to assess the ideal prognostic value of IVCCI. Respiration caused diaphragmatic movement, which resulted in two distinct sites of measurement of the IVC in the respiratory cycle. This might have led to an underestimation of IVCCI (because IVC is less collapsible when the measurement is taken near the diaphragm during inspiration).

To overcome limitations caused by the varying respiratory parameters in spontaneously breathing patients, we can simultaneously take IVC and Aorta measurements to get the Caval-Aorta index. Further research should be directed on this index to assess intravascular volume status to predict intraoperative hypotension.

Conclusion

This study found that IVCCI does not have the same hypotension predicting capability in spontaneously breathing patients undergoing spinal anesthesia that it has in mechanically ventilated patients.

Authors' contributions

Shayak Roy: Acquisition of data, analysis, and interpretation of data, revising it critically for important intellectual content. Nikhil Kothari: Substantial contribution to conception and design, analysis and interpretation of data, final approval of the version to be published. Shilpa Goyal: Acquisition of data and drafting the article. Ankur Sharma: Acquisition of data and drafting the article. Rakesh Kumar: Acquisition of data; manuscript review. Narender Kaloria: Acquisition of data; manuscript review. Pradeep Bhatia: Substantial contribution to conception and design, drafting the article and revising it critically for important intellectual content.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Comparison of onset of neuromuscular blockade with electromyographic and acceleromyographic monitoring: a prospective clinical trial

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KEYWORDS
Accelerometry;
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Neuromuscular junction;
Intraoperative neurophysiological monitoring

Abstract

Background: Reliable devices that quantitatively monitor the level of neuromuscular blockade after neuromuscular blocking agents' administration are crucial. Electromyography and acceleromyography are two monitoring modalities commonly used in clinical practice. The primary outcome of this study is to compare the onset of neuromuscular blockade, defined as a Train-Of-Four Count (TOFC) equal to 0, as measured by an electromyography-based device (TetraGraph) and an acceleromyography-based device (TOFscan). The secondary outcome was to compare intubating conditions when one of these two devices reached a TOFC equal to 0.

Methods: One hundred adult patients scheduled for elective surgery requiring neuromuscular blockade were enrolled. Prior to induction of anesthesia, TetraGraph electrodes were placed over the forearm of patients' dominant/non-dominant hand based on randomization and TOFscan electrodes placed on the contralateral forearm. Intraoperative neuromuscular blocking agent dose was standardized to 0.5 $mg.kg^{-1}$ of rocuronium. After baseline values were obtained, objective measurements were recorded every 20 seconds and intubation was performed using video laryngoscopy once either device displayed a TOFC = 0. The anesthesia provider was then surveyed about intubating conditions.

Results: Baseline TetraGraph train-of-four ratios were higher than those obtained with TOFscan (Median: 1.02 [0.88, 1.20] vs. 1.00 [0.64, 1.01], respectively, $p < 0.001$). The time to reach a TOFC = 0 was significantly longer when measured with TetraGraph compared to TOFscan (Median: 160 [40, 900] vs. 120 [60, 300] seconds, respectively, $p < 0.001$). There was no significant difference in intubating conditions when either device was used to determine the timing of endotracheal intubation.

Abbreviations: AMG, Acceleromyography; BMI, Body Mass iIndex; cMAP, Compound Muscle Action Potential; EMG , Electromyography; IRB, Institutional Review Board; MMG, Mechanomyography; NMB, Neuromuscular Blockade; NMBA, Neuromuscular Blocking agent; REDCap, Research Electronic Data Capture; RSI, Rapid Sequence Induction; TOF, Train-Of-Four; TOFC, Train-Of-Four Count.

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Conclusions: The onset of neuromuscular blockade was longer when measured with TetraGraph than TOFscan, and a train-of-four count of zero in either device was a useful indicator for adequate intubating conditions.
Clinical trial number and registry: URL NCT05120999, https://clinicaltrials.gov/ct2/show/NCT05120999.

Introduction

During routine endotracheal intubation, anesthesia personnel must consider multiple elements such as ensuring adequate depth of anesthesia and appropriate neuromuscular blockade.[1] While this procedure can seem routine, complications have been described with alarming frequency.[2,3] Therefore, the administration of medications to optimize conditions in conjunction with monitors that confirm these medications have provided an adequate response is important to providing optimal intubating conditions.

Neuromuscular Blocking Agents (NMBAs) are a class of medications that have frequently been used to facilitate endotracheal intubation and improve surgical conditions.[4] NMBAs have the potential to decrease vocal cord trauma and their omission has been associated with a higher incidence of unsuccessful first-pass intubation, difficult laryngoscopy, and upper airway discomfort.[5]

Objective (quantitative) neuromuscular monitoring allows for accurate neuromuscular evaluation compared to the subjective techniques with a peripheral nerve stimulator.[6] Electromyography (EMG) and Acceleromyography (AMG) are the two of the more commonly used quantitative monitoring modalities used in clinical practice. While the utility of such monitors has been demonstrated with confirming adequate recovery and avoiding residual weakness, these devices can also be used to identify when optimal intubating conditions have been reached. Our primary aim is to compare the onset of NMB as defined by time from rocuronium administration until a Train-Of-Four Count (TOFC) = 0 was obtained using two different quantitative monitoring modalities. We hypothesized that the TOFC would reach zero faster with the electromyography-based TetraGraph device than the acceleromyography-based TOFscan device, given the fact that AMG is associated with higher baseline values, while both monitors would predict excellent intubating conditions.[7,8]

Methods

After institutional review board approval (#21-007425), and written informed consent was obtained, 100 adult patients were screened and enrolled according to applicable Standards for Reporting Diagnostic Accuracy Studies (STARD).[9] We included patients scheduled for elective surgery requiring NMBAs from October 29th, 2021, to December 31st, 2021. Patients with history of systemic neuromuscular diseases (e.g., myasthenia gravis), active unilateral disorders (e.g., carpal tunnel syndrome, stroke, Dupuytren contracture) and significant organ dysfunction (e.g., end-stage renal and liver diseases) were excluded. Additionally, patients undergoing surgery that involved prepping the arm into the sterile field and receiving Rapid Sequence Induction and Intubation (RSII) were also excluded.

In this open-label investigation, all study participants were assigned to both TetraGraph and TOFscan devices. The randomization was performed utilizing REDCap (Research Electronic Data Capture) and involved the use of dominant vs. non-dominant hand for the placement of the TetraGraph device in an effort to decrease the impact of hand-dominance on objective monitoring. Patients were screened the day before the surgery and written inform consent was collected on the day of surgery after additional discussion and explanation of risks and benefits.

In accordance with recommendations from the Good Clinical Research Practice Guidelines[10] and prior to induction of anesthesia, TetraGraph and TOFscan electrodes were placed on each arm over the ulnar nerve and the thenar eminence at the base of the thumb (adductor pollicis muscle). Prior to placement, the skin along the ulnar nerve at the wrists was cleansed with alcohol and the silver/silver chloride electrodes were allowed to cure for at least 30 seconds prior to neurostimulation. Induction of anesthesia consisted of 2−2.5 mg.kg^{-1} of propofol, 1−1.5 mg.kg^{-1} lidocaine, and 0.5 mg.kg^{-1} of rocuronium based on actual body weight. Per manufacturer recommendations, the TOFscan was not calibrated, and the default current of 60 mA was utilized. The TetraGraph device was placed in the manual mode with a current of 60 mA selected. After baseline measurements were obtained, NMBA was administered followed by a 10 ml saline flush and sets of objective measurements were recorded every 20 seconds in both devices. Duration time from rocuronium administration to TOFC = 0 was manually recorded in both devices for each patient, although the TetraGraph device has internal storage. Intubation was performed using video laryngoscopy once either device displayed a TOFC = 0. The anesthesia provider was then surveyed about intubating conditions. After successful endotracheal intubation, neuromuscular blockade management was at the discretion of the attending anesthesiologist.

Study subjects

A total of 100 patients were included in this prospective, randomized study. Information was collected regarding patient characteristics (age, sex, race, weight, height, Body Mass Index [BMI], dominant hand) and monitoring specifics (location, TOF ratios at baseline, time to neuromuscular blockade onset, defined as the duration of time from rocuronium administration to either device displaying TOFC = 0). Intubating conditions were evaluated using a scale described

Table 1 Intubating conditions survey.

Variables	Intubating conditions		
	Acceptable		Unacceptable
	Excellent	Good	Poor
Ease of laryngoscopy (jaw relaxation)	Easy	Fair	Difficult
Vocal cord position	Abducted	Intermediate	Closed
Vocal cord movement	None	Moving	Closing
Airway reaction (coughing)	None	Diaphragm	Sustained (>10 s)
Movement of the limbs	None	Slight	Vigorous

by the International Consensus Conference held in Copenhagen in 1994 that incorporates jaw relaxation, vocal cord position, vocal cord movement, airway reaction, and movement of the limbs (Table 1).[11] Each of these five components was scored on an ordinal 1−3 scale and summated to obtain a total score. The minimum possible total score of 5 represents excellent intubating conditions while a maximum of 15 represents poor intubating conditions. One patient never reached a TOFC = 0 as measured with TetraGraph and this time duration was considered as 15 min (900 s) for purposes of statistical analysis.

Statistical analysis

Continuous variables were summarized with the sample median and range; normality was assessed using visual examination of histograms. Categorical variables were summarized with number and percentage of patients. Our primary aim was to compare the onset time of neuromuscular blockade (time duration from rocuronium administration to TOFC = 0) between TetraGraph and TOFscan. Comparisons of median TOF ratios at baseline and blockade onset between TetraGraph and TOFscan monitors were made using a paired Wilcoxon signed rank test. Comparisons of intubating conditions and total score according to device that reached TOFC = 0 first were made using a Wilcoxon rank sum test (ordinal categorical variables) or Fisher's exact test (binary categorical variables). The p-values < 0.05 were considered as statistically significant and all statistical tests were two-sided. Statistical analysis was performed using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). Based on paired t-test, 84 enrolled patients give 80% power to detect a difference in TOF ratios with a significance level of 0.05 and an effect size value of 0.75 (JMP Pro Software version 13.0.0 [July 7, 2021]; SAS Institute Inc., Cary, NC). This effect size value and standard deviation of 226.0 seconds were determined during previous investigations comparing another AMG device and TetraGraph. We enrolled 110 patients considering patient dropout or missing data.

Results

Patient characteristics

A total of 110 patients were screened for eligibility. Eight were excluded due to the decision to perform RSII on the day of surgery. One patient was excluded after a positive preoperative test for COVID-19 and surgery was postponed. One patient was excluded from analysis due to incomplete data (Fig. 1). Most of the patients were white (85%), 53 males and 47 females with a median age of 59 years old (22−86 y/o) were examined (Table 2).

Device randomization

Our patient population were equally randomized to receive TetraGraph either on dominant or non-dominant hand (50−50%). Consequently, TetraGraph was placed on the right hand 60% of the times and 40% on the left, while TOFscan was on the left hand 60% of the times and 40% on the right.

Neuromuscular monitoring

The time to onset of NMB (time duration from rocuronium administration to TOFC = 0) was significantly greater for TetraGraph compared to TOFscan (Median: 160 [40, 900] vs. 120 [60, 300] seconds, $p < 0.001$) (Fig. 2). Median baseline TOF ratios were significantly higher when obtained with TetraGraph vs. TOFscan (Median: 1.02 [0.88, 1.20] vs. 1.0 [0.64, 1.01], $p < 0.001$), (Table 2). Accordingly, TOFscan reached a TOFC = 0 first in 57 patients while TetraGraph reached a TOFC = 0 first in 25 patients. Both devices reached a TOFC = 0 zero at the same time in 18 patients.

Intubating conditions assessment

Ease of laryngoscopy (jaw relaxation) was described as "easy" in 81% of patients, and the vocal cords were abducted in 93% of patients. There was no vocal cord movement in 80% of patients, no coughing in 93% of patients, and no limb movement in 88% of patients. A total survey score of 5 was the most prevalent (60%) among all evaluations regardless of which monitor reached a TOFC of zero first (Table 2). There was no significant difference in intubating conditions ($p \geq 0.10$) when either device displayed a TOFC = 0 and triggered intubation (Table 3).

Discussion

In this investigation, we found a significantly longer onset of NMB in TetraGraph compared to TOFscan in patients undergoing elective surgery. The majority of endotracheal intubations (60%) were rated as optimal intubating conditions

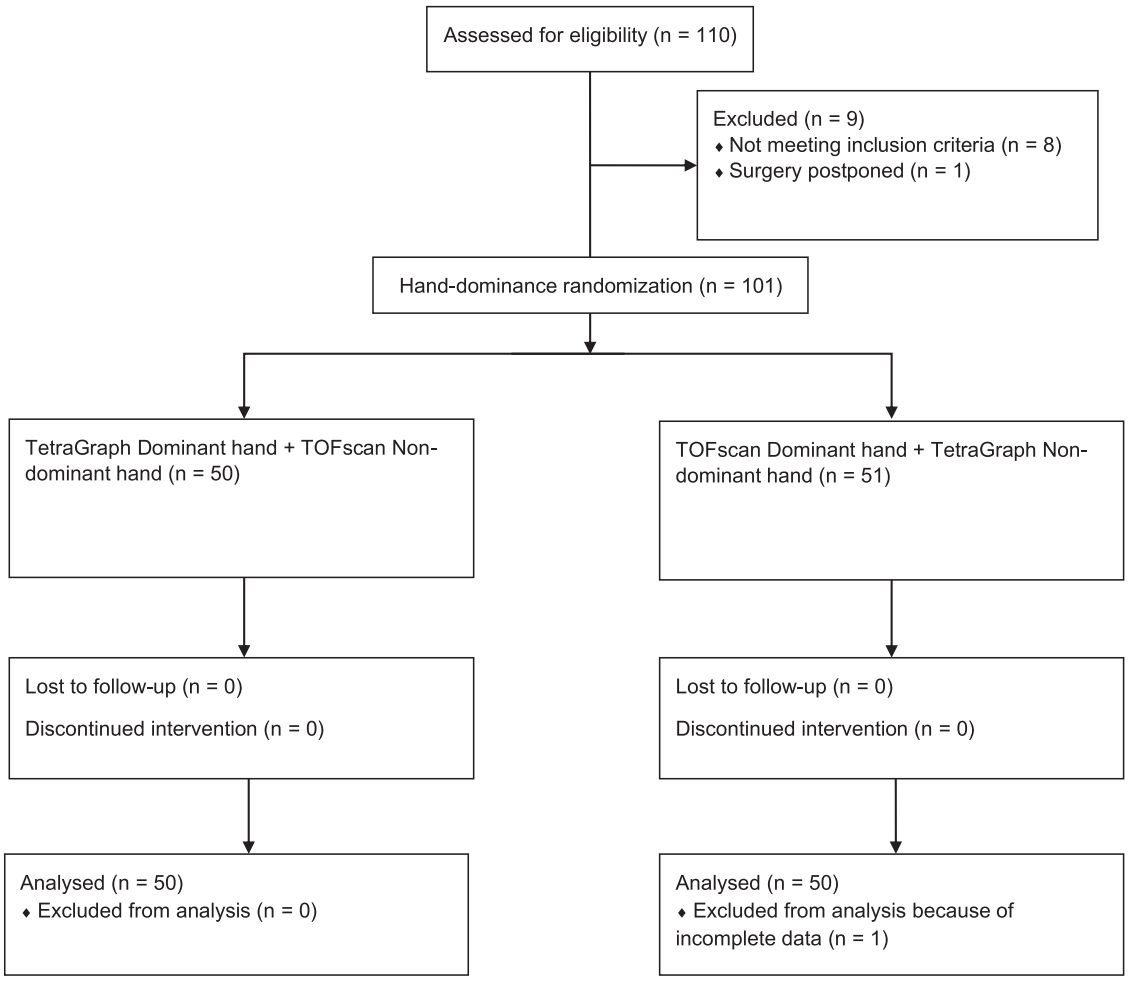

Figure 1 Flow diagram.

regardless of which monitor demonstrated a TOFC = 0 first. No statistical difference in the assessment of intubating conditions was found while comparing TetraGraph vs. TOFscan after reaching a TOFC of zero with either device.

Quantitative neuromuscular monitors have traditionally been used as devices to confirm adequate recovery from neuromuscular blockade. However, these devices can also prove useful in demonstrating the onset of neuromuscular blockade and alert clinicians that optimal intubating conditions have been reached. Relying on predicted time intervals prior to intubation fails to provide optimal conditions as pharmacodynamics varies between patients.[12-14] Our results also demonstrate such variability in the onset of neuromuscular blockade among a large cohort of patients (Fig. 2). Jung et al. demonstrated that either EMG or AMG was able to predict satisfactory intubating conditions in pediatrics, although EMG indicated the onset of neuromuscular blockade faster than AMG.[15] Our study also demonstrated that either device was useful in predicting optimal intubation conditions, although AMG indicated the onset of neuromuscular blockade faster than EMG. During this vulnerable time, objective neuromuscular monitors can provide critical information to clinicians seeking to optimize intubation conditions.

Obtaining baseline TOF ratios prior to the administration of NMBA is a critical step in monitoring as it provides important reference values and reaffirms that the quantitative monitor has been applied appropriately. Baseline values are particularly important with AMG as these values can often exceed 1.0 (reverse fade) and experts have advocated for normalizing recovery TOF ratios to ensure patients are not exposed to residual weakness.[16] In the current study, the median baseline TOF ratios were slightly greater with EMG than with AMG (1.02 vs. 1.0, respectively) and these findings are likely due to the fact that the TOFscan device has a built-in preload adapter that allows the thumb to return to its baseline position and counteract the reverse fade phenomenon.[17] Per the manufacturer, TOFscan does not require calibration and defaults to 60 mA while TetraGraph has an auto-calibration function that finds supramaximal current.

The response to NMBAs is complex and relies upon several factors such as perfusion, muscle fiber composition, density of junctional nicotinic acetylcholine receptors, and motor endplate area.[18,19] Accordingly, variability in measurements even with the same monitor is expected among patients. This variability accounts not only for the mentioned physiologic factors but also due to electrode placement, the type of sensing electrode used per device, and the amount of stimulating current applied. In consequence, objective monitoring to determine optimal intubation conditions would

Table 2 Patient characteristics and neuromuscular blockade information.

Variable	Median (minimum, maximum) or Number
Total Patient characteristics	100
Age (years)	59 (22, 86)
Sex (male)	53 (53.0)
Race (White)	85 (85.0)
Weight (kg)	82.0 (42.6, 127.0)
Height (cm)	172.0 (148.9, 198.1)
BMI	27.2 (17.8, 41.9)
Dominant hand	
Left	22
Right	78
Neuromuscular blockade information	
Randomization	
TetraGraph on dominant hand	50
TetraGraph on non-dominant hand	50
TetraGraph location	
Left hand	40
Right hand	60
TOFScan location	
Left hand	60 (60.0)
Right hand	40 (40.0)
TetraGraph TOF ratio at baseline	1.02 (88, 120)
TOFScan TOF ratio at baseline	1.00 (64, 101)
TetraGraph blockade onset (seconds)	160 (40, 900)
TOFScan blockade onset (seconds)	120 (60, 300)
Device that reached TOFC of zero first	
Same time	18 (18.0)
TetraGraph	25 (25.0)
TOFScan	57 (57.0)

BMI, Body Mass Index; TOF, Train-Of-Four; TOFC, Train-Of-Four Count.
TetraGraph TOF ratio at baseline was slightly higher than TOFScan TOF ratio at baseline (Median: 102 vs. 100, $p < 0.001$). The primary outcome of blockade onset was significantly longer for TetraGraph compared to TOFScan (Median: 160 vs. 120 s, $p < 0.001$).

ideally measure responses at oropharyngeal muscles and the diaphragm. Unfortunately, monitoring at these muscle sites is not currently feasible and clinicians must make inferences from more accessible muscle groups such as the adductor pollicis muscle.[20] Iwasaki et al.[21] demonstrated that there was no significant difference in measuring the onset of blockade when using the TOF-Watch SX at the adductor pollicis muscle versus the TetraGraph at the abductor digiti minimi muscle. While we found TOFscan reached TOFC = 0 faster than TetraGraph, our efforts represent two monitoring modalities on the same muscle group (the adductor pollicis muscle). Previous efforts have demonstrated the abductor digiti minimi muscle to be more resistant to neuromuscular blockade than the adductor pollicis muscle.[20] An intubating dose of 0.5 $mg.kg^{-1}$, less than twice the ED95, was selected in an effort to potentially allow for slower onset and teasing out differences in the monitors. Furthermore, the effect of rocuronium in our study on a single patient is fixed, however, the observed discrepancies result from inherent differences in the monitoring devices that utilize to distinct modalities.

The current effort is not without limitations. While we randomized device placement for patients' dominant/non-dominant hand, clinical considerations precluded us from controlling for all variables. The location of the intravenous (IV) catheter was not considered during randomization, as the precise location was unavailable until just prior to induction of anesthesia; however, IV catheter location has been shown to have minimal effect on the onset of NMB.[22] Our evaluation of intubating conditions has a subjective component that depends on the intubating clinician evaluating the ease of laryngoscopy. However, the use of video laryngoscopy allows for the entire anesthesia team to assess vocal cord position. Additionally, this survey has been previously utilized[23-25] and incorporates objective metrics that strengthen its utility. Our secondary outcomes, such as the difference in intubating conditions, are exploratory in nature and are subject to the presence of type 2 error. Finally, there is potential for variability from the time the decision to intubate is made based on one of the monitors to the actual performance of video laryngoscopy as different clinicians perform this task at different speeds. To minimize this unavoidable confounder, we overpowered this study to investigate the reliability of each device while comparing the onset of NMB and their applicability when seeking optimal intubating conditions in the surgical setting.

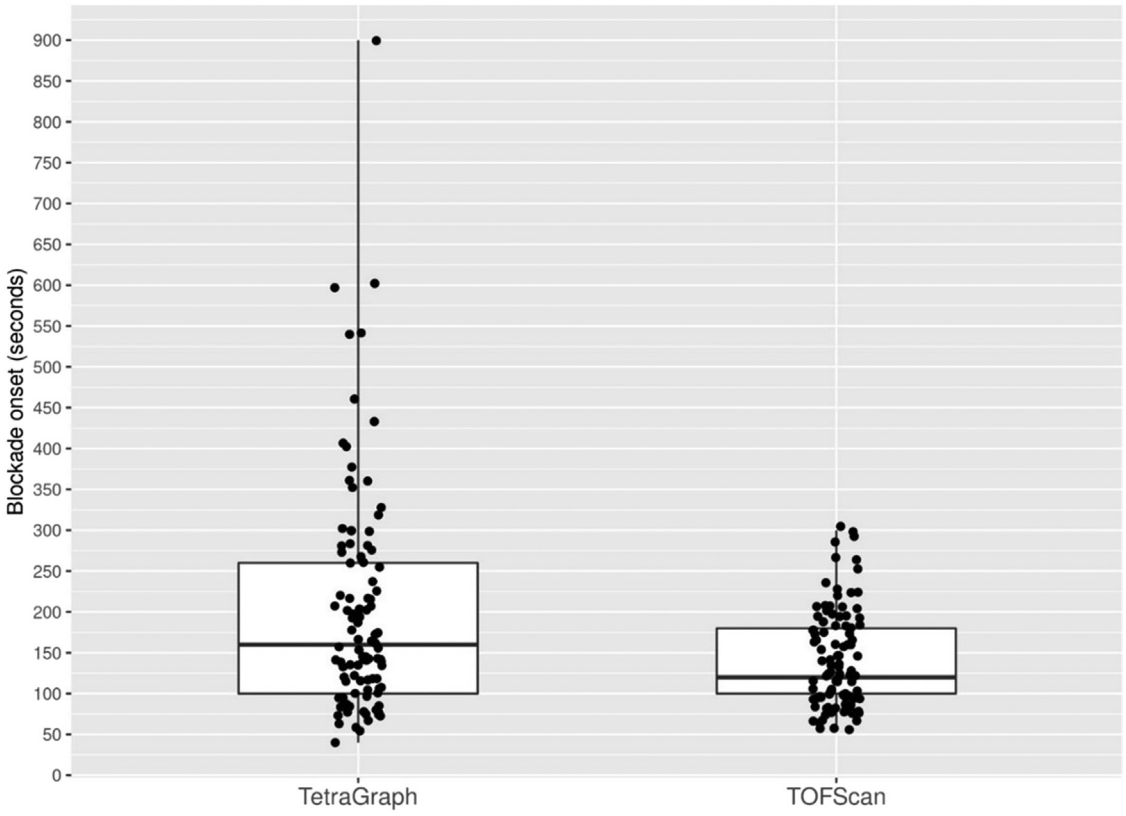

Figure 2 Boxplot of onset of blockade for TetraGraph and TOFScan. This figure presents all measurements from both devices reaching a TOFC = 0. A wider distribution and variability were observed in the onset of NMB values for TG compared to TS. TG median onset of NMB: 160 s, TS median onset of NMB: 120 s. One patient never reached a TOFC = 0 using TG, and this time duration was considered as 15 min (900 s). NMB, Neuromuscular Blockade; TG, TetraGraph; TS, TOFscan; TOFC, Train-Of-Four Count.

Table 3 Comparisons of intubating conditions according to device that reached TOFC of zero first.

	Device that reached TOFC of zero first			
	TetraGraph (n = 25)	TOFScan (n = 57)	Total[a] (n = 100)	*p*-value
Jaw relaxation				1.00
Easy	20 (80.0%)	44 (77.2%)	81 (81.0%)	
Fair	5 (20.0%)	13 (22.8%)	19 (19.0%)	
Vocal cord position				0.90
Abducted	23 (92.0%)	53 (93.0%)	93 (93.0%)	
Intermediate	2 (8.0%)	3 (5.3%)	6 (6.0%)	
Closed	0 (0.0%)	1 (1.8%)	1 (1.0%)	
Vocal cord movement				0.10
None	23 (92.0%)	43 (75.4%)	80 (80.0%)	
Moving	1 (4.0%)	13 (22.8%)	18 (18.0%)	
Closing	1 (4.0%)	1 (1.8%)	2 (2.0%)	
Airway reaction				0.19
None	21 (84.0%)	54 (94.7%)	93 (93.0%)	
Diaphragm	4 (16.0%)	3 (5.3%)	7 (7.0%)	
Movement of the limbs				1.00
None	21 (84.0%)	49 (86.0%)	88 (88.0%)	
Slight	4 (16.0%)	8 (14.0%)	12 (12.0%)	
Total score				0.75
5	16 (64.0%)	31 (54.4%)	60 (60.0%)	

Table 3 (*Continued*)

	Device that reached TOFC of zero first			
	TetraGraph (n = 25)	TOFScan (n = 57)	Total[a] (n = 100)	*p*-value
6	2 (8.0%)	17 (29.8%)	23 (23.0%)	
7	5 (20.0%)	4 (7.0%)	10 (10.0%)	
8	2 (8.0%)	3 (5.3%)	5 (5.0%)	
9	0 (0.0%)	0 (0.0%)	0 (0.0%)	
10	0 (0.0%)	2 (3.5%)	2 (2.0%)	

TOFC, Train-Of-Four Count.

p-values result from a Wilcoxon rank sum test (ordinal categorical variables) or Fisher's exact test (binary categorical variables).

[a] Total number includes 18 patients in which both devices reached TOFC.

In conclusion the EMG-based TetraGraph showed a longer duration to reach TOFC of 0 at the adductor pollicis than the AMG-based TOFscan device after rocuronium administration. No differences were found during evaluation of intubating conditions with either device. Although the onset of NMB was longer as measured by TetraGraph, both devices can predict adequate intubating conditions when the TOFC = 0 at the adductor pollicis muscle. Due to the variability in response to NMBAs, the use of either the TOFscan or the TetraGraph device during induction of anesthesia may be useful to determine when optimal intubating conditions have been reached.

Declaration of Competing Interst

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Cardiac arrest patients admitted to intensive care unit after cardiopulmonary resuscitation: a retrospective cohort study to find predictors for mortality

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Abstract
Background: In-hospital cardiac arrest is a common situation in hospital settings. Therefore, healthcare providers should understand the reasons that could affect the results of cardiopulmonary resuscitation. We aimed to determine the independent predictors for poor outcomes after the return of spontaneous circulation in in-hospital cardiac arrest patients, and also look for a relationship between patient's background parameters and the status at intensive care unit.
Methods: We did a retrospective cohort study using cardiac arrest patients admitted to the intensive care unit after successful cardiopulmonary resuscitation between 2011–2015. Patients' data were gathered from hospital database. Estimated probabilities of survival were computed using the Kaplan-Meier method. Cox proportional hazard models were used to determine associated risk factors for mortality.
Results: In total, 197 cardiac arrest patients were admitted to anesthesia intensive care unit after successful cardiopulmonary resuscitation in a 4-years period. Of 197 patients, 170 (86.3%) died in intensive care unit. Median of survival days was 4 days. Comorbidity ($p = 0.01$), higher duration of cardiopulmonary resuscitation ($p = 0.02$), lower Glasgow Coma Score ($p = 0.00$), abnormal lactate level ($p = 0.00$), and abnormal mean blood pressure ($p = 0.01$) were the main predictors for increased mortality in cardiac arrest patients after intensive care unit admission.
Conclusion: The consequent clinical status of the patients is affected by the physiological state after return of spontaneous circulation. Comorbidity, higher duration of cardiopulmonary resuscitation, lower arrival Glasgow Coma Score, abnormal lactate level, and abnormal mean blood pressure were the main predictors for increased mortality in patients admitted to the intensive care unit after successful cardiopulmonary resuscitation.

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Introduction

In-hospital cardiac arrest (IHCA) is a common situation in hospital settings. After a sudden cardiac arrest (CA), mortality rate is considerably high.[1,2] About 200,000 patients per year were hospitalized for treatment of CA in the USA; and the survival to hospital discharge rate was reported as 7–26%.[3,4] Although there have been improvements in healthcare, patient situation after CA does not seem to improve considerably. There are various factors associated with poor patient outcome after CA. Therefore, healthcare providers should understand the reasons that could affect the results of cardiopulmonary resuscitation (CPR).

We aimed to determine the independent predictors for poor outcomes after return of spontaneous circulation (ROSC) in IHCA patients, and to look for a relationship between patient's background parameters and the status at intensive care unit (ICU).

Methods

The University of Izmir Katip Celebi Institutional Review Board approved all aspects of this study (20.12.2017 Protocol number: 316). Since this is a retrospective cohort study, Institutional Review Board did not require the written informed consent.

Izmir Ataturk Training and Research Hospital (IATRH) is a research and training hospital in Izmir Turkey with over 50,000 hospital admissions per year and a 1400-bed tertiary care referral center affiliated with Izmir Katip Celebi University. The department of anesthesiology has an ICU with a total number of 31 beds. Our ICU is a level 3 ICU and not only provides perioperative care but also primary ICU care for all kinds of adult patients.

We did this retrospective cohort study using CA patients received to the ICU of IATRH after successful CPR from 2011 until 2015. Patient data were gathered from hospital database and ICU patient records. Our inclusion criteria were successful resuscitation from CA after ROSC. We did not include patients of whom we do not know the time of arrest, as well as arterial blood gas (ABG) and physiologic values were unavailable after ROSC. We also excluded the patients for whom extracorporeal membrane oxygenation (ECMO) was used. In addition, patients diagnosed with brain death were not included in this study. Flow diagram of the study is presented in Fig. 1. We used survival to hospital discharge as the primary outcome measure. Because this is a retrospective cohort study from 2011 until 2015, sample size was not calculated.

Demographic characteristics of the patients, admission sources, arrival Glasgow Coma Score (GCS), comorbidity, duration of CPR, ABG, mean blood pressure (MBP), pulse rate (PR), serum glucose levels, patient temperatures, survival periods (days) were analyzed.

Analyzed parameters were defined as: demographic characteristics (age, sex); admission source (operating room or other (emergency department, ward)); comorbidity (cardiac, respiratory, neurologic, renal, hepatic, malignancy, diabetic, intoxication) (no comorbidity, 1–2 comorbidities, or 3 or more comorbidities); duration of CPR (below 20 minutes or above); GCS (3 or above); ABG – pH (between 7.35–7.45 or other), PaO_2 (between 80–100 mmHg or other), $PaCO_2$ (between 35–45 mmHg or other), lactate levels (below 4 $mmol.L^{-1}$ or above); hemodynamic parameters – MBP (between 80–119 mmHg or other), PR (between 60–100/min or other); temperature (between 36.5–37 °C or other); serum glucose levels (between 60–110 $mmol.L^{-1}$ or other).

The first measurement for each physiologic value on ICU arrival were included in the analysis. We calculated frequencies and percentages for categorical variables as well as median and range for continuous variables. Estimated probabilities of survival were computed using the Kaplan Meier method. We used log rank test to evaluate the differences between survival distributions in univariate analysis. We made use of cox proportional hazard models to find out associated risk factors for mortality. For all analysis, we used the statistical software RStudio (rstudio.com, open-source software). We considered the results of statistical tests to be significant if two-sided p-value is < 0.05.

Results

One thousand five hundred sixty-two patients were accepted to the ICU during 4 years, starting 2011 through 2015. During this period, a total of 197 CA patients who met our inclusion criteria were analyzed. Baseline characteristics, blood gas analysis, vital signs, and physiologic values of patients are presented in Table 1. Out of these 197 patients, 27 (13.7%) patients survived and were discharged from the critical care unit whereas 170 (86.3%) died in ICU. Of these 170 patients who died, 115 (58.4%) patients, in fact, survived the first day of hospitalization. Eighty-one (41.1%) patients survived the first 7 days of hospitalization. Median of survival days was 4 days (95% CI: 2–6). More than half of all patients (51.3%) were male. Survival rate within the same day was 60.4% in males and 56.3% in females. The median age of the patients was 70 (Range: 21–93). The median ages of survivors and non-survivors were 68 and 71 years, respectively. The admission rate from the operating room was 8.1%. The rate of the patients had no comorbidity was 10.2% whereas 89.8% had multiple comorbidities. In this context, 71.5% had 1–2 and 18.3% had 3 and above multiple comorbidities. While 59 (29.9%) patients were resuscitated for 20 minutes or less, the others were resuscitated for more than 20 minutes. The median of survival days was 7 days (95% CI: 3–9) in patients resuscitated for 20 minutes or less, and 1 day (95% CI: 1–3) in patients resuscitated for more than 20 minutes. Majority of the patients (70.1%) had a GCS of 3 at the admission in ICU. Survival rate of the patients who had a GCS of 3 was 3.6% and 37.3% in other patients. Median lactate level was considerably higher in non-survivors. We calculated median survival time as 14 days (95% CI: 8–17) in patients with normal lactate levels and 1 day (95% CI: 1–2) with abnormal lactate levels. Survival rate within the same day was 91.5% at normal MBP levels and 52.6% at abnormal MBP levels.

We found comorbidity (p = 0.01), higher duration of CPR (p = 0.02), lower GCS (p = 0.00), abnormal lactate level (p = 0.00), and abnormal MBP (p = 0.01) were the main predictors for increased mortality in CA patients after ICU admission. Demographic factors such as age and sex, physiologic values such as temperature, admission source and

Table 1 Baseline characteristics, blood gas analysis, vital signs, and physiologic values of patients.

Variable	n (%)	Non-survivors (%)	Survivors (%)	Survivors after the first day (%)	Survivors after 7 days (%)	Median survival time – days (95% CI)	*p*-value univariate
Total	**197**	**170 (86.3)**	**27 (13.7)**	**115 (58.4)**	**81 (41.1)**	**4 (2–6)**	
Sex							**0.76**
Male	101 (51.3)	88 (87.1)	13 (12.9)	61 (60.4)	42 (41.6)	4 (2–8)	
Female	96 (48.7)	82 (85.4)	14 (14.6)	54 (56.3)	39 (40.6)	3 (1–7)	
Age (year) – Median (range)	**70 (21–93)**	**71 (22–93)**	**68 (21–83)**				**0.3**
< 65 year	62 (31.5)	51 (82.3)	11 (17.7)	39 (62.9)	25 (40.3)	4 (1–8)	
65 and above	135 (68.5)	119 (88.2)	16 (11.8)	76 (56.3)	56 (41.5)	3 (1–7)	
Admission source							**0.19**
Operating Room	16 (8.1)	11 (68.8)	5 (31.2)	11 (68.8)	9 (56.3)	10 (1–NA)	
Other	181 (91.9)	159 (87.9)	22 (12.1)	104 (57.5)	72 (39.8)	3 (1–5)	
Comorbidity							**0.01**[a]
No	20 (10.2)	14 (70)	6 (30)	12 (60)	11 (55.0)	8 (0–134)	
1–2	141 (71.5)	121 (85.8)	20 (14.2)	87 (61.7)	60 (42.6)	4 (2–7)	
3 and above	36 (18.3)	35 (97.2)	1 (2.8)	16 (44.4)	10 (27.8)	1 (1–4)	
Duration of CPR (minute)							**0.02**[a]
Other	59 (29.9)	56 (94.9)	3 (5.1)	24 (40.7)	16 (27.1)	1 (1–3)	
20 minutes and below	135 (68.5)	111 (82.2)	24 (17.8)	89 (65.9)	65 (48.1)	7 (3–9)	
Missing	3 (1.5)						
GCS							**0.00**[a]
3	138 (70.1)	133 (96.4)	5 (3.6)	73 (52.9)	43 (31.2)	2 (1–4)	
Other	59 (29.9)	37 (62.7)	22 (37.3)	42 (71.2)	38 (64.4)	9 (7–34)	
Arterial Ph – Median (Range)	**7.23 (6.8–7.6)**	**7.2 (6.8–7.6)**	**7.33 (7–7.6)**				**0.42**
7,35–7,45	37 (18.8)	28 (75.7)	9 (24.3)	31 (83.8)	20 (54.1)	8 (4–14)	
Other	141 (71.6)	123 (87.2)	18 (12.8)	79 (56)	56 (39.7)	3 (1–6)	
Missing	19 (9.6)						
Lactate (mmol.L-1) – Median (range)	**4.6 (0.4–27)**	**5.7 (0.4–27)**	**2 (0.5–10.3)**				**0.00**[a]
< 4 mmol.L^{-1}	73 (37.1)	55 (75.3)	18 (24.7)	64 (87.5)	49 (67.1)	14 (8–17)	
Other	85 (43.1)	78 (91.8)	7 (8.2)	36 (42.4)	23 (27.1)	1 (1–2)	
Missing	39 (19.8)						
PR – Median (range)	**100 (45–171)**	**100 (45–171)**	**94 (53–153)**				**0.07**
60–100/minute	97 (49.2)	79 (81.4)	18 (18.6)	65 (67.0)	47 (48.5)	7 (3–9)	
Other	86 (43.7)	77 (89.5)	9 (10.5)	49 (57)	33 (38.4)	3 (1–7)	
Missing	14 (7.1)						
MBP (mmHg) – Median (range)							**0.01**[a]

Table 1 (*Continued*)

Variable	n (%)	Non-survivors (%)	Survivors (%)	Survivors after the first day (%)	Survivors after 7 days (%)	Median survival time – days (95% CI)	*p*-value univariate
80–119 mmHg	47 (23.9)	38 (80.9)	9 (19.1)	43 (91.5)	32 (68.1)	12 (7–20)	
Other	135 (68.5)	117 (86.7)	18 (13.3)	71 (52.6)	48 (35.6)	2 (1–4)	
Missing	15 (7.6)						
Temperature (0C) – Median (range)	**34.9 (34–40)**	**35.5 (34–40)**	**36 (35–37.3)**				**0.28**
36.5–*37 °C*	15 (7.6)	13 (86.7)	2 (13.3	15 (100)	10 (66.7)	15 (6–17)	
Other	166 (84.3)	141 (84.9)	25 (15.1)	99 (59.6)	70 (42.2)	4 (2–7)	
Missing	16 (8.1)		0				
Glucose (mmol.L-1) – Median (range)	**8.2 (0.3–39.8)**	**8.1 (0.3–39.8)**	**8.3 (4.2–28.5)**				**0.37**
3.3–5.6 mmol.L^{-1}	54 (27.4)	48 (88.9)	6 (11.1)	31 (57.4)	23 (42.6)	4 (1–9)	
Other	142 (72.1)	121 (85.2)	21 (14.8)	84 (59.2)	58 (40.8)	4 (2–7)	
Missing	1 (0.5)						
PaO_2 (mmHg) – Median (range)	**92.5 (16–497)**	**92 (16–497)**	**99 (49–202)**				**0.76**
80–100 mmHg	26 (13.2)	22 (84.6)	4 (15.4)	19 (73.1)	14 (53.8)	8 (2–12)	
Other	150 (76.1)	127 (84.7)	23 (15.3)	90 (60.0)	62 (41.3)	4 (2–7)	
Missing	21 (10.7)						
PCO_2 *(mmHg) –Median (range)*	**37 (17–105)**	**37.5 (18–105)**	**36 (17–95)**				**0.72**
35–45 mmHg	50 (25.4)	43 (86)	7 (14)	35 (70)	20 (40.0)	5 (3–8)	
Other	127 (64.5)	107 (84.3)	20 (15.7)	74 (58.3)	55 (43.2)	3 (1–8)	
Missing	20 (10.2)						

[a] 95% confidence level.

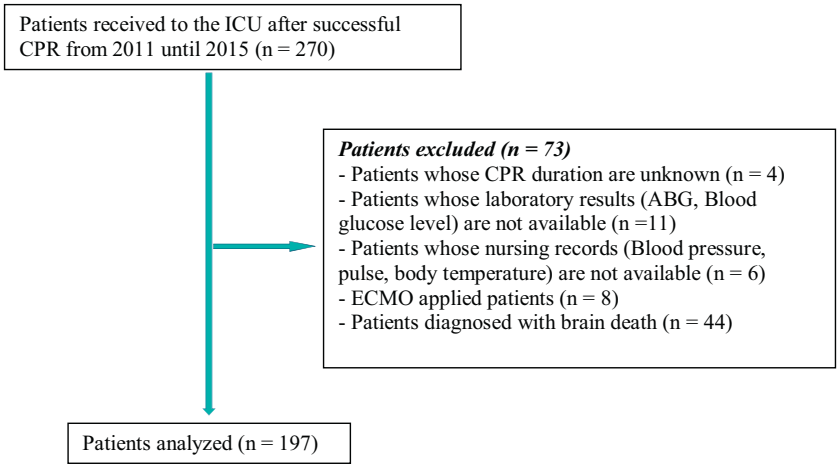


Figure 1 Flow diagram of the study.

laboratory results such as glucose, arterial pH, $PaCO_2$, PaO_2, abnormal PR did not influence mortality significantly.

Kaplan Meier estimate of survival after CA regarding these predictors for CA mortality are shown in Figs. 2-4. Survival was highest in patients without comorbidity. Mortality risk was beginning to decrease in patients who had a GCS of higher than 3 and lower duration of CPR. There was a notable difference in survival distributions at normal and abnormal levels of lactate and MBP.

We used proportional hazards model to evaluate simultaneous effect of risk factors on survival rates. All variables which were significant in univariate analysis were included in the Cox regression model by backward elimination of non-significant covariates ($p > 0.10$). The length of CPR that was significant in univariate analysis was removed from the model. Since the number of patients in the compared groups was very small, the reliability of the cox regression test decreased and could not be calculated. Therefore, we had to perform Cox regression model without duration of CPR. According to the results of the Cox regression analysis, mortality was 1.8 (95% CI: 0.8–3.7) times higher in patients with 1–2 multiple comorbidities and 3.9 (95% CI: 1.7–8.6) times higher in patients with 3 and more multiple comorbidities when compared to those without comorbidity. Lower GCS (HR: 2.7 95% CI: 1.7–4.4) were related with increased mortality. Moreover, the hazard ratios for the abnormal level of lactate and MBP were 2.6 (95% CI: 1.8–3.8) and 2.4 (95% CI, 1.6–3.7), respectively.

GCS at discharge from hospital were 15 in 21 survivors, 10 in 1 survivor, 9 in 1 survivor, 7 in 2 survivors and 6 in 1 survivor.

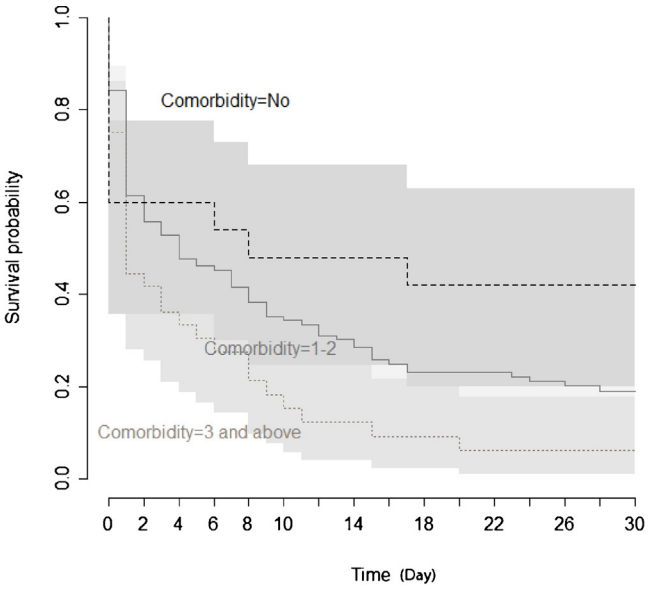
Discussion

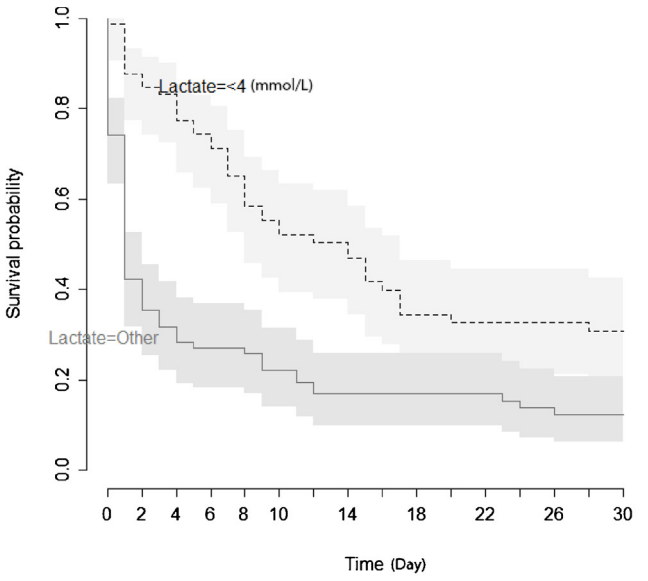
There are studies that found a relationship between survival after CA and age.[5,6] Some studies documented a considerably low survival rate for older patients.[7,8] When these studies are examined, it is seen that there are differences in their methodology and criteria for including patients. Some of them included only adults[5,7,8] whereas some others included children, too.[6] We realized that there was no single cut-off value to determine the children from older adults. In our study, age $\geq$ 65 was not found to be a negative prognostic factor for the patients who were able to restore blood circulation after CA. The reason behind this may be that the complications leading to CA in younger patients are more serious and harder to reverse compared to older patients.

In most of the previous studies about IHCA, gender does not seem to be associated with survival. Nevertheless, one study[9] found out that female gender could be a factor for survival after adjustments are done for cardiac rhythm age, reason, and site of arrest. Gender has not been found to be a prognostic factor in our study.

Some research examined the effect of lactate in the post-cardiac arrest population. One of those studies done retrospectively for post-arrest patients found that the outcome of the patient can be predicted by the initial lactate level in the post-arrest period. Mortality was 39% for post-arrest patients that had an initial lactate < 5 $mmol.L^{-1}$, on the other hand mortality was as high as 92% for patients who had an initial lactate > 10 $mmol.L^{-1}$.[10] In our study, high lactate levels (> 4 $mmol.L^{-1}$) after CA were found to be significantly associated with mortality. Prolonged CA and/or serious consequent hemodynamic failure could be the result of high lactate concentrations.[11–13] Therefore, lactate could be a factor that affects the poor outcomes of the patients. Hence, if there is hemodynamic failure such as CA in patient, it could be better to monitor lactate level rather than just blood pressure or cardiac output. Some research showed that admission blood lactate levels after CA and its fluctuation levels later than CA could be predictive of mortality.[11–14]

There are a few researches that examined the time length of resuscitation on patient outcome. In their retrospective study, Reynolds et al. showed that with each minute of CPR, the probability of survival to hospital discharge decreased.[15] After 15 minutes of CPR, the probability of survival decreased to 2% whereas it was 75% for patients who received 10–15 minutes of CPR.[15] In a similar study, Shih et al. found that patients who received 10 minutes or less of CPR, had a rate of ROSC as high as 90% whereas, ROSC rate for patients who were resuscitated for more than 30 minutes was 50%.[16] These studies indicate that bad patient outcome is related with the longer duration of resuscitation. In contrast, a study showed that when the time length of





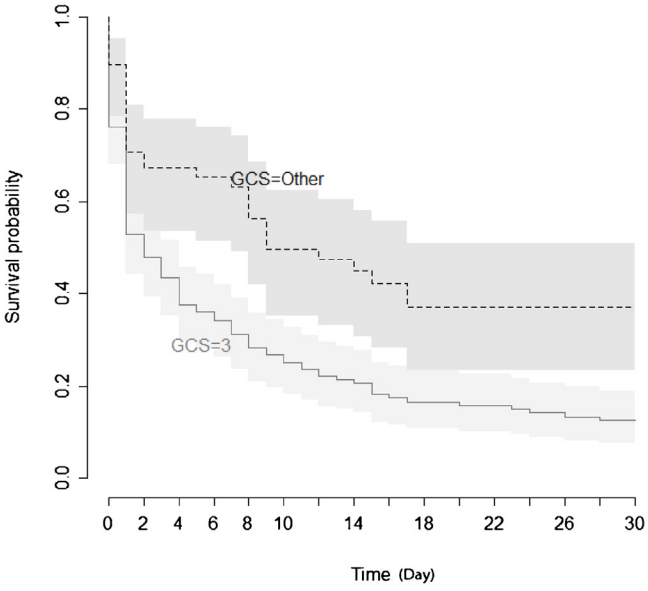


Figure 2 Kaplan Meier estimate of survival after resuscitation from cardiac arrest according to comorbidity and glasgow coma score.

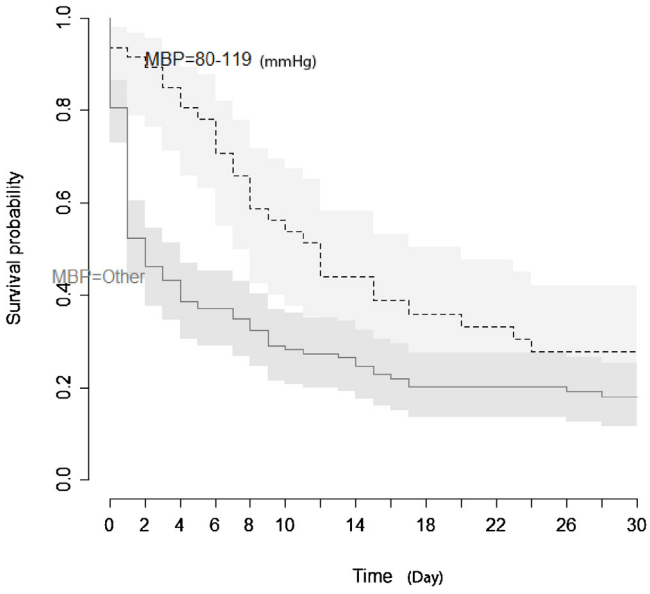


Figure 3 Kaplan Meier estimate of survival after resuscitation from cardiac arrest according to lactate level and mean blood pressure level.

resuscitation increased, so did the survival rate for patients who particularly had asystole or preliminary rhythm of pulseless electrical activity.[17] Lastly, Cha et al. found that if the duration of CPR was more than 30 minutes, the rate of survival was as low as 5.6%.[18] Obviously, there is no clear cut-off CPR duration in the literature. However, as Rohlin et al. mentioned that a duration longer than 20 minutes captures 95% of the 30-day survivors,[19] we chose 20 minutes as a cut-off time. In our study, a CPR duration over 20 minutes was associated with increased mortality among the patients who achieved ROSC and were admitted to ICU.

The presence of comorbid diseases is related with morbidity. It also affects the functional status and life quality of patients adversely. In their study Fabbri et al. found that pre-arrest comorbidities were associated with decreased chances of survival.[20] In another study Chakravarthy et al. showed that in CA patients the best survival rate (64%) was among those who had none or 1 comorbidity.[21] When patients had 2 comorbidities, the chance to survive was 9.6%, whereas no patient survived if they had 2 or more comorbidities.[21] And finally, Andrew et al. concluded that patients' current comorbidities could help to assess and predict the situations of CA patients.[22] In our study we found

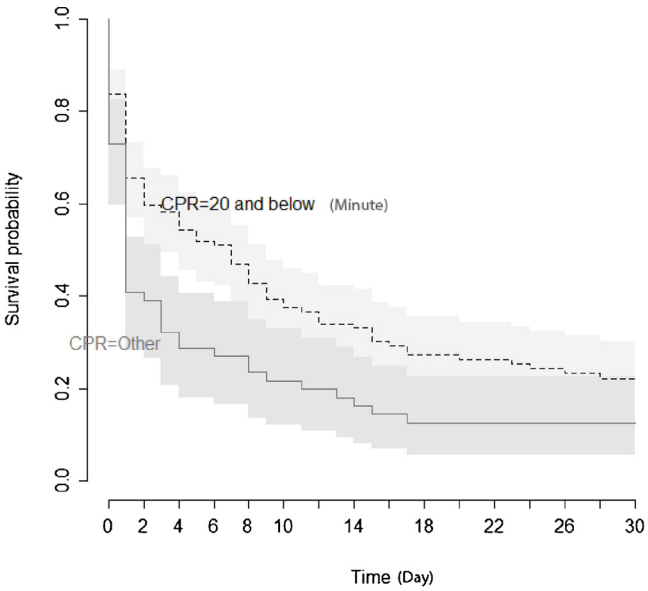


Figure 4 Kaplan Meier estimate of survival after resuscitation from cardiac arrest according to duration of CPR.

that the survival rate decreased in CA patients among those who had 3 or more comorbidities.

GCS is useful for evaluation of a critical care patient's status in the face of changing conditions. Recently Martinell et al. identified low ICU arrival GCS as a predictor of a worse patient situation at 6 months for those patients who initially survived out-of-hospital cardiac arrest.[23] Low arrival GCS (3) was also associated with a poor outcome in our study.

High morbidity and high mortality rates are common after CA. These high rates could be reduced by using mechanical ventilation, maintaining normal hemodynamic parameters, keeping normoxia as well as normocapnia. Recently Sutherasan et al. proposed a general bundle of treatment to enhance the prognosis of patients after CA.[24] But mostly achieving these normal parameters is difficult in CA patients. In our study, among these parameters abnormal mean arterial blood pressure was the predictor for increased mortality in post-cardiac arrest patients.

This study is limited by the fact that we were not able to provide data of the resuscitation process. Every case of CPR is different from one another, therefore the response in each case could change the outcome of the resuscitation. Additionally, the analysis was retrospective. Our main endpoint was survival to hospital discharge, and did not include data on functional outcome, nor follow-up post discharge.

Conclusion

The consequent clinical status of the patient is affected by the physiological state after ROSC. Initial examination and laboratory results following ROSC could be useful in providing predictive information for both physicians and patients' families. We found comorbidity, higher duration of CPR, lower arrival GCS, abnormal lactate level and abnormal MBP were the main predictors for increased mortality in patients admitted to the ICU after successful CPR. Demographic factors as age and gender, physiologic value like temperature, laboratory results like blood glucose, arterial pH, $PaCO_2$, PaO_2, and abnormal PR did not influence mortality significantly.

Conflict of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Association of low-dose naltrexone and transcranial direct current stimulation in fibromyalgia: a randomized, double-blinded, parallel clinical trial

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Abstract

Introduction: Fibromyalgia is a complex, generalized, and diffuse chronic musculoskeletal pain. Pharmacological approaches are widely used to relieve pain and increase quality of life. Low-Dose Naltrexone (LDN) was shown to increase the nociceptive threshold in patients with fibromyalgia. Transcranial Direct Current Stimulation (tDCS) is effective for pain management.

Objective: The purpose of this study was to evaluate the analgesic and neuromodulatory effects of a combination of LDN and tDCS in patients with fibromyalgia.

Methods: This was a randomized, double-blinded, parallel, placebo/*sham*-controlled trial (NCT04502251; RBR-7HK8N) in which 86 women with fibromyalgia were included, and written informed consent was obtained from them. The patients were allocated into four groups: LDN + tDCS (n = 21), LDN + tDCS *Sham* (n = 22), placebo + tDCS (n = 22), and placebo+tDCS *Sham* (n = 21). The LDN or placebo (p.o.) intervention lasted 26 days; in the last five sessions, tDCS was applied (sham or active, 20 min, 2 mA). The following categories were assessed: sociodemographic, Visual Analog Pain Scale (VAS), Pain Catastrophizing Scale (PCS), State-Trait Anxiety Inventory (STAI), Fibromyalgia Impact Questionnaire (FIQ), Beck Depression Inventory (BDI-II),

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Profile of Chronic Pain Scale (PCP:S), Pain Pressure Threshold (PPT), and Conditioned Pain Modulation (CPM). Blood samples were collected to analyze BDNF serum levels.
Results: At baseline, no significant difference was found regarding all measurements. VAS pain was significantly reduced in the LDN + tDCS ($p = 0.010$), LDN + tDCS *Sham* ($p = 0.001$), and placebo+tDCS *Sham* ($p = 0.009$) groups. In the PCP:S, the LDN+tDCS group showed reduced pain frequency and intensity ($p = 0.001$), effect of pain on activities ($p = 0.014$) and emotions ($p = 0.008$). Depressive symptoms reduced after all active interventions ($p > 0.001$).
Conclusion: Combined LDN+tDCS has possible benefits in reducing pain frequency and intensity; however, a placebo effect was observed in pain using VAS, and further studies should be performed to analyze the possible association.

Introduction

Fibromyalgia is a chronic musculoskeletal pain syndrome that manifests as fatigue, morning stiffness, sleep and humor disturbances, and cognitive and memory impairment associated with other clinical symptoms such as anxiety, depression, and pain catastrophizing thought.[1] Besides resulting in impairment in quality of life, patients also show emotional reactions such as anger, depression, anxiety, loneliness, and fear.[1] These negative emotions result in an increase in pain sensitivity, resulting in a catastrophizing thought as a non-adaptive response to pain, which is one of the factors that contribute to chronic pain syndrome.[2]

Low pain threshold, high levels of anxiety, exacerbated fear, and hypervigilance can be associated with cortical dysfunctions related to afferent pathway abnormalities and sensitized cortical processes, which result in impairment of sensory processing in the brain, causing pain chronicity.[3] During the sensitization process, pain perception is amplified in the Central Nervous System (CNS), which results in a continuing pain experience with no nociceptive peripheral stimuli,[4] including psychological suffering, sleep disturbances, allodynia, and hyperalgesia.[5]

This syndrome mainly affects women of reproductive age, with a global prevalence of 2.4% to 6.8%.[6] Diagnosis is clinical because there are no biomarkers or imaging exams that provide evidence of the syndrome.[7] In 2016, the American College of Rheumatology (ACR) established the criteria for fibromyalgia diagnosis: generalized pain in at least four regions, symptoms present for at least 3-months, Generalized Pain Index (GPI) equal to or higher than 7, and severity of symptoms equal or higher than 5.[8]

New drug therapies are needed to control pain, reduce adverse effects, and increase quality of life. In this way, naltrexone, at lower doses than usual, has recently emerged as a potential agent for chronic pain management and is a possible therapeutic option for the treatment of fibromyalgia.[9]

Naltrexone is a pure opioid antagonist that acts on opioid and non-opioid receptors. Naltrexone active metabolites are reversible competitive antagonists of μ-opioids and κ-opioid receptors, with a higher affinity for μ-opioids. However, kappa receptor activation induces anti-inflammatory effects, decreasing IL-6 levels and neutrophil migration.[10] Another potential mechanism for the use of Low-Dose Naltrexone (LDN) is the antagonism of non-opioid receptors, such as Toll-like Receptor-4 (TLR4)[11] found in macrophages. TLR4 blockade inhibits the release of proinflammatory cytokines, substance P, nitric oxide, excitatory amino acids, and Tumor Necrosis Factor (TNF) leading to the downregulation of chemokines and adhesion molecule receptor expression.[12] Randomized clinical trials using 4.5 mg naltrexone have been conducted in Crohn's disease, multiple sclerosis, fibromyalgia, and HIV infection, in which evidence shows efficacy and low toxicity.[10]

Noninvasive brain stimulation techniques have emerged in global scenarios as a treatment option for chronic pain. Transcranial Direct Current Stimulation (tDCS)[13,14] is a potential treatment option because of its safety, portability, relative cost, and ease of use. It modulates the resting membrane potential.[15] A previous review/meta-analysis showed that repeated tDCS decreases pain levels in patients with fibromyalgia.[16] In addition, a recent meta-analysis of data from 8 controlled trials provided tentative evidence of pain reduction after active tDCS.[17] Altogether, it is important to note that patients with fibromyalgia are not drug-free, and the potential synergistic effect between pharmacological and non-pharmacological treatments may present an optimal response.

Therefore, this study aimed to investigate the analgesic and neuromodulatory effects of previous treatment with LDN combined with anodal tDCS in women with fibromyalgia. The secondary objective was to evaluate the effects of psychophysiological measures and peripheral Brain-Derived Neurotrophic Factor (BDNF) levels.

Methods

Study design

This was a randomized, double-blind, parallel, controlled with placebo and *sham* stimulation, clinical trial. This study was conducted from August 2018 to July 2019 at La Salle Saúde, Canoas/RS, Brazil. This study was performed in accordance with the Declaration of Helsinki, approved by the La Salle University Ethics Committee (CAAE 0005317.5.0000.5307), registered on Clinical Trials under the number NCT04502251 (https://clinicaltrials.gov), and registered in the Registro Brasileiro de Ensaios Clínicos (ReBEC) platform (RBR-7HK8N# - www.ensaiosclinicos.gov.br).

Population

All participants signed an informed consent form. The inclusion criteria were as follows: women aged 18—65 years, confirmed diagnosis of fibromyalgia according to the 2016 ACR criteria, capable to read and write, pain higher than 6 on the Visual Analog Scale (VAS) in the past 3 months, and chronic stable treatment in the past 3 months.

The exclusion criteria were as follows: use of opioid drugs, pregnancy or not using contraception methods, history of alcohol or drug abuse in the past six months, history of neurological pathologies, arrhythmia history, history of use of drugs that might change vascular response, history of head trauma, history of neurosurgery, decompensated systemic diseases or chronic inflammatory diseases (lupus, rheumatoid arthritis, Sjogren syndrome, Reiter syndrome), history of non-compensated hypothyroidism, and personal history of cancer.

Interventions

According to randomization, each participant received 21 days of low-dose naltrexone (4.5 mg) or placebo followed by 5 days of the drug combined with anodal tDCS (active or *sham*). The timelines of the intervention and measurements are presented in Figure 1.

Low-dose naltrexone (LDN), produced by a manipulation pharmacy in a 4.5 mg daily dose, was administered orally for 26 days. The placebo presented the same format, size, and color as the LDN capsules; however, starch was used as the excipient.

Transcranial Direct Current Stimulation (tDCS): an anodal electrode was placed on the scalp above the primary motor cortex (M1) contralateral to the dominant cortex. A cathodal electrode was placed in the contralateral supraorbital area. The current used was 2mA for 20 min. A battery stimulator with a constant current was used (tDCS device, TCT Research, 1 × 1).[13,18] Five stimulation sessions were performed, according to previous fibromyalgia studies.[16] *Sham*-tDCS stimulation consisted of an active current for 30s.

Sample size calculation

Sample size calculation was based on previous studies using tDCS in the M1 cortex for pain treatment in fibromyalgia.[19] Based on these data, tDCS was estimated to have a Cohen's *f* effect of 0.37. To reach a power of 80% (β = 0.20) and maintain a statistical significance level alpha of 0.05, 21 patients were required in each arm. With a 10% of total loss, there were 92 patients in total.

Randomization and blinding

Before the recruitment phase, a randomization table was generated using a website (seadenvelope.com), creating a randomization list in blocks of 8. Codes were placed in separately sealed brown envelopes, and the patients were allocated into four groups (Fig. 2). The researcher who applied the simulation and the researcher who applied the questionnaires and pain tests were blinded, and a third person set up the device. Blinding was maintained in all the study phases. To evaluate tDCS blinding, at the end of the five sessions, the patients were questioned about the intervention they believed they received.

Measurements

The primary outcome of this study was measured using the Visual Analog Scale (VAS). Baseline and demographic outcomes were measured using the sociodemographic questionnaire. Quality of life (measured using the Fibromyalgia Impact Questionnaire [FIQ]), depressive symptoms (measured by the Beck Depression Inventory-BDI-II), anxiety symptoms (measured by the State-Trait Anxiety Inventory-STAI), pain catastrophizing thought (measured by the Pain Catastrophizing Scale [PCS]), pain functional impact (measured by the Profile of Chronic Pain Scale [PCP: S]), and adverse effects (LDN and tDCS) were considered secondary outcomes.

Pain measurements were as follows: Pain Pressure Threshold (PPT) was measured using an electronic algometer applied to the right forearm, and patients reported the first pain sensation (minimum pain) and maximum pain. An electronic algometer (JTech Medical Industries) was used. The device consisted of a 1-cm^2 hard-rubber probe, which was applied over all the tender points. The average values of the PPT in $kgf.cm^{-2}$ ($lb.cm^{-2}$) for three successive readings were obtained at intervals of 3—5 min and used as the outcomes. On using Conditioned Pain Modulation (CPM), with an algometer (PPT task), patients reported a pain score of 6 on

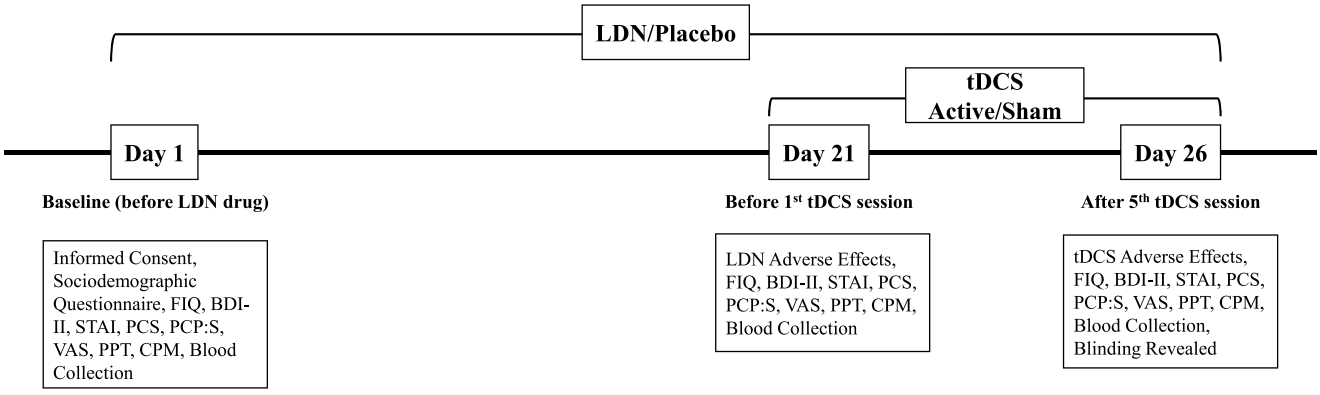

Figure 1 Study timeline.

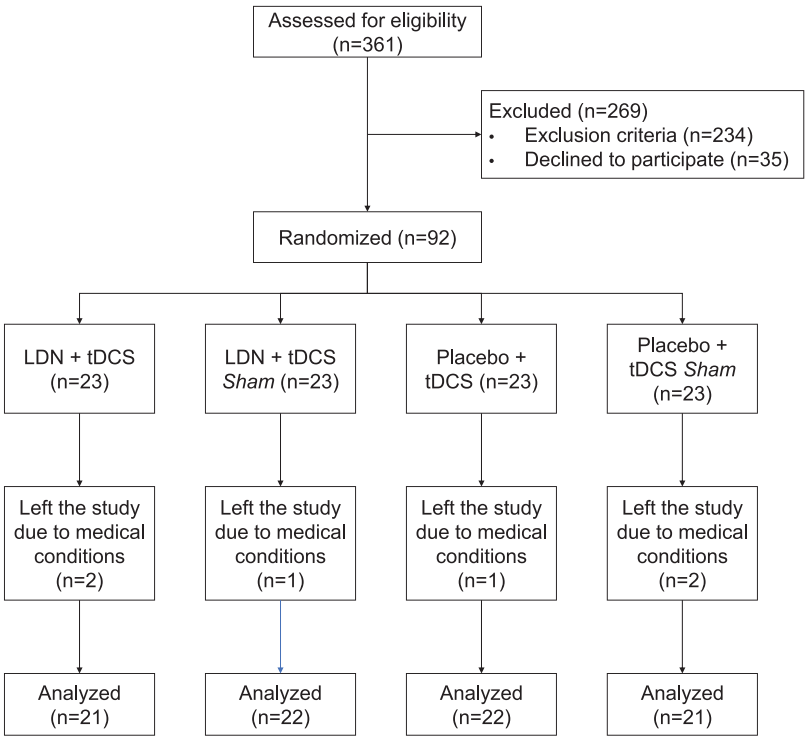

Figure 2 Study Flowchart.

the VAS. This pain level was applied to the right forearm, while the left forearm (non-dominant hand) was submerged in water from 0°C to 1.5°C; after 30 s, patients reported pain in each arm. The CPM formula was right forearm VAS, 6.

Blood was collected and centrifuged, and the supernatant was used for BDNF analysis using ELISA, according to the manufacturer's instructions. Serum BDNF levels were measured using a single method. Blood serum was collected at three time points: on the first day before LDN treatment, before the first tDCS session, and after the last tDCS session.

Statistical analysis

Data are tabulated in red cap. Continuous variables are described as mean ± standard error, while categorical variables are described as percentages. The Shapiro-Wilk test was used for sample distribution, considering a normal distribution when $p > 0.05$. To evaluate baseline data, one-way ANOVA or Kruskal-Wallis test was used for continuous variables, while Fisher's exact test and chi-square test were used for categorical data. The Friedman test followed by the Wilcoxon post-hoc test was used to analyze the effects of treatment over time between groups. Statistical significance was set at $p < 0.05$. Data were analyzed using SPSS (version 20.0; SPSS, Chicago, IL, USA).

Results

Baseline data for the sample are shown in Table 1. No statistically significant differences were found between the groups.

Table 2 presents results from days 1 (baseline), 21, and 26. Visual Analogue Scale (VAS) for pain presented a significant reduction from day 1 to day 26 in the following groups: LDN + tDCS ($p = 0.010$), LDN+tDCS *Sham* ($p = 0.001$), and placebo + tDCS *Sham* ($p = 0.011$). Besides that, the LDN +tDCS *Sham* group also presented a significant reduction on comparing day 26 to day 21.

The Profile of Chronic Pain Scale (PCP:S) enabled us to observe that patients who received active association presented a significant reduction in the frequency and intensity of pain ($p = 0.001$), on comparing day 26 to day 1. Moreover, groups that received LDN presented a significant reduction in interference in activities (LDN + tDCS, $p = 0.014$; LDN + tDCS *Sham*, $p = 0.008$), on comparing day 26 to day 1. Regarding interference in emotions, only the associated group presented a significant reduction over time ($p = 0.008$) (Table 2). Figure 3 presents the data analysis from BDNF performed on days 1, 21, and 26, comparing each value per group. It is possible to identify a significant reduction in BDNF levels in the LDN + tDCS *Sham* group ($p = 0.025$), when LDN was used individually. In addition, it was possible to visualize a significant reduction in the placebo + tDCS group ($p = 0.002$) after the last tDCS intervention (day 26).

Regarding the impact of Fibromyalgia on Quality of life (FIQ), Table 3 shows that there was a significant reduction in the LDN + tDCS group ($p < 0.05$) on comparing day 26 to day 1 in terms of overall impact and function. Regarding the symptoms on the FIQ scale, all groups showed a significant reduction ($p < 0.05$).

In addition, it was possible to observe an improvement in depressive symptoms (BDI-II), in which the group that received LDN+tDCS had significant improvements on days 21 and 26 compared to day 1 ($p < 0.001$). Groups that received active intervention showed a significant reduction from day 26 to day 1 ($p = 0.001$) (Table 3).

Table 1 Sociodemographic profile.

	LDN+tDCS	LDN + tDCS Sham	Placebo+tDCS	Placebo + tDCS Sham	*p*-value
Age (y)	49.74 ± 1.97	48.09 ± 1.56	50.57 ± 2.23	48.95 ± 2.08	0.800[a]
Scholarship (y)	10.00 ± 0.53	11.55 ± 0.99	13.00 ± 0.92	11.95 ± 0.83	0.097[a]
BMI (kg.m^{-2})	27.44 ± 0.88	30.08 ± 1.30	28.37 ± 1.08	27.37 ± 0.87	0.236[a]
Use of Alcohol					0.465[b]
Yes	33.3%	13.6%	18.2%	14.3%	
No	66.7%	86.4%	81.8%	85.7%	
Smoking					0.744[b]
Yes	19%	18.2%	9.1%	9.5%	
No	81%	81.8%	90.9%	90.5%	
Use of medicine					
Tricyclic AD	23.8%	18.2%	22.7%	23.8%	0.953[b]
Serotonergic AD	33.3%	27.3%	18.2%	14.3%	0.523[b]
MAO Inhibitor	0%	4.5%	0%	0%	1.000[b]
Antipsychotic	0%	0%	4.5%	0%	1.000[b]
Anxiolytic	19%	4.5%	9.1%	23.8%	0.302[b]
Carbamazepine	0%	4.5%	0%	0%	0.948[b]
Valproic Acid	0%	0%	0%	4.8%	0.500[b]

AD, Antidepressive; BMI, Body Mass Index; LDN, Low-Dose of Naltrexone; MAO, Mono-Amino Oxidase.
[a] One-Way ANOVA — Data expressed as mean ± standard error.
[b] Fisher's Exact Test — Data expressed as percentage.

Anxiety was evaluated using the State-Trait Anxiety Index (STAI), and it was possible to observe a significant reduction in the state domain from day 21 to day 1 in the group that received only LDN (p = 0.026). The trait domain showed a significant reduction from day 26 to day 1 in the LDN + tDCS group (p = 0.003) (Table 3).

Regarding pain catastrophizing, a significant reduction was observed from day 26 to day 1 in the LDN + tDCS group (p = 0.027), which might be related to a possible reduction in pain levels. In addition, it is important to note that the placebo + tDCS *Sham* group showed a significant reduction in total catastrophism (p = 0.032). The hopelessness domain presented similar results as total catastrophism, in which the group that received both interventions and the group that received both placebo interventions had a significant reduction (p = 0.029 and p = 0.003, respectively) (Table 3).

For tDCS related adverse effects, the tDCS group presented a higher frequency of tingling, itching, and blushing than the *Sham* group ($p < 0.05$). Headache, neck ache, scalp pain, burning sensation, sleepiness, and acute mood changes did not differ between the groups ($p > 0.05$). In LDN adverse effects, there was no significant difference among the groups when the adverse effects (nausea, blurred vision, headache, sleepiness, difficulty in concentrating, and acute mood change) were analyzed ($p > 0.05$).

Discussion

To date, there has been no consensus on a specific treatment for fibromyalgia; however, pharmacological (antidepressant and anticonvulsant drugs) and non-pharmacological approaches (exercise, acupuncture) have been used. In this study, we tested this approach using LDN combined with tDCS to treat pain and other symptoms. It is interesting to point out that the combination of LDN and tDCS was able to decrease pain on VAS, decreased frequency and intensity of pain, decreased interference in activities and emotions on PCP, and the three domains on FIQ. On the other hand, the placebo group (placebo + tDCS *Sham)* was able to decrease pain on VAS, but only the symptoms domain on FIQ and PCS (total and hopelessness).

In addition, new drugs such as Low-Dose Naltrexone (LDN) have been investigated for the treatment of chronic inflammatory diseases.[11] A previous pilot study showed that naltrexone (4.5 mg) decreased auto-related symptoms, particularly pain and fatigue, in women with fibromyalgia.[20] A randomized, double-blinded, clinical trial with 31 women with fibromyalgia, with the same dose (4.5 mg), showed significant reduction in pain and severity of symptoms (humor and quality of life).[21]

In addition, the potential analgesic effect of Noninvasive Brain Stimulation (NIBS) has been investigated. A recent study showed that ten tDCS sessions applied to the M1 cortex promoted pain relief and increased humor in patients with fibromyalgia.[22] A study performed by Fregni et al. (2006)[18] with 32 patients with fibromyalgia, randomized between M1, dorsolateral prefrontal cortex (DLPFC), and *Sham*, for 20 minutes for 5 consecutive days, showed significant pain reduction in groups that received M1 stimulation. In this study, there was no pain reduction in the VAS in the group that received tDCS only (placebo + tDCS). However, after 21 days of LDN/placebo, five sessions of anodal tDCS were added to the last five days of LDN in women with fibromyalgia, and some beneficial results were found in this association, such as reduction in pain frequency and intensity, and interference in activities and emotions. We observed a significant reduction in pain levels in the groups that received LDN (LDN + tDCS and LDN + tDCS *Sham*) and in the placebo + tDCS *Sham* group. It is important to note that the association (LDN + tDCS) was not superior to the group that received only the drug (LDN + tDCS *Sham*), showing that the association may not be as beneficial as the drug used separately.

Table 2 Sample pain profile.

	Day 1	Day 21	Day 26	*p*-value	Effect size
VAS					
LDN + tDCS	7.05 ± 0.34	5.52 ± 0.55	5.10 ± 0.61[a]	**0.010**[c]	**3.948**
LDN + tDCS *Sham*	6.67 ± 0.32	6.12 ± 0.44	4.67 ± 0.58[a,b]	**0.001**[c]	**4.269**
Placebo + tDCS	6.14 ± 0.33	5.50 ± 0.49	4.41 ± 0.55	0.090	–
Placebo + tDCS *Sham*	6.23 ± 0.35	5.20 ± 0.45[a]	5.00 ± 0.59	**0.011**[c]	**2.555**
PPT – Minimum Pain					
LDN + tDCS	0.88 ± 0.15	0.74 ± 0.10	0.98 ± 0.12	0.068	–
LDN + tDCS *Sham*	0.78 ± 0.09	0.72 ± 0.91	0.94 ± 0.10	0.170	–
Placebo + tDCS	0.90 ± 0.11	0.90 ± 0.12	0.95 ± 0.13	0.955	–
Placebo + tDCS *Sham*	1.02 ± 0.14	0.74 ± 0.11	0.98 ± 0.15	0.386	–
PPT – Maximum Pain					
LDN + tDCS	2.74 + 0.40	2.62 + 0.48	3.20 + 0.42	0.919	–
LDN + tDCS *Sham*	2.99 ± 0.34	2.56 ± 0.24	2.95 ± 0.34	0.244	–
Placebo + tDCS	3.70 ± 0.51	2.96 ± 0.37	3.16 ± 0.43	0.083	–
Placebo + tDCS *Sham*	3.02 ± 0.39	2.78 ± 0.44	2.83 ± 0.49	0.140	–
CPM					
LDN + tDCS	-0.57 ± 0.74	-1.02 ± 0.69	-0.02 ± 0.61	0.589	–
LDN + tDCS *Sham*	-1.22 ± 0.56	-0.22 ± 0.50	0.41 ± 0.54	0.129	–
Placebo + tDCS	-0.68 ± 0.47	-1.18 ± 0.55	-0.22 ± 0.56	0.477	–
Placebo + tDCS *Sham*	-1.23 ± 0.69	-0.28 ± 0.59	-0.23 ± 0.70	0.193	–
PCP:S – Frequency and Intensity					
LDN + tDCS	26.80 ± 0.44	26.04 ± 0.50	24.78 ± 0.55[a]	**0.001**[c]	**4.055**
LDN + tDCS *Sham*	25.40 ± 0.42	24.78 ± 0.65	24.02 ± 0.91	0.559	–
Placebo + tDCS	25.88 ± 0.56	25.38 ± 0.56	25.77 ± 0.46	0.784	–
Placebo + tDCS *Sham*	25.65 ± 0.69	24.92 ± 0.72	24.30 ± 0.95	0.069	–
PCP:S – Interference in Activities					
LDN + tDCS	28.61 ± 1.15	23.52 ± 1.65	22.74 ± 2.14[a]	**0.014**[c]	**3.417**
LDN + tDCS *Sham*	28.09 ± 1.56	25.28 ± 1.93[a]	25.76 ± 1.99[a]	**0.008**[c]	**1.305**
Placebo + tDCS	26.36 ± 1.49	25.65 ± 1.32	25.00 ± 1.49	0.387	–
Placebo + tDCS *Sham*	25.40 ± 1.99	23.65 ± 2.11	22.15 ± 2.24	0.432	–
PCP:S – Interference in Emotions					
LDN + tDCS	16.38 ± 0.99	13.61 ± 1.11[a]	13.23 ± 1.34[a]	**0.008**[c]	**2.673**
LDN + tDCS *Sham*	17.31 ± 0.85	15.95 ± 1.21	14.90 ± 1.32	0.080	–
Placebo + tDCS	15.90 ± 1.22	14.68 ± 1.25	14.09 ± 1.26	0.084	–
Placebo + tDCS *Sham*	15.71 ± 1.05	14.61 ± 1.18	14.38 ± 1.32	0.267	–

CPM, Conditioned Pain Modulation; PCP:S, Profile of Chronic Pain Scale; PPT, Pain Pressure Threshold; VAS, Visual Analogue Scale.
Data presented as mean ± standard error. Friedman Test.
[a] Different from Day 1.
[b] Different from Day 21.
[c] Significant difference.

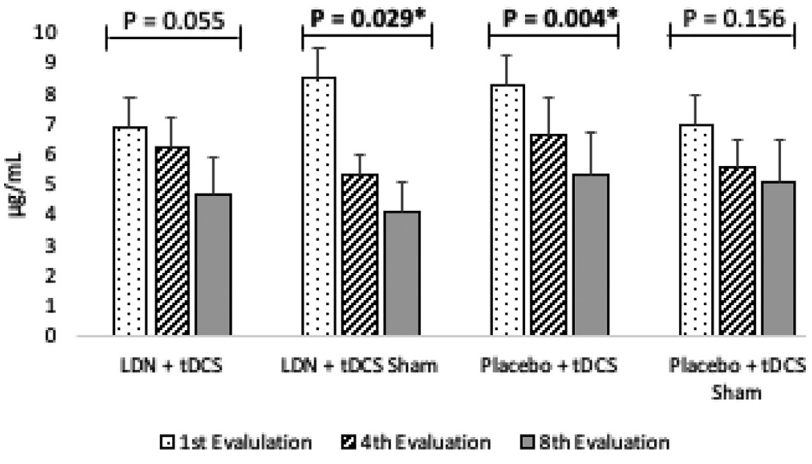

Figure 3 BDNF serum levels analysis during time. Friedman test. Data expressed as mean ± standard error.

Table 3 Data from questionnaires.

	Day 1	Day 21	Day 26	*p*-value	Effect size
FIQ-Function					
LDN + tDCS	15.88 ± 1.53	11.67 ± 0.97[a]	12.67 ± 1.06	**0.005**[c]	**3.286**
LDN + tDCS *Sham*	13.30 ± 1.38	14.00 ± 1.87	13.89 ± 1.33	0.625	-
Placebo + tDCS	15.02 ± 1.37	13.78 ± 1.30	13.82 ± 1.39	0.403	–
Placebo + tDCS *Sham*	12.95 ± 1.21	13.79 ± 1.06	13.61 ± 1.07	0.918	–
FIQ-Overall Impact					
LDN + tDCS	6.16 ± 0.25	5.85 ± 0.24	5.20 ± 0.23[a]	**0.004**[c]	**3.996**
LDN + tDCS *Sham*	5.80 ± 0.31	5.23 ± 0.26	5.20 ± 0.27	0.112	–
Placebo + tDCS	5.23 ± 0.29	5.17 ± 0.22	4.69 ± 0.18	0.304	–
Placebo + tDCS *Sham*	6.04 ± 0.23	5.43 ± 0.25	5.28 ± 0.26	0.054	–
FIQ-Symptoms					
LDN + tDCS	8.01 ± 0.33	6.62 ± 0.46	5.94 ± 0.47[a]	**<0.001**[c]	**5.097**
LDN + tDCS *Sham*	7.96 ± 0.28	6.50 ± 0.42	6.00 ± 0.43[a]	**0.003**[c]	**5.401**
Placebo + tDCS	7.68 ± 0.33	6.20 ± 0.45	5.40 ± 0.47[a]	**0.003**[c]	**4.630**
Placebo + tDCS *Sham*	7.73 ± 0.36	6.60 ± 0.40	5.97 ± 0.49[a]	**0.003**[c]	**4.093**
BDI-II					
LDN + tDCS	24.38 ± 2.18	20.05 ± 1.92	17.33 ± 1.76[a]	**<0.001**[c]	**3.558**
LDN + tDCS *Sham*	28.86 ± 2.29	23.29 ± 2.52	20.90 ± 2.67[a]	**0.001**[c]	**3.200**
Placebo + tDCS	24.18 ± 1.82	21.36 ± 2.29	17.86 ± 2.45[a,b]	**0.001**[c]	**2.928**
Placebo + tDCS *Sham*	22.20 ± 2.35	19.25 ± 2.09	16.40 ± 2.32	0.086	–
STAI – State					
LDN + tDCS	26.33 ± 0.54	27.50 ± 0.72	27.19 ± 0.70	0.590	–
LDN + tDCS *Sham*	27.86 ± 0.91	26.43 ± 0.86[a]	27.71 ± 1.00	**0.026**[c]	**1.615**
Placebo + tDCS	27.82 ± 0.76	27.68 ± 1.02	28.27 ± 1.00	1.000	–
Placebo + tDCS *Sham*	27.40 ± 0.94	28.10 ± 1.21	27.25 ± 0.71	0.607	–
STAI – Trait					
LDN + tDCS	24.86 ± 0.65	23.52 ± 0.75	21.86 ± 1.26[a]	**0.003**[c]	**2.992**
LDN + tDCS *Sham*	25.67 ± 0.63	25.24 ± 0.75	25.43 ± 0.61	0.607	–
Placebo + tDCS	25.45 ± 0.66	24.64 ± 0.65	24.27 ± 0.72	0.277	–
Placebo + tDCS *Sham*	24.60 + 0.74	24.75 + 0.78	23.95 + 0.74	0.520	–
PCS – Total					
LDN + tDCS	36.57 + 2.13	33.71 + 2.34	30.62 + 2.88[a]	**0.027**[c]	**2.349**
LDN + tDCS *Sham*	35.10 + 2.42	32.43 + 3.13	33.19 + 2.91	0.645	–
Placebo + tDCS	37.09 + 2.41	32.00 + 1.79	31.23 + 2.56	0.071	–
Placebo + tDCS *Sham*	37.10 + 2.12	31.75 + 2.81	30.20 + 3.41[a]	**0.032**[c]	**2.430**
PCS – Hopelessness					
LDN + tDCS	16.19 + 1.03	14.62 + 1.10	12.67 + 1.42[a]	**0.029**[c]	**2.837**
LDN + tDCS *Sham*	15.14 + 1.35	14.14 + 1.50	14.95 + 1.39	0.681	–
Placebo + tDCS	16.77 + 1.09	14.59 + 0.86	13.82 + 1.22	0.170	–
Placebo + tDCS *Sham*	16.85 + 0.99	14.05 + 1.30	12.70 + 1.62[a]	**0.003**[c]	**3.091**
PCS – Magnification					
LDN + tDCS	8.05 + 0.65	7.62 + 0.62	7.05 + 0.73	0.638	–
LDN + tDCS *Sham*	8.10 + 0.56	7.29 + 0.85	7.29 + 0.77	0.520	–
Placebo + tDCS	7.86 + 0.70	6.82 + 0.57	7.05 + 0.72	0.326	–
Placebo + tDCS *Sham*	8.10 + 0.62	6.90 + 0.81	6.45 + 0.94	0.050	–
PCS – Rumination					
LDN + tDCS	12.33 + 0.64	11.48 + 0.77	10.90 + 0.84	0.067	–
LDN + tDCS *Sham*	11.86 + 0.63	11.00 + 0.87	10.95 + 0.90	0.513	–
Placebo + tDCS	12.45 + 0.87	10.59 + 0.63	10.36 + 0.83	0.058	–
Placebo + tDCS *Sham*	12.15 + 0.77	10.80 + 0.92	11.05 + 0.92	0.348	–

FIQ, Fibromyalgia Impact Questionnaire; BDI-II, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; PCS, Pain Catastrophizing Scale.
Data presented as mean ± standard error. Friedman Test.
[a] Different from Day 1.
[b] Different from Day 21.
[c] Significant difference.

An important placebo effect was observed in the VAS, PCS, and FIQ symptoms. Corroborating, a meta-analysis performed by Migliorini et al. (2021)[23] showed an important placebo effect in patients with fibromyalgia; however, the treatment was superior to placebo in most of the studies analyzed. Another meta-analysis performed by Chen et al. (2017)[24] highlighted an improvement in pain, fatigue, sleep quality, and function in patients who received placebo when compared to those who received no treatment.

Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin that plays an important role in pain modulation by increasing the efficiency of glutamatergic synapses and decreasing the efficiency of GABAergic synapses.[25] In addition, chronic pain with high levels of sensitization is positively correlated with the dysfunction level of the descending inhibitory system of pain and with high serum levels of BDNF.[26] Patients with fibromyalgia present higher levels of serum BDNF[27] than healthy individuals, which suggests an important role of BDNF in fibromyalgia physiopathology. This study found that when the treatments were applied separately (LDN + tDCS *Sham* and placebo+tDCS), there was a decrease in serum BDNF levels. According to these results, the association may not be as efficient as when both the treatments are applied separately, since BDNF is a biomarker and not a self-reported measure.

Patients with fibromyalgia present important characteristics that directly affect its relationship with pain as well as treatment effectiveness. Patients with fibromyalgia present higher pain vigilance than patients with chronic lumbar pain as well as higher pain intensity and pain catastrophizing thought.[28] High levels of catastrophizing are correlated with more generalized pain and emotional disturbances in patients with fibromyalgia.[29] Additionally, a study showed that there is a positive correlation between catastrophizing and tender points in patients with musculoskeletal pain and fibromyalgia,[30] as well as high levels of catastrophizing are related to a low pain threshold and pain tolerance. This study found an improvement in pain-catastrophizing thoughts in patients who received LDN+tDCS and placebo + tDCS *Sham*.

Depression and fibromyalgia might be interconnected, and once serotonergic and norepinephrine drugs were used in both conditions, duloxetine (selective serotonin and norepinephrine reuptake inhibitor) and milnacipran were approved for fibromyalgia treatment in the United States.[31] This study demonstrated that both interventions are capable of reducing depressive symptoms, since LDN+tDCS, placebo +tDCS, and LDN + tDCS *Sham* improved their symptoms.

Mood disturbances, such as anxiety and depression, are among the most common psychological factors in patients with fibromyalgia, with a higher incidence in these patients than in healthy individuals.[8] Regarding anxiety, a study performed by Khedr et al. (2017)[22] reported that the related anxiety decreased using anodal tDCS in the M1 cortex when compared to tDCS *Sham*. Fregni et al. (2006)[18] reported a decrease in anxiety with active tDCS applied to the DLPFC and M1; however, a significant reduction was also found in the *Sham* group, with a similar reduction in all groups. This study demonstrated that the use of LDN associated with tDCS reduced trait anxiety in patients with fibromyalgia; however, when their anxiety-state was analyzed, only patients who received LDN + tDCS *Sham* reduced their symptoms.

The FIQ is an instrument widely used to evaluate the function of patients with fibromyalgia and is one of the most indicated questionnaires by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) guidelines to be used in rheumatological clinical trials. In addition, the FIQ has been shown to be the most responsive self-imported improvement measurement in changes of pain intensity and total tender points and is recommended as a primary variable for fibromyalgia clinical trials. This study observed that patients who received the combination (LDN+tDCS) had a great improvement in the three domains (function, overall impact, and symptoms), and the other groups showed improvement only in the symptom domain.

This study also analyzed the adverse effects related to tDCS and found a significant prevalence of tingling, itching, and blushing in the tDCS active group compared to the *Sham* group. Overall, tDCS is a safe neuromodulation technique, even with low and transient adverse effects.[16] Regarding the adverse effects of LDN, there was a high prevalence of nausea, blurred vision, sleepiness, difficulty in concentrating, and acute mood change in patients who received LDN and placebo, which did not show a significant difference among the groups. As for limitations, this study was conducted by a large group of researchers, who may have influenced the results using different approaches. In addition, most of the variables studied were subjective (such as VAS) and within the short period of tDCS post-effect analysis.

Conclusion

The results of this study allowed us to conclude that combined LDN + tDCS has possible benefits in reducing pain frequency and intensity; however, a placebo effect was observed in pain on VAS. In addition, it was possible to conclude that it was safe and did not present severe adverse effects. Therefore, further studies need to be conducted with a sufficient methodology to supply the placebo effect. Future studies should be conducted to elucidate the effects of this association on different chronic pain conditions. In addition, further studies should be performed to evaluate the effect of this association on depression and anxiety.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Effect of intraoperative alveolar recruitment maneuver on intraoperative oxygenation and postoperative pulmonary function tests in patients undergoing robotic-assisted hysterectomy: a single-blind randomized study

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Robot-assisted surgery;
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Abstract
Background: Robotic-Assisted Hysterectomies (RAH) require Trendelenburg positioning and pneumoperitoneum, which further accentuate alteration in respiratory mechanics induced by general anesthesia. The role of Recruitment Maneuver (RM) as a lung-protective strategy during intraoperative surgical settings has not been much studied. We planned this study to evaluate the effect of RM on perioperative oxygenation and postoperative spirometry using PaO_2/FiO_2 and FEV1/FVC, respectively in patients undergoing RAH.
Methods: Sixty-six ASA I–II female patients scheduled for elective RAH were randomized into group R (recruitment maneuver, n = 33) or group C (control, n = 33). Portable spirometry was done one day before surgery. Patients were induced with general anesthesia, and mechanical ventilation started with volume control mode, with Tidal Volume (TV) of 6—8 $mL.kg^{-1}$, Respiratory Rate (RR) of 12 min, inspiratory-expiratory ratio (I: E ratio) of 1:2, FiO_2 of 0.4, and Positive End-Expiratory Pressure (PEEP) of 5 cmH_2O. Patients in group R received recruitment maneuvers of 30 cmH_2O every 30 minutes following tracheal intubation. The primary objectives were comparison of oxygenation and ventilation between two groups intraoperatively and portable spirometry postoperatively. Postoperative pulmonary complications, like desaturation, pulmonary edema, pneumonia, were monitored.
Results: Patients who received RM had significantly higher PaO_2 (mmHg) (203.2+-24.3 vs. 167.8 +-27.3, $p < 0.001$) at T2 (30 min after the pneumoperitoneum). However, there was no significant

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difference in portable spirometry between the groups in the postoperative period (FVC, 1.40 ± 0.5 L vs. 1.32 ± 0.46 L, $p = 0.55$).
Conclusion: This study concluded that intraoperative recruitment did not prevent deterioration of postoperative spirometry values; however, it led to improved oxygenation intraoperatively.

Introduction

As technology is advancing day by day, there is a trend for "minimally invasive surgical techniques". Abdominal hysterectomy has been transitioned from laparotomy to laparoscopy and even further to robotic-assisted surgery. Lower estimated blood loss and fewer intraoperative complications are seen in Robotic-Assisted Hysterectomy (RAH)[1] hence robotic-assisted gynecological procedures are on an increasing trend. However, robotic hysterectomy is done under general anesthesia and requires pneumoperitoneum and a steep Trendelenburg position.

The induction of general anesthesia itself is associated with altered respiratory mechanics, reduced lung volumes, and atelectatic zone formation. RAH frequently requires Trendelenburg positioning of > 30° slopes, and a patient must stay in a fixed position while the robot is docked. Trendelenburg position itself decreases pulmonary compliance, functional residual capacity and can worsen arterial oxygenation. The addition of pneumoperitoneum further accentuates respiratory compromise. The respiratory consequence of robotic surgery is the development of atelectatic zones, which further lead to increased peak airway pressures, low tidal volume, increased inspired-to-arterial oxygen gradient, and increased arterial to end-tidal carbon dioxide gradient. These changes altogether may lead to postoperative respiratory complications.[2]

The majority of previous studies have used low tidal volume and low PEEP as lung protective strategies in intraoperative settings. However, a low level of PEEP itself leads to repeated opening and closing of small airways which may further promote atelectrauma.[3,4]

The role of Recruitment Maneuver (RM) as a lung-protective strategy has been studied in critical care settings.[5] However, studies regarding the role of recruitment maneuver as a lung-protective strategy during intraoperative surgical settings are scarce. Thus, we planned this study to evaluate the efficacy of RM in addition to PEEP and low tidal volume ventilation in the prevention of deterioration of postoperative pulmonary function.

The primary objectives of this study were the comparison of oxygenation-ventilation perioperatively and spirometry values postoperatively between the two groups. The secondary objectives were to compare intraoperative respiratory mechanics and hemodynamics of the patients.

Methods

Ethics

The study protocol was approved by the institutional ethical committee (208/IEC/PGM/2018) of AIIMS Rishikesh (India). Before enrollment of the patient, the study protocol was also registered at the clinical trials registry — India [CTRI/2019/04/018862]. Written informed consent was obtained from all the participants.

Study design

This was a single-center, randomized, single-blind study done at the Anesthesiology Department at AIIMS Rishikesh, India. Sixty-six female patients were randomly assigned into a 1:1 ratio to receive intraoperative recruitment maneuvers with standard mechanical ventilation or only standard mechanical ventilation.

Participants

American Society of Anesthesiologists (ASA) physical status I and II female patients aged 30 to 70 years, scheduled for elective RAH under general anesthesia from May 2019 to September 2019 were recruited. Patients with obesity (BMI > 31 $kg.m^{-2}$), significant hepatic (elevated liver enzymes > 3 times, INR > 1.5, elevated bilirubin levels more than 3 $mg.dL^{-1}$, cirrhotic liver disease, hepatocellular carcinoma, acute on chronic liver failure, active hepatitis) or renal disease (creatinine > 1.2, chronic kidney disease, patients on regular hemodialysis, post renal transplantation), moderate to severe respiratory diseases (chronic obstructive airway disease, active pulmonary tuberculosis, uncontrolled asthma, interstitial lung diseases, lung carcinoma), significant cardiac illness (ejection fraction < 40%, Ischemic heart disease, valvular heart disease), neuromuscular disease, having neurologic sequelae due to neurologic disease (poliomyelitis, Myasthenis gravis, Guillain barre syndrome, etc.), and dementia were excluded. Patients who had severe hemodynamic instability due to recruitment maneuver and severe blood loss were also excluded. Hemodynamic instability was defined in these patients as fall in systolic blood pressure of more than 20% from the baseline value. Our safety concerns in relation to recruitment maneuver were severe hypotension, desaturation (SpO_2 < 85%), bradycardia (< 60 min), new onset of arrhythmias. These patients were randomized into two groups (R and C) by a computer-generated random table (simple randomization).

Interventions

Portable spirometry (with a computer-based spirometer [Innotech Respi Scan]) was done one day before surgery. Values of Forced Vital Capacity (FVC); Forced Expiratory Volume in 1sec (FEV1); Peak Expiratory Flow (PEF) and Maximal Expiratory Flow (MEF) were recorded. Patients were given alprazolam 0.25 mg and ranitidine 150 mg as premedication.

Once the patient was shifted to the operating room, standard monitoring including Electrocardiogram (ECG), Noninvasive Arterial Blood Pressure (NIBP), Heart Rate (HR), and Pulse Oximetry (SpO_2) were applied. Adequate intravenous access was established. Patients were induced with intravenous fentanyl, propofol, and vecuronium. Neuromuscular Monitoring (NMT) was applied following induction of anesthesia. Patients were mask ventilated till the Train Of Four (TOF) ratio value was 0, and the trachea was intubated with Polyvinyl Chloride (PVC) endotracheal tube. The correct position of the tube was confirmed. Anesthesia was maintained with oxygen, nitrous oxide, sevoflurane, and intermittent top-up of vecuronium. Depth of hypnosis was monitored with Bi-Spectral Index (BIS) and maintained within 45 to 55. NMT was continued intraoperatively and intermittent top-up of vecuronium was administered according to TOF ratio. Analgesia was maintained with 0.5 $mcg.kg^{-1}.h^{-1}$ bolus of fentanyl. The last dose of fentanyl was given approximately 30 min before the completion of surgery. All enrolled patients received mechanical ventilation by volume control mode, with ventilatory settings of Tidal Volume (TV) of 6–8 $mL.kg^{-1}$, Respiratory Rate (RR) of 12 min, inspiratory- expiratory ratio (I: E ratio) of 1:2, FiO_2 of 0.4 and Positive End-Expiratory Pressure (PEEP) of 5 cmH_2O. The respiratory rate was adjusted to keep $EtCO_2$ between 35–45 mmHg. If Peak Airway Pressure (Peak) rose to > 35 cmH_2O, ventilator parameters were altered to maintain Ppeak < 35 cmH_2O and such incidences were noted. Intra-abdominal insufflation of carbon dioxide was done to create pneumoperitoneum and intra-abdominal pressure was maintained in physiological limits of 10–15 mmHg throughout the procedure in both groups. Patients in the recruitment maneuver group (group R) received recruitment maneuvers. Patients in the control group (group C), did not receive recruitment maneuver. The first recruitment maneuver was given 30 min after intubation.[11] Later on, RM was repeated every 30 minutes. Each recruitment maneuver consisted of applying a continuous positive airway pressure of 30 cm of water for 30 seconds. For episodes of arterial desaturation (defined as peripheral oxygen saturation of ≤ 92%), a transient increase in the Fraction of Inspired Oxygen (Fio_2) to 100% was permitted. Hemodynamic parameters such as Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), HR, SpO_2 were recorded as a baseline and at 5 min following induction, then at every 15-min throughout the surgical procedure. Peak pressure (Ppeak), Mean Airway Pressure (Pmean), Plateau Airway Pressure (Pplat), total lung compliance (tidal volume/Pplat), and End-Tidal Carbon Dioxide ($EtCO_2$) were recorded. Arterial Blood Gas analysis (ABG) was done after induction (T1), 30 min after induction of pneumoperitoneum (T2), 90 min after induction of pneumoperitoneum (T3), and 30 min after arrival in a Post-Anesthesia Care Unit (PACU) on room air. An arterial blood sample was taken following the pricking radial artery. PaO_2/FiO_2 ratio was calculated. Patients were given diclofenac (1 $mg.kg^{-1}$) intravenous (IV) and inj. ondansetron (0.1 $mg.kg^{-1}$) at the end of surgery. Neuromuscular block was reversed with neostigmine (0.05 $mg.kg^{-1}$) and glycopyrrolate (0.01 $mg.kg^{-1}$), and patients were extubated and shifted to the Postanesthesia Care Unit (PACU). Portable spirometry was repeated on the first postoperative day (24 hours after surgery) performed at the bedside, while making the patient sit in a comfortable position. Assessors of PFT were not blinded to group assignment. A Numerical Rating Scale (NRS) for pain was also recorded before performing PFTs. For NRS > 4, patients were first given inj. diclofenac (1 $mg.kg^{-1}$), and once NRS was ≤ 4, then only PFTs were repeated. Postoperative pulmonary complications, like desaturation, pulmonary edema, and pneumonia, were monitored during follow-up.

Statistics

Based on a study done by Eun-suchol et al. on the effect of recruitment maneuver on perioperative pulmonary complications in patients undergoing robotic prostatectomy, we considered a reduction in the incidence of atelectasis by 90% to be statistically significant.[6] Using G- Power 3.0.10 software and on the application of *t*-test with FEVI/FVC mean of 87.9 and standard deviation of 10.8 in one group, FEVI/FVC mean of 77.2 and standard deviation of 15.1 in another group, the effect size was calculated to be 0.81% with 90% power, 5% α error, and the total sample size was calculated to be 66 with 33 in each group.

Statistical analysis was performed using R Statistical software version 3.6.0. The results were presented as descriptive statistics and summarized as mean (Standard Deviation [SD]), median (Interquartile Range [QR]), number (percentage), whichever appropriate. Data were analyzed by Mann-Whitney *U* test (Wilcoxon rank-sum test), Wilcoxon signed-rank test, Student's *t*-test, repeated measures ANOVA, Friedman test, and Shapiro-Wilk test. A *p*-value of < 0.05 was considered significant.

Results

Recruitment

A total of 100 female patients were assessed for the study, of which 30 patients were excluded based on exclusion criteria. Out of the remaining 70 patients, 4 patients declined consent. A total of 66 patients were included in this study, and they were randomly assigned to group R (recruitment maneuver, n = 33) or group C (control, n = 33). All the randomized patients were analyzed at the end of the study (Fig. 1).

Baseline data

The two groups were comparable for demographic data including age, height, weight, BMI, and ASA physical status. The anesthesia and surgical time were also comparable between the groups (Table 1). Overall surgery duration was less than 90 minutes hence blood gas analysis, respiratory mechanic parameters and hemodynamic parameters at T3 could not be calculated.

Primary outcomes

Baseline (T1) ABGs were comparable in both groups. There was a statistically significant improvement in arterial gas parameters like PaO_2 levels, PaO_2/FiO_2, $P(A\text{-}a)O_2$ difference at the end of T2 (after 30 minutes of creation of

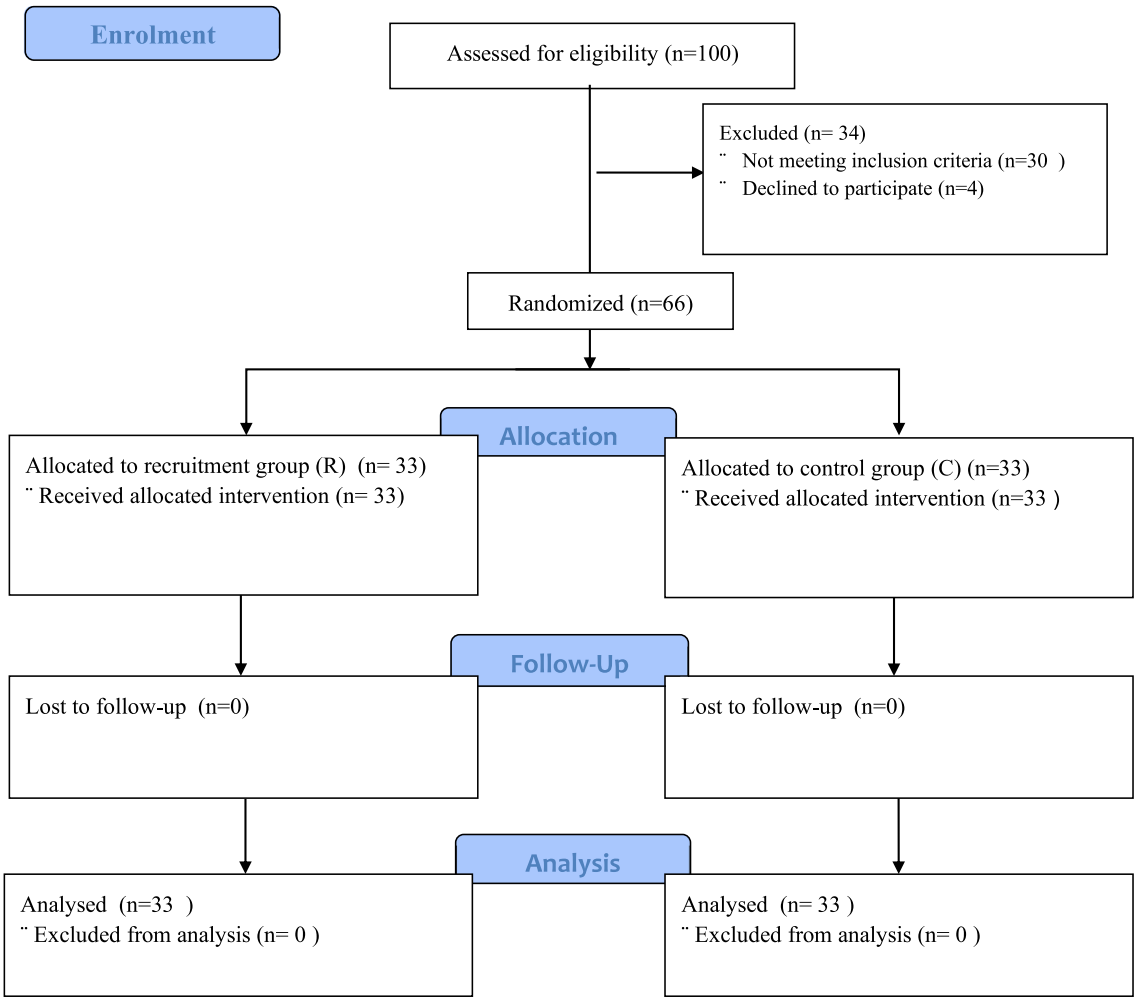

Figure 1 CONSORT flow diagram.

pneumoperitoneum) in group R ($p \leq 0.0001$) as compared to group C. However, there was no significant difference in arterial blood gas parameters at the end of T4 (postoperatively in PACU) (Table 2). There was no significant difference in pulmonary function test parameters between group C and group R in the pre and postoperative period. However, when comparing pulmonary function test results between the preoperative and postoperative period in both groups (R and C) there was a statistically significant reduction of FVC ($p \leq 0.001$), FEV1 ($p \leq 0.001$), PEF ($p \leq 0.001$), MEF ($p \leq 0.001$) (Table 3).

Table 1 Baseline characteristic of patients.

Parameters	Group R (n = 33)	Group C (n = 33)
Age (Years)	45.09 ± 5.22	47.06 ± 6.26
Weight (Kg)	59.36 ± 7.00	58.27 ± 7.04
Height (cm)	157.85 ± 5.02	156.00 ± 4.20
BMI ($Kg.m^{-2}$)	23.82 ± 2.65	23.90 ± 2.42
Duration of surgery	54.09±9.18	54.42±9.38
Duration of Anesthesia	69.63±9.20	70.33±8.63
ASA I	21 (63.6%)	23 (69.7%)
ASA II	12 (36.4%)	10 (30.3%)

BMI, Body Mass Index; ASA, American Society of Anaesthesiologists.

Secondary outcomes

Other parameters of respiratory mechanics, like peak pressure, plateau pressure, static compliance, and dynamic compliance, were not significantly different between the groups at T1 and T2. There was a significant rise in peak and plateau pressures from baseline to T2 in both groups. There was a significant reduction in static and dynamic compliance from baseline to T2 in both groups (Table 4).

Hemodynamic parameters such as systolic blood pressure, diastolic blood pressure, mean arterial pressure were comparable at all the time points in both the groups, except at T2, when the DBP was higher in group R (Table 5). There were no significant pulmonary complications like desaturation episodes, pulmonary edema, or pneumonia in both groups.

Discussion

The main findings of this study in patients undergoing RAH were that intraoperative oxygenation significantly improved

Table 2 Arterial gas analysis parameters.

	Group C (n = 33)	Group C median (IQR)	Group R (n = 33)	Group R median (IQR)	*p*-value
PaO_2					
After induction (T1)	153.97 ± 17.72	152.00 (21.00)	153.67 ± 21.13	153.00 (27.00)	0.950
30 min (T2)	167.88 ± 27.3	160.00 (27.00)	203.24 ± 24.3	200.00 (40.00)	**< 0.001**
PACU (T4)	86.48 ± 8.31	86.00 (11.00)	87.64 ± 8.87	89.00 (10.21)	0.583
$PaCO_2$					
After induction (T1)	36.27 ± 5.55	36.00 (6.00)	36.36 ± 4.81	36.00 (6.00)	0.944
30 min (T2)	40.39 ± 5.54	40.00 (8.00)	40.98 ± 5.33	40.00 (7.00)	0.660
PACU (T4)	34.3 ± 5.05	35.00 (7.00)	34.15 ± 4.38	34.00 (4.00)	0.897
PaO_2/FiO_2					
After induction (T1)	384.45 ± 43.56	380.00 (52.05)	384.21± 52.74	382.50 (67.50)	0.984
30 min (T2)	422.73 ± 68.64	402.50 (75.00)	508.11 ± 60.74	500.00 (100.00)	**< 0.001**
PACU (T4)	411.47 ± 39.9	409.52 (52.38)	417.33 ± 42.17	423.80 (48.62)	0.564
$P(A\text{-}a)O_2$					
After induction (T1)	85.83 ± 18.64	89.45 (27.25)	85.93 ± 23.37	87.95 (30.25)	0.984
30 min (T2)	64.79 ± 27.85	66.45 (27.00)	30.84 ± 27.09	40.70 (43.00)	< 0.001
PACU (T4)	24.57 ± 29.02	15.98 (16.75)	23.5 ± 25.38	19.73 (13.70)	0.913

PaO_2, Partial Pressure of Oxygen; $PaCO_2$, Partial Pressure of Carbon-di oxide; FiO_2, Fraction of Inspired Oxygen; $P(A\text{-}a)O_2$, Alveolar-Arterial Gradient of Oxygen, IQR, Inter Quartile Range. PACU, Postanesthesia Care Unit.

in group R, however, there was no significant difference in spirometry values in both the groups postoperatively.

Deterioration of pulmonary functions postoperatively and postoperative pulmonary complications are frequent. They may be associated with significant morbidity and even mortality. Most of them are related to V/Q mismatch associated with mechanical ventilation, hypoxemia, hypercapnia, residual sedative effect of anesthetic drugs, inadequate reversal of neuromuscular blockade, etc. This can be prevented by careful use of anesthetic drugs, vigilant monitoring of patient's vitals and blood gases during the perioperative period, implication of various lung-protective ventilation strategies, early ambulation, and physiotherapy in the postoperative period.

Robotically assisted hysterectomy needs a much steeper Trendelenburg position and high-pressure pneumoperitoneum, which decrease Functional Residual Capacity (FRC) and compliance of lungs.[7] Moreover, during Trendelenburg position, most of the lung is below the left atrium. Hence patients are prone to perfusion mismatch and pulmonary interstitial edema.[8]

Recruitment maneuver is a sustained increase in pressure in the lungs with the purpose of opening as many collapsed lung units as possible.[9] It is commonly used in the management of patients with ARDS and may also be utilized in the postoperative treatment of atelectasis in postanesthesia patients.[10] Lungs are recruited from the range of residual volume to total lung capacity. Several types of RMs have been used in the clinical setting. These include sustained high pressure in the CPAP mode, PC-CMV with a single high PEEP level imposed, PC-CMV with progressive increases in PEEP level.

Table 3 Postoperative pulmonary function tests.

	Group C (n = 33)	Group R (n = 33)	*p*-value
FEV1			
Pre op	1.61 ± 0.38	1.71 ± 0.43	0.361
Post op	1.26 ± 0.43	1.33 ± 0.48	0.509
FVC			
Pre op	1.69 ± 0.39	1.79 ± 0.47	0.330
Post op	1.32 ± 0.46	1.4 ± 0.5	0.559
PEF			
Pre op	4.43 ± 1.73	4.7 ± 1.58	0.512
Post op	3.12 ± 1.39	3.18 ± 1.27	0.744
MEF			
Pre op	2.78 ± 0.93	3.01 ± 1.14	0.357
Post op	2.1 ± 0.83	2.11 ± 1	0.653
FEV1/FVC			
Pre op	95.68 ± 7.04	95.73 ± 5.91	0.843
Post op	95.71 ± 8.32	95.01 ± 6.68	0.347

FEV1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; PEF, Peak EFxiratory Flow; MEF, Maximal Expiratory Flow. Pre op, preoperative; Post op, postoperative.

Table 4 Intraoperative respiratory mechanics.

	Group C (n = 33)	Group C median (IQR)	Group R (n = 33)	Group R median (IQR)	*p*-value
Static compliance					
5 min after induction (T1)	45.03 ± 11.53	42.22 (16.06)	44.23 ± 11.35	41.66 (11.25)	0.677
30 min after pneumoperitoneum (T2)	23.37 ± 3.9	22.50 (5.59)	22.83 ± 3.09	23.15 (4.28)	0.599
Dynamic compliance					
5 min after induction (T1)	40.21 ± 8.57	38.00 (13.22)	39.12 ± 8.78	37.27 (8.67)	0.564
30 min after pneumoperitoneum (T2)	21.61 ± 2.96	21.11 (4.85)	21.31 ± 2.71	21.73 (3.27)	0.672
Ppeak					
5 min after induction (T1)	15.48 ± 2.39	16.00 (3.00)	16.03 ± 2.34	16.00 (4.00)	0.390
30 min after pneumoperitoneum (T2)	24 ± 2.99	24.00 (4.00)	24.7 ± 2.66	25.00 (4.00)	0.416
Pplat					
5 min after induction (T1)	14.36 ±2.4	15.00 (4.00)	14.85 ± 2.29	15.00 (3.00)	0.351
30 min after pneumoperitoneum (T2)	22.91 ± 2.96	23.00 (4.00)	23.42 ± 2.65	24.00 (4.00)	0.583

Ppeak, Peak Airway Pressure; Pplat, Plateau Pressure.

In our institute, we routinely practice low tidal volume ventilation with low PEEP, thus in this study we studied the effect of recruitment maneuver in addition to low tidal volume and PEEP to further minimize intraoperative and postoperative pulmonary complications.

The recruitment maneuver used in this study was described by Emmanuel Fu tier et al.[11] It was a slight modification of sustained inflation. We observed significant improvement ($p \leq 0.0001$) in PaO_2, PaO_2/FiO_2, P [(A-a)O_2] levels following the recruitment maneuver. Even though we did not calibrate recruited lung volume, the significant improvement in PaO_2, PaO_2/FiO_2 levels and P [(A-a)O_2] caused by recruitment maneuver might be alveolar recruitment,[12-14] which leads to reduced V/Q (Ventilation-Perfusion) mismatch.[15] We did not find any significant effect of intraoperative recruitment in any of the pulmonary function tests postoperatively. Both groups showed worse postoperative spirometry values without a difference between them. However, postoperatively, portable spirometry values deteriorated significantly in both the groups (FEV1 and FVC reduced by 25% in both the groups). The difference in the postoperative PFTs of the two groups might have been larger if we would have used the conventional mechanical ventilation technique (TV = 10—12 mL.kg^{-1}, PEEP = 0). However,

Table 5 Perioperative hemodynamics.

	Group C (n = 33)	Group C median (IQR)	Group R (n = 33)	Group R median (IQR)	*p*-value
SBP					
After induction (T1)	120.36 ± 18.44	120.00 (30.00)	123.39 ± 19.1	124.00 (27.00)	0.514
30 min (T2)	117.52 ± 14.38	118.00 (20.00)	119.54 ± 15.83	120.00 (22.00)	0.587
PACU (T4)	121.79 ± 17.13	126.00 (25.00)	123.85 ± 17.28	125.00 (26.00)	0.628
DBP					
After induction (T1)	76.76 ± 11.51	78.00 (11.00)	80.15 ± 12.6	80.00 (17.00)	0.257
30 min (T2)	74.15 ± 9.36	76.00 (11.00)	79.18 ± 11	80.00 (14.00)	0.050
PACU (T4)	76.67 ± 10.18	78.00 (13.00)	76.64 ± 10.81	76.00 (12.00)	0.991
MAP					
After induction (T1)	89.84 ± 14.93	92.33 (13.67)	94.86 ± 14.18	96.67 (15.00)	0.166
30 min (T2)	88.32 ± 10	89.33 (12.33)	91.71 ± 11.68	91.33 (13.00)	0.211
PACU (T4)	91.7 ± 11.49	94.67 (15.34)	92.37 ± 11.92	91.67 (14.67)	0.815
HR					
After induction (T1)	75.69 ± 14.02		75.96 ± 14.80		0.429
30 min (T2)	76.09 ± 12.59		74.06 ± 15.03		0.294
PACU (T4)	77.0 ± 13.06		76.84 ± 16.71		0.901

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; HR, Heart Rate. PACU, Postanesthesia Care Unit.

despite the shorter duration of surgery and minimal postoperative pain, there was a significant deterioration in PFT parameters in both groups. This was also consistent with the large trials such as iPROVE, PROVHILO, and PROBESE trials, where different perioperative open lung approaches, high PEEP, or intraoperative recruitment did not reduce the risk of postoperative complications as compared to standard lung-protective ventilation in a patient with high to moderate risk for PPCs undergoing abdominal surgery of $\geq$ 2-hour duration.[16-18] In our study the duration of surgery was less than 2 hours, thus it is not appropriate to correlate it with the findings of the above trials.

There was no significant difference in lung compliance between the two groups. This was consistent with the results of a study conducted by Severgnini et al.[19] However, many of the previously done studies concluded that pulmonary compliance increases after recruitment maneuver.[12-14] Still, these studies were done in a patient with a high risk for the development of PPCs (elderly and morbidly obese patients). In our study most of our patients were lean and were at low risk for the development of PPCs, that's why the difference in compliance might not be significant. The emphasis of this study is that short duration of surgery ($\sim$1 hour) in non-obese patients with healthy lungs led to significant deterioration of spirometry values even after 24 hours postoperatively. Different lung protective strategies need to be further explored to prevent postoperative pulmonary complications especially in vulnerable patients.

In our study, a fall in blood pressure was not seen as expected.[20] However, the majority of studies done with recruitment maneuvers are in ARDS patients and these are the patients who commonly have co-existent hemodynamic instability.[21] We did not find this complication in our patients, who were healthy, and surgery was done in a head-down position which might have led to better preload to heart. After the recruitment maneuver, diastolic blood pressure in group R (p = 0.05) was higher as compared to group C. This might be due to a reduction in intrapulmonary shunt following the recruitment maneuver.[22]

Limitations

Our study had certain limitations such as lack of titration of recruitment maneuver and PEEP in group R. The chosen method of recruitment maneuver was simpler and was very limited only considering peak pressure and taking no consideration on PEEP administration. The Contrast-Enhanced Chest Computed Tomography (CECT) (standard to diagnose postoperative atelectasis) was not done postoperatively due to economic burden to the patient and ethical problems, which might have supported the study. Lung injury biomarkers were not also measured due to financial restraints, which also might have supported the results.

Conclusions

In this population of patients undergoing elective robotic-assisted hysterectomies, there was significant deterioration in spirometry values in both groups 24 hours postoperatively. Intraoperative recruitment maneuver even with lung-protective ventilation was not preventive of postoperative deterioration of pulmonary function tests in our study population.

Conflicts of interest

There is no financial support provided for this research work contained in the manuscript. The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Efficacy of a single dose of esmolol to prevent extubation-related complications during emergence from anesthesia: a randomized, double-blind, placebo-controlled trial

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KEYWORDS
Esmolol;
Hypertension;
Tachycardia;
Tracheal extubation

Abstract
Background: Few trials have examined the efficacy of esmolol to attenuate hemodynamic and respiratory responses during extubation. However, the most appropriate dose of esmolol and an optimal protocol for administering this beta-blocker are uncertain.
Methods: Ninety patients ASA physical status I, II, and III (aged 18–60 years) scheduled to procedures with general anesthesia and tracheal extubation were selected. Patients were randomized into esmolol and placebo group to evaluate the efficacy and safety of a single bolus dose of esmolol (2 $mg.kg^{-1}$) on cardiorespiratory responses during the peri-extubation period. The primary outcome was the rate of tachycardia during extubation.
Results: The rate of tachycardia was significantly lower in esmolol-treated patients compared to placebo-treated patients (2.2% vs. 48.9%, relative risk (RR): 0.04, 95% confidence interval (95% CI) = 0.01 to 0.32, $p = 0.002$). The rate of hypertension was also significantly lower in the esmolol group (4.4% vs. 31.1%, RR: 0.14, 95% CI 0.03 to 0.6, $p = 0.004$). Esmolol-treated patients were associated with higher extubation quality compared to patients who received placebo ($p < 0.001$), with an approximately two-fold increase in the rate of patients without cough (91.1%) in the esmolol group compared to the placebo group (46.7%). The rate of bucking was approximately 5-fold lower in the esmolol group (8.9% vs. 44.5%, respectively, RR: 0.20 (95% CI, 0.1 to 0.5, $p = 0.002$, with an NNT of 2.8).
Conclusion: A single bolus dose of esmolol is an effective and safe therapeutic strategy to attenuate cardiorespiratory responses during the peri-extubation period.

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Introduction

Tracheal extubation is a critical step during anesthetic care when cardiovascular and respiratory decompensations can occur, such as tachycardia, hypertension, arrhythmias, myocardial ischemia, bronchospasm, or laryngospasm.[1,2] These potentially fatal complications related to extubation result from stimulation of the larynx, trachea, and bronchi, which increase the release of catecholamines. As a result, detailed monitoring of the cardiovascular stress response to extubation may be necessary, especially in high-risk patients.[3,4] Importantly, it has been demonstrated that the incidence of respiratory complications can be higher after extubation than during the induction of anesthesia or tracheal intubation.[1]

While several strategies have been employed to control the cardiovascular and respiratory responses to airway manipulation during the intubation period,[5–7] no standard therapy or guidelines have been established to prevent hemodynamic responses during the peri-extubation period. It has long been recognized that pharmacological strategies, such as local anesthetics, N-methyl D-aspartate (NMDA) antagonists, alpha-2 agonists, and beta-blockers can significantly reduce the rate of serious outcomes related to tracheal intubation.[5–9] In this respect, the prophylactic use of beta-blockers in the peri-extubation period has suggested a potential intervention to attenuate cardiovascular responses and decrease unfavorable events such as the reflexes of airway manipulation.[9]

Esmolol is a unique selective β1-adrenoceptor antagonist leading to reduced heart contractility, slowed atrioventricular conduction and increased atrioventricular refractoriness, which ultimately results in decreased myocardial oxygen demand.[10] Besides its cardioselectivity, this beta-blocker has become an attractive therapeutic choice in the peri-extubation period due to its rapid onset of action as well as its effects with a short duration. However, few trials have assessed whether the administration of esmolol could improve patient safety and outcomes after extubation.[11–13] Therefore, in this study, we examined the hypothesis that the administration of esmolol can reduce the incidence of cardiorespiratory responses during the peri-extubation period. Thus, this randomized trial aimed to evaluate the efficacy and safety of a single dose of esmolol (2 $mg.kg^{-1}$) infused over 2 minutes to attenuate cardiovascular and respiratory responses during the period of tracheal extubation.

Methods

Trial design

This is an investigator-initiated, double-blind, placebo-controlled trial (allocation ratio 1:1) conducted at the Hospital de Base, a tertiary hospital in Brasília, Brazil. The trial was registered at ClinicalTrials.gov (NCT04264286). Patients were recruited from February 2020 through July 2020. Ethical approval for the study was granted by the Fundação de Ensino e Pesquisa em Ciências da Saúde (FEPECS, Brasília, Brazil), with record number 3.732.847, on 28 November 2019, and registered in the Brazil platform (http://aplicacao.saude.gov.br/plataformabrasil) under the number CAAE 22078619.6.0000.8153. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

We randomly assigned 90 eligible patients to esmolol or placebo. Patients were eligible for inclusion in the trial if they were between 18 and 60 years of age with American Society of Anesthesiologists (ASA) physical status I to III. Patients scheduled to urgent or elective procedures with general anesthesia and tracheal extubation were selected. All medical specialties were evaluated.

Patients were excluded from the study if there was any contraindication or history of hypersensitivity to esmolol. Other exclusion criteria were: patients with atrioventricular block in any degree, cardiac arrhythmias, heart failure, kidney disease, a body mass index (BMI) $\geq 35\ kg.m^{-2}$, and history of asthma. Besides, we excluded patients in whom neuraxial block was performed before anesthetic induction, users of beta-blockers or calcium channel blockers, and the patients whose tracheal extubation would take place outside the operating room (e.g., in the intensive care unit [ICU]).

Procedures and interventions

Patients were identified and underwent clinical assessments according to the center's local standard practice, which included triage history, noninvasive blood pressure monitoring, oxygen saturation (SpO2), and body (tympanic) temperature measurements, assessment of bispectral index (BIS) values, and electrocardiogram recording. Patients were monitored with an A-2000 BIS monitoring system (Aspect Medical Systems, Inc., Newton, MA), and received either sevoflurane or propofol that were titrated to maintain BIS between 40 and 60. Neuromuscular monitoring was performed by acceleromyography with the recording of four sequential 50 mA stimuli (TOF-Watch® SX). Venoclysis was performed at the discretion of the anesthesiologist, based on the anesthetic needs of each participant. Midazolam (0.05 $mg.kg^{-1}$) was administered intravenously at the patient's arrival to the operating room.

Patients were maintained under general anesthesia after intubation, at the discretion of the anesthesiologist. After surgery, when the train-of-four (TOF) count was $\geq$2 responses, the dose of all anesthetics was reduced and sugammadex (2 $mg.kg^{-1}$) was used to reverse deep neuromuscular blockade. When the T4/T1 ratio exceeded 90%, anesthetics were discontinued, and the study interventions (esmolol or placebo) were infused over two minutes (two minutes before extubation). Extubation was performed after postoperative neurological assessment indicating spontaneous respiration, eye-opening, and/or voluntary movements.

For the patients in the esmolol group, a solution of 2 $mg.kg^{-1}$ diluted in 20 ml was used, while for the placebo group 0.9% saline solution (20 ml) was applied.

Vital measurements such as heart rate (HR) and systolic blood pressure (SBP) were evaluated at multiple time points: T_0: Pre-infusion (one minute before the study drugs were infused), T_1: First minute of the infusion (after one minute of

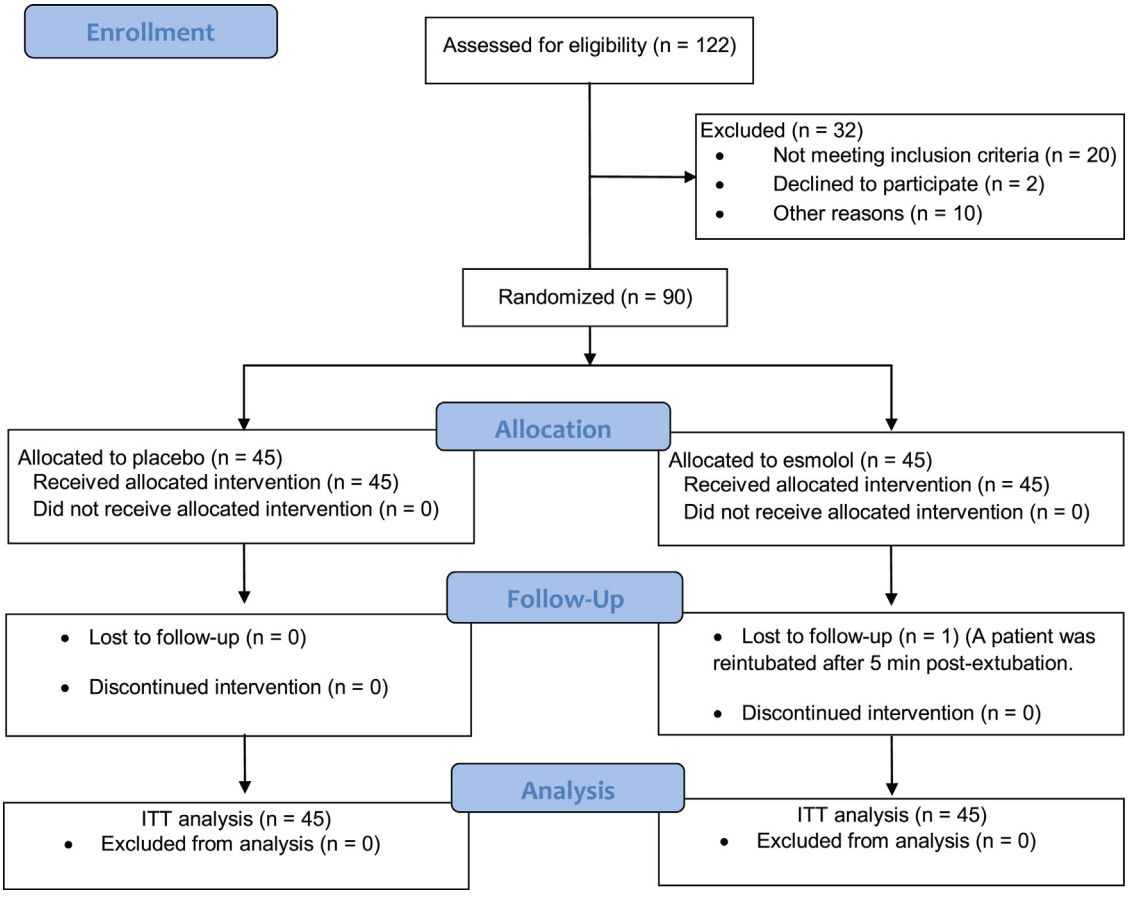

Figure 1 Flow diagram of participants through the trial. ITT denotes intention-to-treat.

the infusion); T_2: End of infusion (at the end of infusion); T_3: Extubation (during extubation); T_4: One minute after extubation; T_5: Three minutes after extubation. T_6: Five minutes after extubation. T_7: Ten minutes after extubation.

The quality of extubation was assessed using a 5-point numeric rating scale with lower scores representing better quality of extubation: 1 = no coughing, 2 = minimal coughing (1 or 2 coughing episodes) or transient cough in response to the removal of the tube that resolved with extubation, 3 = moderate coughing (3 or more coughing episodes lasting up to 5 seconds), 4 = severe coughing (4 or more coughing episodes lasting more than 5 seconds) and symptoms of labored breathing, and 5 = serious coughing with laryngospasm.[13]

Bradycardia cases were managed by a bolus dose of atropine 0.5 mg intravenous, whereas clonidine 1 $mcg.kg^{-1}$ was used to control hypertension and/or tachycardia. Patients that developed hypotension were administered ephedrine (5 mg). In the case of laryngospasm, treatment consisted of the administration of 100% oxygen with positive pressure. Unresponsive cases were further treated with intravenous administration of 0.25 $mg.kg^{-1}$ of succinylcholine. All patients were given oxygen (concentration of 100% at 5 $l.min^{-1}$ via standard face mask.

According to the hospital standard care guidelines, all patients received metamizole (2 g) [except when any allergy was reported], parecoxib (40 mg), or tenoxicam (40 mg) [except in cases of contraindication to anti-inflammatory drugs], and morphine or tramadol for postoperative analgesia at the end of the surgical procedure and before extubation. Opioid choice was at the discretion of the anesthesiologist according to the patient's profile and surgical size. While we verified that all patients received adequate analgesia at the end of the surgery, individual records were not acquired.

Outcomes

The primary outcome was the rate of patients with tachycardia during and after extubation. Secondary outcomes were the rate of hypertension, bradycardia, hypotension, coughing, bucking, extubation quality scores, and variations in SBP and HR levels and adverse events. Hypertension was defined as SBP above 120% of the baseline value or >140 mmHg, while hypotension was defined as SBP below 80% of baseline value or <90 mmHg. Tachycardia was defined as HR above 120% of the baseline value or >100 bpm. Absolute bradycardia was defined as HR less than 50 bpm. The incidence of hypertension, hypotension, tachycardia, bradycardia, and adverse events were recorded throughout the study period.

Sample size

Sample size calculations were based on a pilot cross-sectional study, which found a prevalence of 45% of

tachycardia among patients undergoing surgical procedures at our center. Thus, assuming a type-I error (alpha) of 5% (two-tailed), 38 patients in each group were randomized to detect a reduction of 35% percentage points in the rate of tachycardia in the esmolol group compared to placebo (45% vs. 10%) with 90% power. The final sample size was increased by a further 15% (90 patients in total, 45 participants in each group) to allow potential dropouts.

Randomization and allocation concealment

We used a computer-generated, centrally concealed randomization sequence. Furthermore, we employed syringes sequentially numbered and packaged in opaque and sealed containers. Specifically, syringes containing esmolol or placebo were centrally prepared, pre-coded based on the randomization list, and sent sequentially to the operating room immediately before administration. Blinding occurred at the level of patients, surgery staff and outcome assessors. Both drug and placebo solutions were identical in appearance, volume, viscosity, and odor and were prepared by an investigator no involved in recruitment or patient care.

Statistical analysis

Results are summarized as mean (standard deviation), number (percentage), and relative risk (RR) with a 95% confidence interval (95% CI). Dichotomous and categorical variables were compared with chi-square tests. The Student's *t*-test was used to compare the treatment groups with respect to continuous variables. We used linear mixed-effects models to investigate the effect of esmolol and placebo on blood pressure and heart rate levels over time. Time and treatment groups were considered fixed-effects and were treated as categorical variables. Interaction terms between time and treatment group were used in addition to a random intercept for each patient. All statistical analyses were based on an intention-to-treat (ITT) principle, in which all patients randomized were included in the analyses, regardless of protocol deviations or actual treatment received. A p-value < 0.05 (two-tailed) was considered statistically significant. We also estimated the number of patients who needed to be treated to prevent one event (NNT) as the reciprocal of the risk difference between the esmolol and placebo groups. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Macintosh (Chicago, IL, USA) and Stata 14 (College Station, Texas, USA).

Results

A total of 122 patients were screened in this randomized trial. Of these, 32 did not meet the eligibility criteria (Fig. 1). Thus, 90 patients were assigned to either the esmolol group (n = 45 participants) or the placebo group (n = 45 participants). The mean age was 46.7 years (range 18 to 70 years), 53 participants (58.9%) were female, and the study sample had an average BMI of 24.8 $kg.m^{-2}$ (range 16 to 32.3 $kg.m^{-2}$). As shown in Table 1, central randomization generated groups well balanced in terms of prognostic factors and demographic characteristics. Moreover, the distribution of surgical procedures across different specialties was comparable between the groups, and no medical specialty was seriously over-represented in the study sample. Perioperative care measures were also similar between groups (Table 2).

Table 1 Participant demographics, clinical baseline characteristics and perioperative care measures.

Variable	Placebo (n = 45)	Esmolol (n = 45)
Age (years), mean (SD)	44.2 (15.1)	49.2 (12.8)
Height (meters), mean (SD)	1.65 (0.1)	1.67 (0.1)
Weight (kg), mean (SD)	68.9 (10.3)	68.7 (9.7)
BMI ($kg.m^{-2}$), mean (SD)	25.1 (3.5)	24.4 (2.5)
Female, n (%)	29 (64.4)	24 (53.3)
ASA, n (%)		
I	9 (20.0)	10 (22.2)
II	24 (53.3)	27 (60.0)
III	12 (26.7)	8 (17.8)
Hypertension, n (%)	13 (28.9)	20 (44.4)
Diabetes, n (%)	7 (15.6)	11 (24.4)
Obesity, n (%)	4 (8.9)	2 (4.4)
Type of surgery, n (%)		
Elective	40 (88.9)	39 (86.7)
Urgency	5 (11.1)	6 (13.3)
Medical specialty, n (%)		
Bronchoesophagology	4 (8.9)	0
Maxillofacial surgery	4 (8.9)	4 (8.9)
Head and neck surgery	5 (11.1)	1 (2.2)
Coloproctology	1 (2.2)	3 (6.7)
General surgery	8 (17.8)	7 (15.6)
Mastology	3 (6.7)	4 (8.9)
Neurosurgery	5 (11.1)	6 (13.3)
Oncological surgery	5 (11.1)	3 (6.7)
Orthopedics	2 (4.4)	1 (2.2)
Otorhinolaryngology	3 (6.7)	6 (13.3)
Thoracic surgery	4 (8.9)	5 (11.1)
Urology	0	3 (6.7)
Vascular surgery	1 (2.2)	2 (4.4)

ASA, American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation.

A patient in the esmolol group was reintubated after 5 minutes because of a seizure event, whereas a patient in the placebo group was given clonidine for the management of a serious hypertensive episode. However, both patients were included in the ITT analysis.

Primary outcome

The rate of tachycardia was 48.9% in the placebo group (22 of 45 patients), as compared with 2.2% (1 of 45 patients) in the esmolol group (relative risk [RR], 0.04; 95% confidence interval [CI], 0.01 to 0.3; $p = 0.002$) (Table 2), with an NNT of 2.1.

Table 2 Perioperative care measures.

Variable	Placebo (n = 45)	Esmolol (n = 45)	p[a]
General anesthetic (anesthesia maintenance), n (%)			
Sevoflurane	29 (64.4)	24 (53.3)	0.28
Propofol	16 (35.6)	21 (46.7)	
Opioid supplement to general anesthesia, n (%)			
Fentanyl (induction and maintenance)	15 (33.3)	16 (35.6)	0.82
Fentanyl (induction) and remifentanil (maintenance)	30 (66.7)	29 (64.4)	
Duration of anesthesia, mean (SD), min	215.8 (104.5)	222.3 (94.1)	0.76
Operative time, mean (SD), min	163.3 (91.4)	171.3 (89.0)	0.68

[a] Continous variables were tested by t-tests. Categorical variables were tested via chi-squared tests.

Table 3 Primary and secondary outcomes.

	Placebo (n = 45)	Esmolol (n = 45)	RR (95% CI)	p-value
Primary outcome				
Tachycardia, n (%)	22 (48.9)	1 (2.2)	0.04 (0.01 to 0.3)	0.002[a]
Secondary outcomes				
Bradycardia, n (%)	0	1 (2.2)	3.00 (0.1 to 71.7)	0.50
Hypertension, n (%)	14 (31.1)	2 (4.4)	0.14 (0.03 to 0.6)	0.007[a]
Hypotension, n (%)	0	5 (11.1)	11.0 (0.6 to 193.0)	0.10
Quality of extubation, n (%)				
No coughing	21 (46.7)	41 (91.1)	1.95 (1.4 to 2.7)	< 0.001[a]
Minimal coughing	14 (31.1)	3 (6.7)	0.31 (0.1 to 0.9)	0.003[a]
Moderate coughing	8 (17.8)	1 (2.2)	0.20 (0.03 to 1.3)	0.01[a]
Severe coughing	0	0	–	–
Serious coughing with laryngospasm	2 (4.4)	0	0.20 (0.01 to 4.1)	0.30
Safety outcomes				
Bucking, n (%)	20 (44.4)	4 (8.9)	0.20 (0.1 to 0.5)	0.002[a]
Laringoespasm, n (%)	2 (4.4)	0	0.20 (0.01 to 4.1)	0.30
Broncoespasm, n (%)	1 (2.2)	0	0.33 (0.01 to 8.0)	0.50

RR denotes relative risk. 95% CI denotes 95% confidence interval. For 2 × 2 tables with zero events in a cell, a continuity correction was applied by adding 0.5 to each cell.
[a] $p < 0.05$ was considered statistically significant. Results are based on chi-square tests.

Secondary outcomes

Fewer patients in the esmolol group than in the placebo group developed hypertension (RR, 0.14; 95% CI, 0.03 to 0.6, with an NNT of 3.1). However, the rate of bradycardia or hypotension did not differ significantly between the two groups.

A significant difference in heart rate levels between esmolol and placebo was found from extubation (T_3) to 10 minutes after extubation (T_7) (Fig. 2 and Table 4). Patients who received esmolol had, on average, heart rate levels approximately 20% lower compared to patients who received placebo. Similar results were observed for systolic blood pressure levels, which were approximately 12% lower in patients that received esmolol compared to patients that received placebo between time points T_3 and T_7 (Fig. 2 and Table 4).

Esmolol-treated patients were associated with a higher quality of extubation compared to patients who received placebo (chi-squared test, $p < 0.001$), with an approximately two-fold increase in the rate of patients without cough (91.1%) in the esmolol group compared to the placebo group (46.7%) (Table 3).

Safety

One patient in the esmolol group was reintubed due to seizure episode. This event was considered unrelated to the study drug by the treating clinical team. The rate of bucking was approximately 5-fold lower in the esmolol group compared to placebo (8.9% vs. 44.5%, respectively, RR: 0.20 (95% CI, 0.1 to 0.5, $p = 0.002$, with an NNT of 2.8). The overall rate of laryngospasm and bronchospasm was low in the study population, with two episodes of laryngospasm and only one episode of bronchospasm, all in the placebo group (Table 3).

Discussion

In this randomized trial, treatment with esmolol resulted in a significantly lower rate of tachycardia and hypertension compared to placebo. Analyses considering the trajectory of systolic blood pressure and heart rate levels over time confirmed the findings of the primary outcome, indicating that esmolol offers persistent effects for up to 10 minutes after extubation.

In the present trial, we examined the efficacy of esmolol 2 mg.kg^{-1} in a single dose to attenuate the hemodynamic response to extubation. Other drugs have been used to control hemodynamic changes to endotracheal intubation and extubation. For instance, Bostan et al. investigated the effects of esmolol (1 mg.kg^{-1}), fentanyl (1 μg.kg^{-1}), and lidocaine (1 mg.kg^{-1}) during laryngoscopy, intubation, and extubation. Esmolol treatment was associated with significantly lower systolic and diastolic blood pressure and heart rate levels compared to the other drugs, primarily in the first, third, and fifth minutes after extubation. Nonetheless, the rates of tachycardia and hypertension were not investigated.[14] Shrestha et al. also compared esmolol to lidocaine 1 mg.kg^{-1} in relation to their hemodynamic effects on extubation.[15] The authors observed that a higher dose of esmolol (1.5 mg.kg^{-1}) offered better control of heart rate than lidocaine at the moment of oropharyngeal suctioning and at 1 minute after extubation. Additionally, esmolol-treated patients displayed lower SBP levels during oropharyngeal aspiration, extubation, and 3 minutes after extubation. In contrast to the results reported by Bostan et al.,[14] esmolol at the dose of 1.5 mg.kg^{-1} failed to control heart rate levels during or after the first minute post-extubation. Similar results were observed for SBP levels, which were indistinguishable between the esmolol and lidocaine groups after the third minute of post-extubation. By using a higher dose of esmolol, our results are in partial agreement with those findings and complement those previous findings demonstrating the efficacy and adequate safety profile of a higher dose of esmolol in achieving longer hemodynamic stability during the peri-extubation period.

Of note, while a single dose of esmolol 2 mg.kg^{-1} infused over 2 minutes was administered in our trial, our results are consistent with those reported Alkaya et al. who compared esmolol (infused over 10 minutes at a dose of 0.2 μg.kg^{-1}.min^{-1}) to placebo in the prevention of hemodynamic responses to tracheal extubation after craniotomy.[11] Lower levels of SBP were observed in the esmolol group during extubation and 1, 3, and 5 minutes after extubation. There was also evidence for lower heart rate levels in the esmolol group compared to the placebo-treated patients 10 minutes after extubation. Thus, our results may indicate that the strategy employed in our trial not only facilitates administration but also augments adherence by anesthesiologists, without jeopardizing clinical outcomes.

The safety of beta-blockers to blunt hemodynamic response after extubation has been discussed previously.[16–18] In a head-to-head trial examining beta-blockers only, Prajwal et al. compared the hemodynamic effects of esmolol (an ultra-short-acting β-blocker) at a dose of 1.5 mg.kg^{-1} to labetalol (a nonselective β-antagonist with α1-antagonist activity with a longer half-life) at a dose of 0.25 mg.kg^{-1}.[16] This trial showed that labetalol promoted a lower heart rate at 5 and 15 minutes after extubation, with no significant difference compared to esmolol during extubation or in the first initial minutes post-extubation. Esmolol-treated patients, on the other hand, displayed significantly lower SBP levels in the second and third minutes after extubation than patients treated with labetalol. Nonetheless, for SBP levels, no difference between these two beta-blockers was detected during extubation and at 4 and 5 minutes after extubation. According to the authors, labetalol might be more effective at controlling heart rate levels, whereas esmolol might be more effective at controlling blood pressure levels. A major limitation of that trial was that the rates of tachycardia or hypertension were not assessed.[16] Overall, our trial corroborates the notion that treatment with esmolol 2 mg.kg^{-1} offers a significant control of blood pressure and heart rate levels, and may be associated with a lower risk of adverse events than other longer-life beta-blockers, such as atenolol or metoprolol.[17,18]

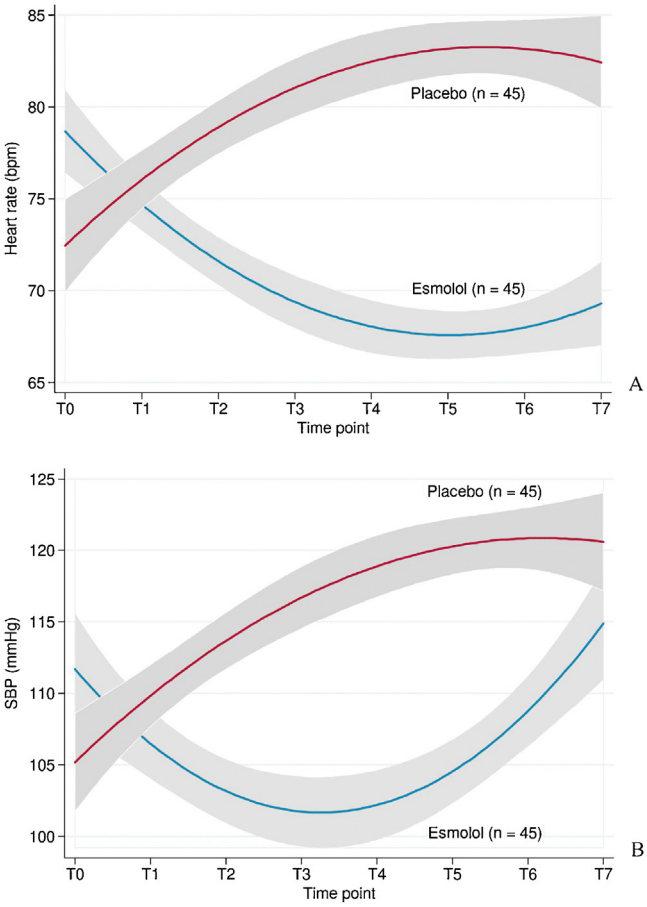

Figure 2 Prediction plots for heart rate (panel A) and systolic blood pressure (panel B). A quadratic model was used to represent graphically the trajectory of systolic blood pressure (SBP) and heart rate levels over time. Results are displayed as predicted means (lines) and approximate 95% confidence intervals (shaded areas). The esmolol group is represented by blue lines, whereas the placebo group is represented by red lines. T_0: Pre-infusion (one minute before the study drugs were infused), T_1: First minute of the infusion; T_2: End of infusion (at the end of infusion); T_3: Extubation; T_4: One minute after extubation; T_5: Three minutes after extubation. T_6: Five minutes after extubation. T_7: Ten minutes after extubation.

Regarding the optimal doses of esmolol, a previous placebo-controlled trial in patients undergoing lumbar disc herniation surgery tested the effect of esmolol using a bolus dose of 0.5 mg.kg^{-1} followed by a dose maintenance interval of 0.1 (experimental group 1) or 0.2 mg.kg^{-1}.min^{-1} (experimental group 2) until the 10th minute after extubation.[19] Although the authors did not report any difference between the placebo and esmolol groups in the hemodynamic

Table 4 Heart rate and systolic blood pressure levels during the peri-extubation period.

Variable	Placebo (n = 45)	Esmolol (n = 45)	Mean difference (95% CI)	*p*-value
Heart rate, mean (SD), bpm				
T_0	74.3 (10.2)	77.8 (10.1)	3.83 (-0.2 to 7.9)	0.06
T_1	74.7 (10.8)	74.7 (9.3)	0.37 (-3.7 to 4.4)	0.96
T_2	74.8 (10.7)	70.7 (9.2)	-3.62 (-7.7 to 0.4)	0.08
T_3	86.1 (10.3)	71.2 (8.7)	-13.5 (-17.6 to -9.5)	< 0.001[a]
T_4	85.0 (9.6)	68.7 (9.4)	-14.6 (-18.6 to -10.5)	< 0.001[a]
T_5	84.0 (9.2)	65.4 (7.7)	-16.8 (-20.9 to -12.8)	< 0.001[a]
T_6	84.2 (9.6)	65.4 (7.6)	-17.7 (-21.8 to -13.7)	< 0.001[a]
T_7	83.1 (8.2)	71.2 (7.5)	-11.1 (-15.2 to -7.1)	< 0.001[a]
Systolic blood pressure, mean (SD), mmHg				
T_0	108 (13.4)	110.4 (15.1)	2.47 (-3.6 to 8.6)	0.43
T_1	107.6 (13.1)	107.5 (14.3)	-0.18 (-6.3 to 5.9)	0.95
T_2	108.3 (12.9)	102.9 (13.6)	-5.40 (-11.5 to 0.7)	0.08
T_3	120.4 (14.5)	104.9 (15.6)	-15.5 (-21.6 to -9.4)	< 0.001[a]
T_4	121.0 (16.2)	101.7 (17.5)	-19.2 (-25.3 to -13.1)	< 0.001[a]
T_5	119.4 (14.3)	101.0 (17.4)	-18.4 (-24.5 to -12.3)	< 0.001[a]
T_6	121.7 (13.1)	108.5 (17.1)	-13.3 (-19.5 to -7.2)	< 0.001[a]
T_7	119.4 (12.1)	116.3 (14.6)	-3.14 (-9.3 to 3.0)	0.31

Mean differences and 95% confidence intervals (95% CI) are marginal predictions based on the mixed-effects models. T_0: Pre-infusion (one minute before the study drugs were infused), T_1: First minute of the infusion ; T_2: End of infusion (at the end of infusion); T_3: Extubation; T_4: One minute after extubation; T_5: Three minutes after extubation. T_6: Five minutes after extubation. T_7: Ten minutes after extubation.

[a] $p < 0.05$ was considered statistically significant. Results are based on mixed-effects models.

response in the initial minutes, the rate of hypertension was notably lower in patients treated with esmolol. In that trial, there was evidence of dose-response effects, with faster recovery times observed in patients who received the highest dose of the beta-blocker. Thus, it is possible that the dose of esmolol is a critical factor in attenuating the response to extubation, with smaller doses being less effective compared to higher doses, even when associated with a continuous maintenance dose.

In line with the abovementioned observations, another trial found that a high dose of esmolol (2 $mg.kg^{-1}$ in bolus) reduced systolic blood pressure during extubation, but that a lower dose (1 $mg.kg^{-1}$ in bolus) was insufficient to prevent the incidence of hypertension.[12] Our trial adds further evidence suggesting that a single large dose of esmolol might be an optimal strategy to attenuate the increases in heart rate and systolic blood pressure levels simultaneously.

Concerning the most suitable administration protocol, a previous trial indicated that the proportion of patients without cough and with normal breathing was higher in the esmolol group (2 $mg.kg^{-1}$) compared to the placebo group.[11] In contrast to that trial, in which a dose of esmolol of 2 $mg.kg^{-1}$ via a 10-minute infusion was used, our trial used a 2-minute infusion protocol. Thus, our findings strengthen the hypothesis that the suppressive effects of esmolol on airway reflexes during the peri-extubation period could be independent of administration protocol.

Further investigations would be valuable in determining how the respiratory effects are mediated by esmolol. It is conceivable that a higher dose of esmolol is sufficient to inhibit cough triggering mechanisms via blockage of ion channels. The majority of the vagal afferent nerves responsible for triggering the cough reflex are composed of unmyelinated C fibers,[20] and the afferent nerve endings are found in abundance in the mucosa and the walls of the upper airways to the proximal bronchioles.[21] These fibers express a variety of receptors and ion channels that trigger coughing when activated, with the onset and spread of action potentials in afferent sensory nerves being mediated by voltage-dependent sodium channels.[22] A preclinical study investigated the properties of ultra-short-acting β1 blockers, and demonstrated that esmolol can block voltage-dependent sodium channels in sensory neurons in a dose-dependent manner.[23] Another study also showed that esmolol can inhibit L-type calcium channels, which would have an additional effect on fast sodium channels, being responsible for suppressing the conduction of the action potential.[24]

Some limitations of this trial should be considered. First, for safety concerns, we excluded patients with coronary artery disease and those who had been prescribed beta-blockers. Thus, the generalizability of our results can be limited. Second, our trial was underpowered to detect uncommon or rare adverse events. Third, we were unable to follow-up patients to examine the impact of esmolol treatment on postoperative pain levels, recovery time, and hospital length of stay. Fourth, we enrolled both emergency and elective cases, used different agents for postoperative analgesia, and the trial protocol did not specify the time intraoperative administration of analgesic agents. All these aspects could introduce clinical and methodological heterogeneity, causing our estimates to be less precise. Fifth, we included patients undergoing different surgical procedures, making the study conclusions more pragmatic than trials conducted within a single medical specialty. However, although the distribution of surgeries within medical spe-

cialties was similar between esmolol-treated patients and placebo-treated patients, it is possible that the specific type of surgeries differed slightly between the groups. However, the randomization was performed with adequate computer-generated methods and allocation concealment, decreasing the risk of selection biases. Finally, our trial may be underpowered to detect the effects of esmolol on the secondary outcomes. However, our study can serve as the basis for further investigations appropriately designed to elucidate the effects of esmolol on respiratory outcomes.

Conclusion

Altogether, our findings indicate that a single bolus dose of esmolol (2 mg.kg^{-1}) infused over 2 minutes is effective and safe to attenuate cardiovascular and respiratory responses in the period of peri-extubation. Our results suggest that esmolol has great potential to be included as a standard therapy during extubation.

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Role of melatonin in attenuation of hemodynamic response to intubation and anesthetic requirements: a randomized, controlled, double-blind study

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Abstract

Background: Melatonin has been studied to have anxiolytic, sedative, and analgesic effects. However, there is limited data on the effect of melatonin in the attenuation of hemodynamic response to intubation. We aimed to study whether preanesthetic oral melatonin attenuates hemodynamic responses to intubation and anesthetic requirements.

Methods: Sixty-four patients scheduled for laparoscopic cholecystectomy were randomized into melatonin or placebo group (n = 32 each). Melatonin group received two tablets (3 mg each) of melatonin, and the placebo group received two tablets of vitamin D3 120 min before induction. Hemodynamic parameters were recorded during induction and postintubation for 15 minutes. Total induction dose of propofol, total intraoperative fentanyl consumption, and adverse effects of melatonin were also noted.

Results: Postintubation rise in heart rate (HR) was less in the melatonin group compared to the placebo group (10.59% vs. 37.08% at 1 min, respectively) ($p < 0.0001$). Maximum percentage increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) was lesser in melatonin group than placebo group (SBP 9.25% vs. 37.73%, DBP 10.58% vs. 35.51%, MBP 9.99% vs. 36.45% at 1 min postintubation. respectively) ($p < 0.0001$). Induction dose of propofol (1.42 $mg.kg^{-1}$ vs. 2.01 $mg.kg^{-1}$) and the number of patients requiring additional fentanyl intraoperatively (3 vs. 11) were also significantly reduced in the melatonin group.

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Conclusion: Premedication with 6 mg of oral melatonin resulted in significant attenuation of postintubation rise in HR, SBP, DBP, and MBP. It also reduced the induction dose of propofol, total intraoperative fentanyl consumption without any adverse effects.

Introduction

Laryngoscopy and endotracheal intubation are some of the most noxious stimuli in anesthesia, which trigger reflex responses resulting in a marked increase in heart rate and blood pressure.[1] Such response is well tolerated by healthy individuals, but is associated with increased morbidity and mortality in patients with underlying coronary artery disease or cerebrovascular pathology. Various techniques and drugs have been used to attenuate these stress responses but each agent or technique has some limitation and therefore, there has always been a search for a new therapeutic option.[2–4]

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally-occurring hormone in the human body secreted by the pineal gland. Various studies have evaluated its hypnotic, sedative, analgesic, anxiolytic, anti-inflammatory, and antioxidative effects.[5] Melatonin has also been studied to decrease blood pressure along with the reduction of norepinephrine concentration.[6] Considering the above effects of melatonin and very limited study on the effect of melatonin on the attenuation of hemodynamic response to intubation as well as anesthetic requirements, we aimed to study whether preanesthetic oral melatonin attenuates hemodynamic responses to intubation and anesthetic requirements. Our hypothesis was that oral melatonin premedication will attenuate hemodynamic response to intubation and will decrease the induction dose of propofol and intraoperative fentanyl consumption. The primary objective of the present study was to observe the changes in hemodynamics during laryngoscopy and intubation.

Methods

This prospective, randomized, double-blinded study was conducted after obtaining approval from Institutional Ethics Committee (Reference no. F. 1/Acad/MC/JU/17/17558), and registered under the clinical trial registry of India (CTRI/2018/12/016498). After written informed consent, 64 patients of either sex, aged 18 to 60 years, American Society of Anesthesiologists (ASA) physical status I/II, who were scheduled to undergo elective laparoscopic cholecystectomy surgery under general anesthesia requiring tracheal intubation were included in the study. The exclusion criteria were anticipated difficult airway, body mass index (BMI) > 30 $kg.m^{-2}$, patients taking anxiolytics, sedatives, antipsychotic, or antiepileptic drugs, patients having a sleep disorder, hiatus hernia, gastroesophageal reflux, known allergy to melatonin, and a known case of coronary artery disease.

Using computer-generated random number table, 64 consecutive eligible patients were randomly allocated to either the melatonin group (n = 32) or placebo group (n = 32), and allocation concealment was done using sealed opaque envelopes. Melatonin group patients received two tablets (3 mg each) of melatonin and placebo group patients received two tablets of vitamin D3, 120 minutes before induction. The study drugs of both groups were the same in size and color, given by the nursing staff in the preoperative ward. The contents of tablets were unknown to the anesthesiologist involved in providing general anesthesia and recording observations.

One day before surgery, all patients underwent a detailed preoperative anesthesia evaluation and were kept fasting as per standard ASA protocol. All patients received oral alprazolam 0.25 mg and pantoprazole 40 mg the night before the surgery. On arrival to the operation theater, standard monitoring – pulse oximetry, noninvasive arterial blood pressure, electrocardiography, and capnography (S/5™DatexOhmeda USA) – was applied, and baseline parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and arterial oxygen saturation (SpO2) were recorded.

After recording baseline parameters, all patients received injection of fentanyl 2 $\mu g.kg^{-1}$. After preoxygenation with 100% oxygen for 3 minutes, anesthesia was induced with propofol 1% injection mixed with preservative-free lignocaine hydrochloride (20 mg in 10 ml propofol) administered by slow manual bolus till the loss of verbal response. Vecuronium bromide 0.1 $mg.kg^{-1}$ injection was administered to facilitate tracheal intubation, and the patient's lungs were manually ventilated for 3 minutes with 100% oxygen. Direct laryngoscopy was performed with Macintosh laryngoscope, and the trachea was intubated with an appropriate size cuffed endotracheal tube by the same person each time. The lungs were ventilated with a tidal volume of 6–8 $mL.kg^{-1}$ using volume-controlled ventilation with 5 cmH2O positive end-expiratory pressure (PEEP). The respiratory rate was adjusted to maintain an end-tidal carbon dioxide partial pressure ($EtCO_2$) 30–35 mmHg with an inspiratory/expiratory ratio of 1:2. Anesthesia was maintained with air (50%), oxygen (50%), isoflurane with a minimum alveolar concentration (MAC) of 1.0. Intraoperatively, supplemental analgesia was provided with fentanyl (0.5 $\mu g.kg^{-1}$) injection bolus if HR or mean blood pressure (MBP) exceeded 30% of the preoperative values after excluding other causes like a light plane of anesthesia or creation of pneumoperitoneum. At the end of the surgery, all the patients received ondansetron 0.1 $mg.kg^{-1}$ and diclofenac sodium 1 $mg.kg^{-1}$ injection for postoperative emesis and analgesia, respectively. After completion of the surgery, residual neuromuscular blockade was antagonized with neostigmine 0.05 $mg.kg^{-1}$ and glycopyrrolate 0.01 $mg.kg^{-1}$. Once awake and responsive, the patient was extubated and shifted to the postanesthesia care unit (PACU).

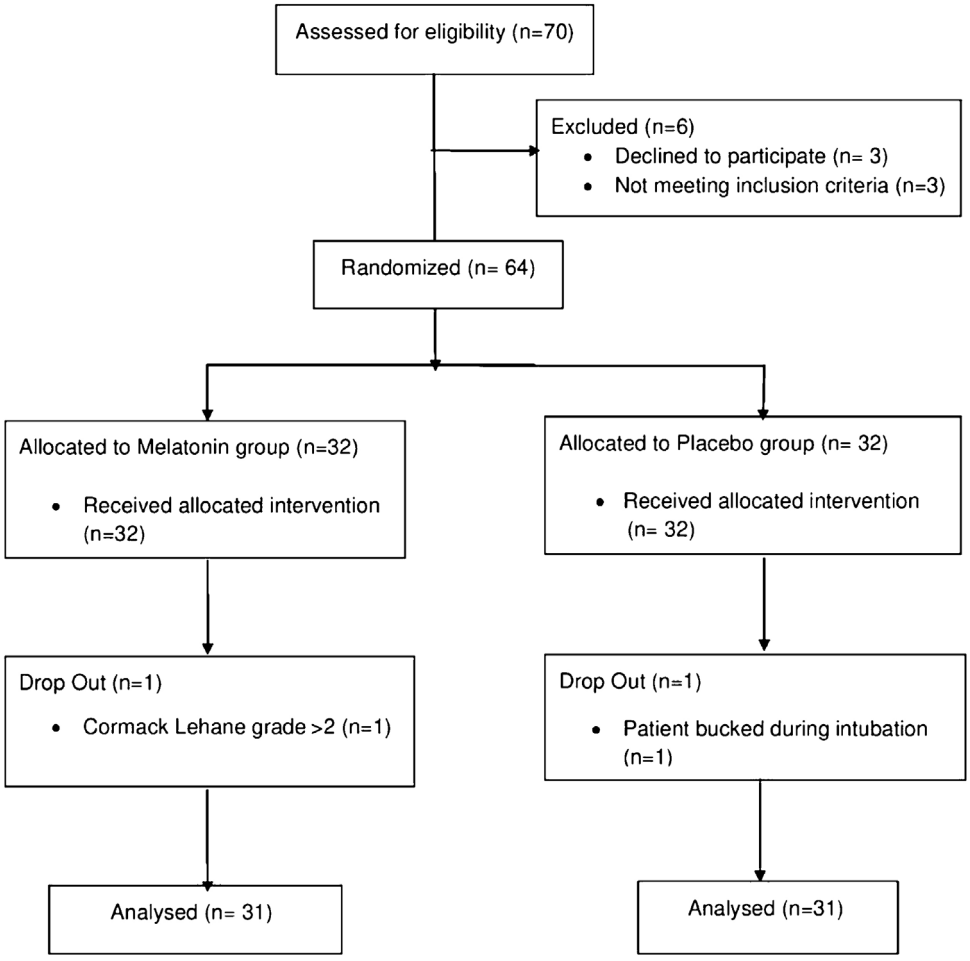

Figure 1 CONSORT flow diagram.

The primary objective of the present study was to observe the changes in hemodynamics during laryngoscopy and intubation for which HR, SBP, DBP, MBP, SpO_2, $EtCO_2$ were continuously monitored and recorded at baseline (T0), 120 minutes after administration of study drug on arrival to operation theater (T1), after induction (T2), just before laryngoscopy and intubation (T3), after intubation at 1-min (T4), 3-min (T5), 5-min (T6), 10-min (T7) and 15-min (T8) intervals. During the study, the total dose of propofol required for induction and the number of patients requiring additional fentanyl intraoperatively were also recorded, which were the secondary objectives of study. Side effects of the study drugs like bradycardia, hypotension, nausea, vomiting, dizziness, headache, and respiratory depression were also observed till 24 hours postoperatively. The case was dropped from the study if the patient moved or bucked during laryngoscopy or intubation, Cormack Lehane grade[7] more than 2, or more than one attempt required for intubation.

The sample size was calculated for the primary objective to detect a minimum significant difference in heart rate at 1-min postintubation based on results of the pilot study conducted on 10 patients in each group. Based on the results of the pilot study, to detect a minimum of 19 ± 22 beats/min difference in HR between the two groups 1-min postintubation a sample size of a minimum of 28 in each group was required with a power of 90% and alpha error of 0.05. Considering 10% attrition, the sample size was further enhanced and rounded to 31 in each group.

Statistical analysis was done using SPSS software version 20 (trial version) (SPSS Inc., Chicago, IL, USA). All quantitative variables were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation and standard error). The normality of data was checked by measures of skewness and Kolmogorov-Smirnov tests of normality. Demographic data were analyzed by Student's t-test and Chi-square test. ANOVA was used to analyze changes over time. Intergroup comparisons for hemodynamic parameters were made with unpaired t-test.

Results

A total of 70 patients were assessed for eligibility, 6 patients were excluded, and 64 patients were included in the study and of which 2 were dropped out and finally, the results of 62 patients were analyzed (Fig. 1). The demographic characteristics of the patients, ASA physical status, patients on beta-blockers as antihypertensives, and duration of surgery were comparable between both groups (Table 1). Baseline

Table 1 Demographic characteristics.

	Melatonin Group (n = 31)	Placebo Group (n = 31)	*p*
Age (years) (mean ± SD)	41.13 ± 10.43	40.13 ± 11.00	0.720
Weight (kg) (mean ± SD)	52.66 ± 5.03	52.26 ± 2.85	0.706
Sex (M/F) (numbers)	20/11	18/13	0.789
ASA (I/II) (numbers)	23/8	25/6	0.731
Patients on beta-blockers (n)	3	3	1
Duration of surgery (mean ± SD)	47.90 ± 8.08	49.30 ± 6.22	0.414

ASA, American Society of Anesthesiologists physical status.
Unpaired t-test used for comparing age, weight, and duration of surgery. Chi-Square test used for comparing sex, ASA physical status, and patients on beta-blockers.

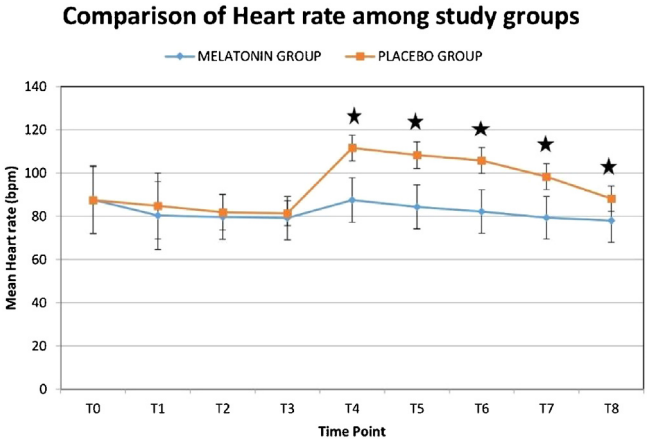

Figure 2 Comparison of heart rate among the study groups. T0, baseline; T1, 120 min after administration of study drug on arrival to operation theater; T2, after induction; T3, just before laryngoscopy and intubation; T4, 1 min after intubation; T5, 3 min after intubation; T6, 5 min after intubation; T7, 10 min after intubation; T8, 15 min after intubation.
p-value < 0.0001.
ANOVA used to analyze changes over time. Unpaired *t*-test used for intergroup comparisons.

hemodynamic parameters were comparable between the two groups.

Figure 2 depicts the trend of HR in the melatonin and placebo groups. Two hours after administration of the study drug, a fall in HR was observed in the melatonin group as compared to baseline value and was also lower than that of the placebo group at all time intervals. After laryngoscopy and intubation an increase in HR was seen in both groups compared to preintubation value but the rise in HR was significantly less in the melatonin group compared to the placebo group (10.59% vs. 37.08% at 1 min and 6.60% vs. 33.08% at 3 min, respectively) which stabilized after 5 minutes in melatonin group, but the increased HR persisted even till 15 minutes postintubation in the placebo group. A significant difference in HR was observed between the two groups at all time points postintubation ($p < 0.001$) (Fig. 2).

After oral intake of the study drug, significantly lower SBP, DBP, and MBP were seen in the melatonin group compared to baseline and was also lower than that of the placebo group, at almost all time intervals (Fig. 3A-C). After laryngoscopy and tracheal intubation, compared to preintubation value, the increase in SBP, DBP, and MBP were significantly lower in the melatonin group than in the placebo group (SBP 9.25% vs. 37.73%, DBP 10.58% vs. 35.51%, MBP 9.99% vs. 36.45% at 1 min postintubation, respectively). Postintubation at all time points, a significant difference in SBP, DBP, and MBP was observed between the two groups ($p < 0.001$) (Fig. 3A-C).

The mean total induction dose of propofol in the melatonin and placebo group was 74.21 ± 12.483 mg and 118.00 ± 16.361 mg, respectively, which was equivalent to 1.42 $mg.kg^{-1}$ and 2.01 $mg.kg^{-1}$ respectively, and the difference was statistically significant ($p < 0.001$). In addition to an induction dose of fentanyl (2 $\mu g.kg^{-1}$), 11 patients in the placebo group and 3 patients in the melatonin group needed additional fentanyl boluses (0.5 $\mu g.kg^{-1}$) intraoperatively ($p = 0.031$) (Table 2).

None of the patients in either group had any adverse events such as bradycardia, hypotension, nausea, vomiting, dizziness, headache, or respiratory depression.

Discussion

The results of the present study show that 6 mg melatonin administered 120 minutes before induction of anesthesia resulted in significant attenuation of hemodynamic responses to laryngoscopy and tracheal intubation, and also reduced dose of propofol required for induction and total intraoperative fentanyl consumption. Melatonin has several advantages over other drugs such as opioids, alpha agonists, beta-blockers used for attenuation of hemodynamic responses to laryngoscopy and intubation. Melatonin is easily available and is easy to administer, is effective in attenuating the rise in both heart rate and blood pressure with no risk of bradycardia and hypotension. Exogenous melatonin has its peak effect ranging from 60 to 150 minutes. So, in the present study melatonin was administered 120 minutes before induction of anesthesia, and a dose of 6 mg was used based on our pilot study where desired effects were obtained with 6 mg, without any adverse effects.

The heart rate-lowering effect of melatonin as seen in the present study may be because of its anxiolytic action due to the synergy between melatonergic and GABAergic systems. Melatonin reduces mean blood pressure in healthy volunteers as shown in the present and previous studies, through a complex mechanism of action on the circulatory system by binding to specific melatonin receptors present in the blood vessels and interfering with the vascular response

Table 2 Comparison of propofol and fentanyl requirements.

	Melatonin Group (n = 31)	Placebo Group (n = 31)	*p*
Induction dose of propofol (mg. kg^{-1}) (mean ± SD)	1.42 ± 0.31	2.01 ± 0.37	<0.001
N° of patients requiring additional fentanyl boluses (0.5 μg.kg^{-1}) intraoperatively (n)	3	11	0.031

Unpaired t-test used for comparing induction-dose of propofol. Chi-Square test used for comparing patients requiring additional fentanyl boluses.

to catecholamine,[8] and also by smooth muscle relaxation of the arterial walls by increasing nitric oxide availability.[9] In the present study, after administration of melatonin, both HR and blood pressure were lower than baseline values at all time points. After laryngoscopy and tracheal intubation, rise in the HR and blood pressure was significantly less compared to the placebo group. Hemodynamic response to tracheal intubation is attributed to a rise in a plasma catecholamine, and we observed significant attenuation of this response with oral melatonin, which is known to cause a reduction in adrenergic outflow and catecholamines levels by interfering with the peripheral and central autonomic system.[10] Our results were in agreement to the study by Gupta et al.[11] and Choudhary et al.[12] where 6 mg of orally administered melatonin resulted in attenuation of the rise in both HR and blood pressure after intubation, however in the above studies, the requirement of anesthetic agents like propofol and fentanyl were not compared, and were also compared and found to be decreased in the melatonin group of our study. In another study by Mohammed et al., oral melatonin 6 mg and 9 mg were compared with placebo for attenuation of hemodynamic response to intubation and significant reduction of blood pressure was observed in both melatonin groups compared to the placebo group. However, no difference was observed in the changes in HR in the melatonin and placebo group postintubation.[13]

The hemodynamic stability seen after melatonin administration may also be due to its anxiolytic and analgesic effect, as seen in the present study and also reported in a few previous studies.[14] The precise mechanism and site of action for the analgesic action of melatonin are not clear. The analgesic effect may be due to G(i)-coupled melatonin receptors, or G(i)-coupled opioid μ-receptors or GABA-B receptors resulting in unknown downstream changes leading to decreased anxiety and pain.[15] In the present study, the melatonin analgesic effect was clinically evident by the lesser number of patients who needed additional intraoperative fentanyl boluses with a reduction in the intraoperative fentanyl consumption. But postoperative pain scores were not assessed in our study, which is one of the limitations of the study. Our results are similar to a study by Ismail et al. in which perioperative verbal pain scores were significantly lower in the melatonin group with less intraoperative fentanyl requirement compared with the control group in patients undergoing cataract surgery with topical anesthesia.[16] In another clinical study by Caumo et al.[17] on female patients undergoing abdominal hysterectomy under epidural anesthesia, it was seen that melatonin premedication enhanced postoperative analgesia. Melatonin has also been studied to improve tourniquet tolerance and enhance postoperative analgesia in patients receiving intravenous regional anesthesia.[18] The present study also showed that melatonin resulted in a significant reduction in the induction dose of propofol. Our results were similar to the previous studies, where oral melatonin premedication in a dose of either 3 or 5 mg reduced the dose of propofol to achieve a Bispectral Index score of 45.[19] Also, Naguib et al.[20] studied that oral melatonin premedication decreased the doses of both propofol and thiopental required to induce anesthesia when used in a dose of 0.2 mg.kg^{-1}.

In our study, 6 mg of oral melatonin was well tolerated, and no adverse effects like bradycardia, hypotension, headache, nausea, vomiting, dizziness, or respiratory depression were noticed in any patient. Our results are in agreement with the results of Kain et al. where 0.4 mg.kg^{-1} oral melatonin was safely used in children without any adverse effects.[21] However, Rosenberg et al. reported that hypotension and bradycardia occurred more frequently after melatonin administration.[22] This difference in results may be due to the high dose (9 mg) of melatonin used by Rosenberg et al. resulting in a higher incidence of hypotension and bradycardia. In a few past studies, using very high doses of melatonin for its anxiolytic action dizziness, irritability and headache were seen in some patients.[23]

The strength of the present study includes its randomized controlled double-blind design and the homogeneous nature of the study population. Moreover, through a single study, we have highlighted multiple roles of melatonin, useful for attenuating hemodynamic response to intubation as well as reducing the requirement of anesthetic agents like propofol and fentanyl. However, the present study has few limitations. One is that we did not measure melatonin plasma levels after melatonin premedication, and also we did not measure plasma catecholamine levels, which is more objective means for evaluating hemodynamic response. Moreover, intraoperative bispectral index (BIS) monitoring and measurement of the effect-site concentration of propofol would have been a more objective method in deciding the depth of anesthesia and the requirement of an induction dose of propofol, which was not used in our study. In the present study, though reduced requirement of anesthetic agents like propofol and fentanyl was seen with use of melatonin, it was not designed or powered to study the effect of melatonin on anesthetic requirements, which is another limitation.

In conclusion, 6 mg melatonin administered orally 120 minutes before induction of anesthesia significantly attenuated the hemodynamic responses to laryngoscopy and intubation. It also reduced the dose of propofol required

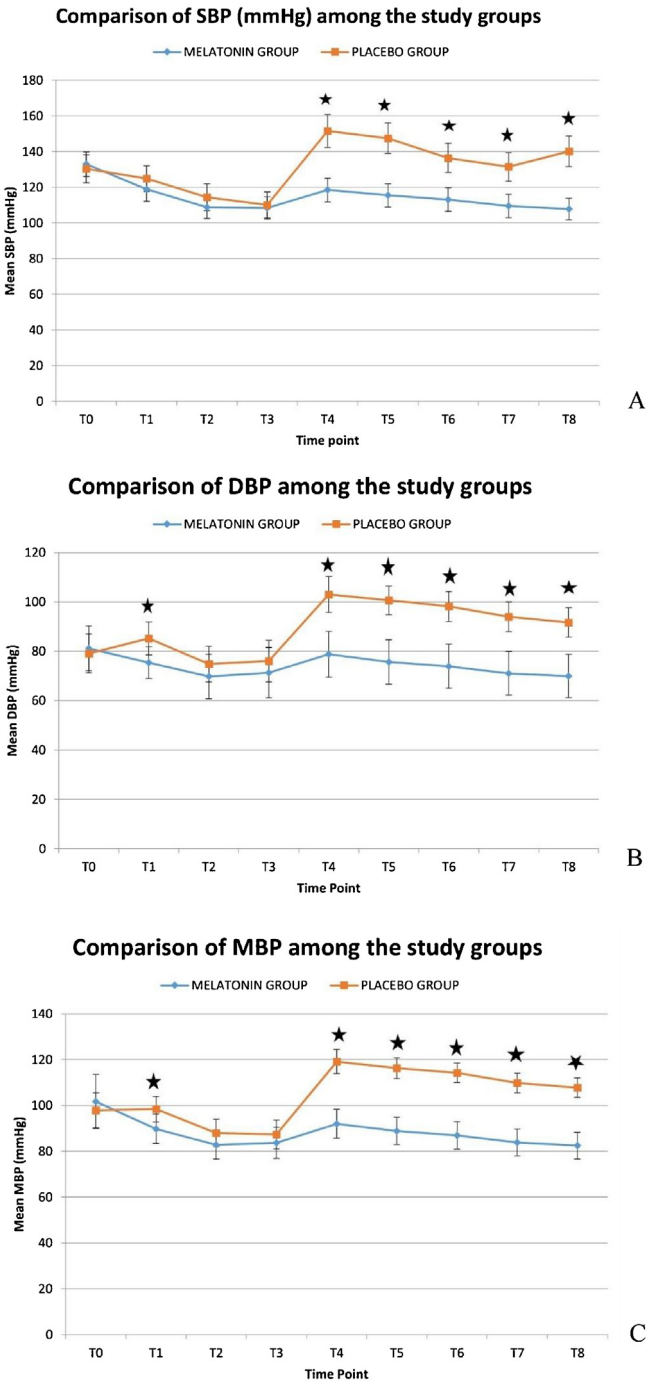

Figure 3 A, comparison of systolic blood pressure (SBP) among the study groups; B, comparison of diastolic blood pressure (DBP) among the study groups; C, comparison of mean blood pressure (MBP) among the study groups.
T0, baseline; T1, 120 min after administration of study drug on arrival to operation theater; T2, after induction; T3, just before laryngoscopy and intubation; T4, 1 min after intubation; T5, 3 min after intubation; T6, 5 min after intubation; T7, 10 min after intubation; T8, 15 min after intubation.
p-value < 0.0001.
ANOVA used to analyze changes over time. Unpaired *t*-test used for intergroup comparisons.

for induction and total intraoperative fentanyl consumption, and was not associated with any adverse effects.

Conflicts of interest

The authors declare no conflicts of interest.

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EXPERIMENTAL TRIALS

Morphine promotes migration and lung metastasis of mouse melanoma cells

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KEYWORDS
Morphine;
toll-like receptor-4;
melanoma;
metastasis

Abstract

Background: Morphine is an analgesic agent used for cancer pain management. There have been recent concerns that the immunosuppressant properties of morphine can also promote cancer metastasis. Morphine is an agonist for toll like receptor 4 (TLR4) that has a dual role in cancer development. The promotor or inhibitor role of morphine in cancer progression remains controversial. We investigated the effects of morphine on migration and metastasis of melanoma cells through TLR4 activation.

Methods: Mouse melanoma cells (B16F10) were treated with only morphine (0, 0.1, 1, and 10 μM) or in combination with a TLR4 inhibitor (morphine10 μM +CLI-095 1μM) for either 12 or 24 hours. Migration of cells was analyzed by transwell migration assays. Twenty C57BL/6 male mice were inoculated with B16F10 cells via the left ventricle of the heart and then randomly divided into two groups (n = 10 each) that received either morphine (10 mg.kg^{-1}, sub-q) or PBS injection for 21 days (control group). Animals were euthanized and their lungs removed for evaluation of metastatic nodules.

Results: Morphine (0.1, 1, and 10 μM) increased cell migration after 12 hours ($p < 0.001$) and after 24 hours of treatment with morphine (10 μM) ($p < 0.001$). Treatment with CLI-095 suppressed migration compared to cells treated with morphine alone ($p < 0.001$). Metastatic nodules in the morphine-treated group (64 nodules) were significantly higher than in the control group (40 nodules) ($p < 0.05$).

Conclusion: Morphine increases the migration and metastasis of mouse melanoma cells by activating TLR4.

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Introduction

Pain associated with cancer severely impacts the patient's quality of life and treatment protocols.[1] Opioids such as morphine are frequently applied in surgery for tumor removal in patients with cancer.[2,3] However, the use of morphine can have immunosuppressant effects which can paradoxically promote cancer progression and metastasis,[4,5] although other studies have reported a protective role of morphine against cancer spread.[6-8] Numerous studies conducted *in vivo* and *in vitro* demonstrate dual effects of morphine on cancer cell proliferation, survival and migration, which are related to the dose, duration of drug use and receptor subtypes activated by morphine.[9-15] The μ-opioid receptor subtype is the primary target for the analgesic effects of morphine, although recent studies suggest opioid-receptor independent effects mediated by other pathways such as the activation of toll-like receptor 4 (TLR4).[16-18]

Morphine and its metabolites activate TLR4 during innate immunity responses.[19] TLR4 is expressed in various immune and non-immune cell types,[20] and also in malignant cells and cells in the tumor microenvironment that can influence metastasis.[21] Morphine activates TLR4 but suppresses lipopolysaccharide (LPS)-induced TLR4 activation.[22,23]

TLR4 is overexpressed during the cellular transformation of some cancers.[24,25] An overexpression of TLR4 is associated with a poor prognosis of tumor size, invasion and metastasis.[26] We hypothesized that using morphine in cancer pain management, increases cancer cell metastasis by activating TLR4 signaling pathways. We recently reported that the overexpression of TLR4 in melanoma and breast cancer cells increased cell proliferation and tumor size, and that inhibition of TLR4 suppressed melanomas *in vitro* and *in vivo*.[27-29] Our previous investigation showed that the effects of morphine on TLR4 expression in breast cancer cells were time and concentration dependent.[30] The current study further investigates the role of TLR4 in morphine induced migration and metastasis of melanoma cells *in vitro* and *in vivo*.

Methods

Cells and reagents

Mouse melanoma cells (B16F10) were obtained from the National Cell Bank of Iran (affiliated to the Pasteur Institute, Tehran, Iran). Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), penicillin, and streptomycin were purchased from Gibco BRL (Carlsbad, CA, USA). CLI-095 [resatorvid, ethyl (6R)-6-[N-(2-chloro-4-fluorophenyl) sulfamoyl] cyclohex-1-ene-1-carboxylate] was provided by InvivoGen (San Diego, CA, USA). Morphine sulfate was purchased from Temad (Temad Co, Tehran, Iran).

Cell culture

Mouse melanoma cancer cells (B16F10) were maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum at 37°C in a 5% CO_2 atmosphere. Cells were sub-cultured in fresh media when they reached 80% confluence.

Trans-well migration assay

To estimate the effects of morphine on melanoma cell migration and its interaction with TLR4, B16F10 cells were cultured in T-25 flasks and treated with morphine (0.1, 1, and 10 μM) for either 12 or 24 hours. Untreated B16F10 cells (no morphine) were used as controls. The interaction of morphine with TLR4 was examined in other groups of B16F10 cells cultured in T-25 flasks and treated with CLI-095 (a TLR4 inhibitor, 1 μM) with or without morphine (10 μM) for 12 or 24 hours. The culture medium was discarded after incubation and cells were washed three times with phosphate-buffered saline (PBS).

Cell migration was assayed using transwell chambers with 8 μm pore size inserts (BD Biosciences, USA). In brief, 1×10^3 serum-starved cells from each group were suspended in serum free medium and transferred to the upper chambers of each transwell plate. The lower chambers contained fresh medium either with or without FBS (10%) as a chemo-attractant. The cells remaining on the upper surface of the membrane were removed with a swab after 24 hours, while those cells that migrated to the lower membrane surface were fixed with 100% methanol (5 minutes) and stained with 0.5% crystal violet (5 minutes). The number of cells that migrated through the filter were photographed and counted using a Leica microscope equipped with a Leica camera (DFC450 C) at a magnification of 200 x. Pictures of five randomly chosen visual fields were taken and the number of cells that migrated were counted using ImageJ 1.8.0 software (National Institutes of Health).[31] The average percent of migrating cells was calculated.

Experimental metastasis by intra-cardiac injections

All animal experiments followed the ARRIVE (Animals in Research: Reporting In vivo Experiments) guidelines and ethical standards of the Iran National Committee for Ethics in Biomedical Research. The project was approved by the Ethics Committee of Isfahan University of Medical sciences (approval ID: IR.MUI.MED.REC.1398.118). In total, twenty male C57BL/6 mice (eight weeks old, weighing 23 $\pm$ 2 g) were purchased from the Pasteur Institute of Iran (Tehran). The mice were housed using a 12/12 hour light/dark cycle at 25 $\pm$ 2°C for one week before starting the experiments. The mouse model of experimental metastasis was created using an intracardiac injection of tumor cells after they were anesthetized (100 mg.kg^{-1} ketamine and 10 mg.kg^{-1} xylazine). Mice were restrained on their backs, shaved, and disinfected with antiseptic solution. A single-cell suspension of B16F10 cells (3×10^5/100 μL PBS) was then introduced into the left ventricle of the heart.[30] Mice were then randomly divided into two groups (n = 10 per group) after three days: mice in the control group received only vehicle while those in the treated group received daily injections of morphine (10 mg.kg^{-1}, subcutaneous) for 21 days.[32] Animals were euthanized at the end of the treatments and their lungs removed for evaluation of metastatic nodules.

Counting of lung metastatic nodules

Lungs were removed from the mice after 21 days and tumor nodules on the lung surface were counted using a light

microscope. The combined sum of the gross and microscopic counts was taken as the final count of metastatic lung nodules; a false count was defined as no metastatic nodules reported under gross or microscopic observations. All experiments were done in a blind manner.

Statistical analysis

Results are expressed as means ± standard error of the mean (SEM). Changes observed in treated groups compared with the control group were analyzed with a one-way ANOVA followed by Bonferroni's post-test and Student's *t*-test. Statistical significance was set for *p*-values of < 0.05.

Results

Morphine enhances the *in vitro* migration of melanoma cells

The migration of B16F10 mouse cancer cells increased after 12 hours treatment with morphine, 0.1 (25.43 ± 0.87%), 1 (25.12 ± 0.26%) and 10 μM (27.2 ± 0.92%), compared with 19.57 ± 0.67% in the control group ($p < 0.001$) (Fig. 1). Treatment with different doses of morphine indicated that only morphine (10 μM) increased cell migration (27.8 ± 1.07%) compared to the control group (19.36 ± 0.39%) ($p < 0.001$) (Fig. 2).

Effects of CLI-095, an inhibitor of TLR4, on morphine induced cell migration

Mouse melanoma cells were pre-incubated with CLI-095 (1 μM) for 1 hour at 37°C to examine the role of TLR4 in morphine-induced migration of melanoma cells. Migration of melanoma cells induced by morphine (10 μM) was significantly decreased after pretreatment with CLI-095 for either 12 or 24 hours, ($p < 0.001$) (Figs. 1 and 2).

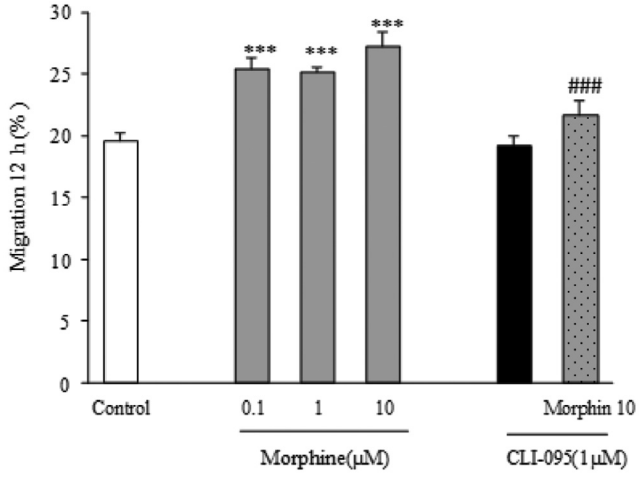

Figure 1 Effect of morphine on B16F10 cell migration after 12 h treatment. B16F10 cells were incubated with morphine (0, 0.1, 1, 10 μM) for 12 h. In the other experiment the cells were treated with morphine (10 μM) with or without CLI-095. After incubation a transwell migration assay was done. *$p < 0.001$ compared to the negative control, #$p < 0.001$ compared to morphine 10 μM. One representative experiment of three is depicted. Each graph has been represented as mean ± SEM.

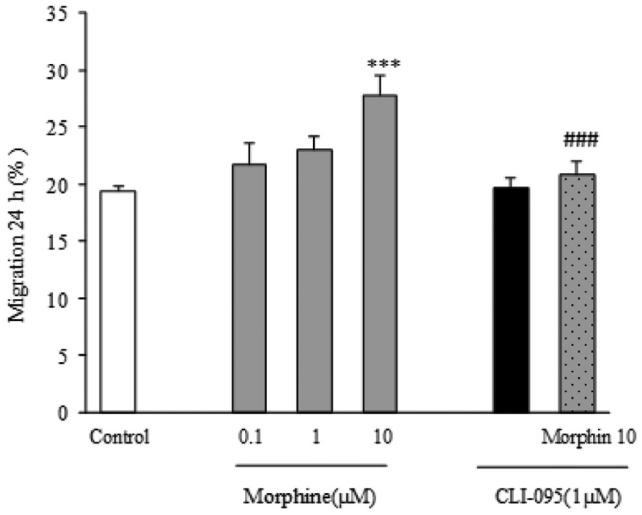

Figure 2 Effect of morphine on B16F10 cell migration after 24 h. B16F10 cells were incubated with morphine (0, 0.1, 1, 10 μM) for 24 h. In the other experiment the cells were treated with morphine (10 μM) with or without CLI-095. After incubation a transwell migration assay was done. *$p < 0.001$ compared to the negative control, $^{\#}p < 0.001$ compared to morphine 10 μM. One representative experiment of three is depicted. Each graph has been represented as mean ± SEM.

Effect of morphine on lung metastasis induced by B16F10

The mouse model of experimental metastasis was created using an intracardiac injection of B16F10 cells. None of the mice died before the end of the study and there were no significant differences in body weight between the two groups. Mice were sacrificed 21 days after treatment with morphine (10 mg.kg^{-1}) and metastasis nodules in their lungs counted. The lungs of mice injected with morphine contained more metastatic nodules ($p < 0.05$) (Fig. 3).

Discussion

We examined the ability of morphine to stimulate melanoma metastasis by activation of TLR4. Our findings indicate that morphine increased the number of migrating B16F10 cells *in vitro* and promoted pulmonary metastasis *in vivo*.

Melanoma is an aggressive form of skin cancer characterized by rapid growth and early metastasis to other organs such as the lungs, liver, bone or brain.[33-35] Activation of inflammation promotes melanomas,[36] with increases in the inflammation level related to the over-expression of TLR.[37,38] Morphine can both inhibit or stimulate immune cell function to affect cancer progression.[39] Morphine binds to myeloid differentiation protein 2 (MD-2), a TLR4 accessory protein, and activates TLR4 to increase cancer metastasis.[40]

The effect of morphine on cell migration is time and dose dependent.[41] Our results indicate that morphine (0.1, 1, 10 μM) increases the migration of B16F10 cells after 12 hours, or after treatment with morphine (10 μM) 24 hours. Treating

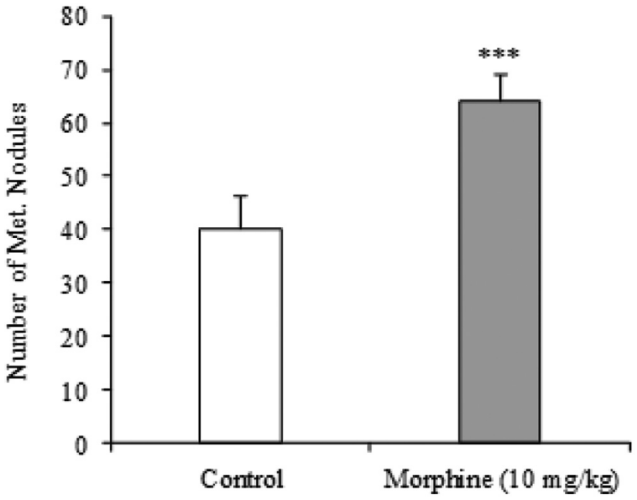

Figure 3 The number of tumor nodules on the lung. The C57BL/6 mice received left heart ventricle injection of B16/F10 melanoma cells and were treated with morphine (10 mg.kg^{-1}) or PBS for 21 days. ***$p < 0.001$ compared to the negative control, each graph has been represented as mean ± SEM.

cells with low concentrations of morphine for 24 hours mimicked the effects of a single dose of morphine,[6] as shown in Figures 1 and 2. The underlying mechanism has not been understood yet, the nature of opioid receptor may be the key to this mechanism.[42] Morphine increased the number of lung metastatic nodules compared to the control group.

Reports on the effects of morphine on metastasis are contradictory, as both inhibitory and stimulatory effects have been observed. For example, some studies suggested that morphine inhibited metastasis in animal models of cancer,[7,8] while other studies report that clinically relevant doses of morphine increased tumor growth and angiogenesis in a mouse model of breast cancer,[43,44] and tumor growth and sarcoma in a mouse model of leukemia.[14] These contradictory results are likely due to differences in the concentration, type and time of administration of morphine.[13] Administration of low daily doses or a single dose of morphine enhances tumor growth,[45] while high doses of morphine inhibit tumor progression.[7,8,12] Generally, the effect of morphine on cancer progression is dependent on the cancer type because, different cancer cells express different opioid receptors[42]; we show that TLR4 may be one of key receptors involved in morphine effects.

This study has some limitations. First is that we did not evaluate the *in vivo* effect of the TLR4 inhibitor in the presence of morphine. Second, we did not evaluate the dose related effects of the TLR4 inhibitor. Third, we did not measure activation of the downstream targets of TLR4 activation. Next, we did not evaluate the activity of TLR4 after its increase in expression. Last, we did not evaluate cancer pain of mice in this study.

Conclusion

Our results suggest that morphine increases melanoma cell migration by activating TLR4. Overexpression of TLR4 is associated with tumor metastasis. Further studies are needed to determine the role of TLR4 in the management of cancer pain with morphine. However, we still need to fully understand the adequate dose of morphine required to reduce cancer pain in patients.

Conflicts of interest

The authors declare no conflicts of interest.

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EXPERIMENTAL TRIALS

Sildenafil in endotoxin-induced pulmonary hypertension: an experimental study

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KEYWORDS
Phosphodiesterase V inhibitors;
Acute lung injury;
LPS;
Septic shock;
Experimental model;
Swine

Abstract

Background: Sepsis and septic shock still represent great challenges in critical care medicine. Sildenafil has been largely used in the treatment of pulmonary arterial hypertension, but its effects in sepsis are unknown. The aim of this study was to investigate the hypothesis that sildenafil can attenuate endotoxin-induced pulmonary hypertension in a porcine model of endotoxemia.

Methods: Twenty pigs were randomly assigned to Control group (n = 10), which received saline solution; or to Sildenafil group (n = 10), which received sildenafil orally (100 mg). After 30 minutes, both groups were submitted to endotoxemia with intravenous bacterial lipopolysaccharide endotoxin (LPS) infusion (4 $\mu g.kg^{-1}.h^{-1}$) for 180 minutes. We evaluated hemodynamic and oxygenation functions, and also lung histology and plasma cytokine (TNFα, IL-1β, IL6, and IL10) and troponin I response.

Results: Significant hemodynamic alterations were observed after 30 minutes of LPS continuous infusion, mainly in pulmonary arterial pressure (from Baseline 19 $\pm$ 2 mmHg to LPS30 52 $\pm$ 4 mmHg, $p < 0.05$). There was also a significant decrease in PaO_2/FiO_2 (from Baseline 411 $\pm$ 29 to LPS180 334 $\pm$ 49, $p < 0.05$). Pulmonary arterial pressure was significantly lower in the Sildenafil group (35 $\pm$ 4 mmHg at LPS30, $p < 0.05$). The Sildenafil group also presented lower values of systemic arterial pressure. Sildenafil maintained oxygenation with higher PaO_2/FiO_2 and lower oxygen extraction rate than Control group but had no effect on intrapulmonary shunt. All cytokines and troponin increased after LPS infusion in both groups similarly.

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Conclusion: Sildenafil attenuated endotoxin-induced pulmonary hypertension preserving the correct heart function without improving lung lesions or inflammation.

Introduction

Sepsis and septic shock are still one of the major causes of morbidity and mortality in critically ill patients and the pathophysiology involves a dysregulated host response to infection leading to a life-threatening organ dysfunction.[1] Acute lung injury, a frequent complication of sepsis, is characterized by pulmonary edema and atelectasis that result in impaired gas exchange and hypoxemia. Pulmonary hypertension induced by hypoxemia, microthrombi, and increased production of vasoconstrictive agents is considered an aggravator factor.[2] Pulmonary hypertension increases the right ventricular afterload, which tends to reduce the right ventricular output, leading to right ventricular dysfunction.[3] Its etiology is attributed to several factors such as pulmonary microthrombosis due to platelet activating factor release or increase of inflammatory mediators such as tumor necrosis factor-α (TNF-α) and nitric oxide (NO).[2,4] There is no consensus on the therapeutic approach of pulmonary hypertension in sepsis. The effectiveness of a pulmonary vasodilator therapy has been limited by the lack of selectivity and potency. Most pulmonary vasodilators drugs have associated systemic vasodilator action, as well as an effect on pulmonary circulation not such prominent.[3]

Sildenafil inhibits phosphodiesterase type V increasing intracellular cGMP which causes hyperpolarization of smooth-muscle membranes and vascular relaxation.[5] Sildenafil has been largely used in the treatment of pulmonary arterial hypertension, with a significant reduction in pulmonary artery pressure values, improvement of functional capacity and quality of life.[6] There are some evidences suggesting that sildenafil have anti-inflammatory effects, reducing cytokines and improving endothelial function.[7,8] Despite these attractive attributes, very little data are available for the use of sildenafil in sepsis, mostly due to its hypotensive effects which could aggravate sepsis vasoplegic hypotension.[9,10]

The aim of this study was to investigate the hypothesis that sildenafil pretreatment can attenuate LPS-induced lung injury and pulmonary hypertension in a porcine model of endotoxemia. Further, we investigated the effects on hemodynamic, oxygenation parameters, and lung morphology. Lastly, we investigated the effects of sildenafil on the plasma cytokine levels (TNFα, IL-1β, IL6, and IL10), mediators of inflammation, and on troponin I, early indicator of right ventricular dysfunction related to pulmonary hypertension.

Methods

Animals

A total of 20 Large White pigs weighting 23.7 ± 2.5 kg were obtained from a commercial laboratory pig farm (Granja RG, Suzano, Brazil). The animals were fasted overnight with free access to water and transported to the laboratory facilities on the day of the experiment. The study was approved by the Ethics Committee of the Faculdade de Medicina da Universidade de Sao Paulo (n. 262/13).

Anesthesia and preparation

Following premedication with ketamine (5 $mg.kg^{-1}$ intramuscular) and midazolam (0.25 $mg.kg^{-1}$ intramuscular), a catheter was inserted into the auricular vein and anesthesia was induced with propofol (5 $mg.kg^{-1}$ intravenous). Anesthesia was maintained by isoflurane (1.4%). The lungs were mechanically ventilated (Primus ventilator, Dräger, Lübeck, Germany) with a tidal volume of 8 $mL.kg^{-1}$, 5 cmH_2O of positive end-expiratory pressure (PEEP), and respiratory rate was adjusted to maintain $EtCO_2$ between 35–45 mmHg, on volume-controlled ventilation with a FiO_2 of 40%. Pancuronium (0.1 $mg.kg^{-1}$ bolus followed by 5 $\mu g.kg^{-1}.min^{-1}$ continuous infusion) and normal saline (5 $mL.kg^{-1}.h^{-1}$) were administered during the experiment. Core temperature was maintained between 37–39 °C by using a heating pad. The right internal jugular vein was surgically exposed and a 7.5F pulmonary artery catheter was inserted (774F75, Edwards Lifesciences, Irvine, CA, USA) into the pulmonary artery to measure cardiac output (thermodilution technique), mean pulmonary artery pressure (MPAP), and central venous pressure (CVP). Cardiac index (CI), the systemic and pulmonar vascular resistance index (SVRI and PVRI), and left and right ventricular stroke work indices (LVSWI and RVSWI) were obtained directly from cardiac monitor (Vigilance II, Edwards Lifesciences, Irvine, CA, USA). A catheter was inserted into the right femoral artery for continuous blood pressure monitoring (Pulsiocath Picco PV2015L20, Pulsion Medical Systems, München, Germany) and blood gas sampling. Oxygenation data (DO_2i, VO_2i, O_2ER, and Shunt fraction) were calculated using standard equations: $DO_2i = CaO_2 \times CI \times 10$; $VO_2i = C(a\text{-}v)O_2 \times CI \times 10$; $O_2ER = (SaO_2 - SvO2)/SaO_2 \times 100$; Shunt fraction = $[(Cc'O_2\text{-}CaO_2)/(Cc'O_2\text{-}CvO_2)] \times 100$.

The right femoral vein was also cannulated for endotoxin infusion and fluid-administration. Urinary bladder was catheterized for urinary output.

Sildenafil dose

The dose of sildenafil was based on literature[5] and pilot studies in which increasing doses of sildenafil (20, 40, 80, and 100 mg) were administered till attenuation of pulmonary hypertension induced by LPS, which was defined as a MPAP value below 40 mmHg.

Experimental protocol

The animals were previously randomized by a computer program (Random.org) in one block and allocated into two groups using consecutive numbered envelopes to be opened after animal preparation by the laboratory technician responsible for drug preparation and administration: Control (CTL, n = 10), and Sildenafil (SIL, n = 10). After a 30-minute stabilization period, baseline parameters were collected and a single-dose of 100 mg sildenafil (Viagra, Pfizer) or saline was administered through a gastric tube. All measurements were performed by a researcher unaware of group allocation. After 30 minutes of sildenafil/saline administration, endotoxemia was induced by a bacterial lipopolysaccharide (LPS) endotoxin infusion at 4 $\mu g.kg^{-1}.h^{-1}$ intravenously from LPS0 until the end of study (*Escherichia coli* O111:B4 LPS, 2.000.000 EU. mg^{-1}, product number L2630, Sigma-Aldrich, St. Louis, MO, USA).

Blood gas analysis, hemodynamic, and oxygenation measurements were performed at baseline, prior to LPS infusion (T0), and every 30 minutes until 180 minutes of LPS infusion. A timeline for interventions and measurements is shown in Figure 1.

No vasopressors or fluid bolus were administered during protocol, even if hypotension was present.

Animals were euthanized at the end of the experimental procedure by deepening anesthesia (5% isoflurane) and potassium chloride administration (19.1%, 10 mL). Immediately after killing, lung samples were collected for histopathological analysis.

Transesophageal echocardiography

The echocardiographic study was conducted by a qualified professional, using an ultrasound system with transesophageal transducer 7.5/5.0 MHz (En CHD Display, Minnesota, USA). Echocardiographic images of the heart were obtained in apical four-chamber views. We measured left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), right ventricular end-diastolic volume (RVEDV), and left ventricular ejection fraction (LVEF) was calculated by Simpson's method.

Plasma cytokines and troponin

Seven milliliters of blood was withdrawn at baseline and at the end of the study (LPS180). The samples were centrifuged spun at 1200 g and plasma was stored at -80 °C for TNFα, IL-1β, IL6 and IL10 analysis, by standard kits of sandwich enzyme immunoassay technique (Quantikine, R&D Systems, Abingdon, UK). All measurements were performed in duplicate and according to the manufacturer's instructions. The plasma troponin I was analyzed using chemiluminescence immunoassay technique employing the diagnostic set Immulite Turbo Troponin I in semi-automatic analyzer equipment (Immulite Analyzer – Diagnostic Products Corporation DPC).

Histology

Samples of the non-dependent portion of right diaphragmatic lung were collected for histology, from the same location in all animals. Hematoxylin-eosin-stained lung slices were evaluated by an experienced investigator blinded to group allocation. Ten random non-coincident fields (100x magnification) were evaluated using a scoring system (ranging from 0 to 4) for intra- and extra-alveolar hemorrhage, intra-alveolar edema, inflammatory infiltration of the interalveolar septa, and airspace, atelectasis and overinflation.[11]

Statistical analysis

Sample size calculation was based on cytokine decrease observed by Cardici et al. (2011)[12] in a rat model of sepsis treated with sildenafil.

Data are expressed as mean $\pm$ SD or median (interquartile range or minimum and maximum) for parametric and non-parametric data, respectively. Normality was tested using D'Agostino & Pearson test. For normally distributed data, a two-way ANOVA for repeated measures was applied with treatment (Sildenafil or Control) and time as fixed effects *p*-values for the effects of both treatment and time are given, and a value ≤ 0.05 was considered significant. If a significant effect due to treatment was detected, the data were further analyzed *post hoc* using the Tukey's test. For non-parametric data, Mann-Whitney test was used. All animals were included in the analysis. Statistical analysis was performed with Prism 6 for windows (GraphPad Software) and SigmaPlot 11 (Systat Sofware).

Results

Hemodynamic data

Heart rate and cardiac index increased significantly without differences between groups at LPS 60 and LPS90 (Fig. 2). The MPAP and PVRI increased significantly in both groups; however, the Sildenafil group showed significantly lower values compared to Control group ($p < 0.05$) during all the LPS infusion period except for PVRI at LPS90. The MAP increased significantly at 30-minute of LPS infusion (LPS30) in all animals, and then decreased significantly below baseline values in the Sildenafil group.

Although fluid administration was similar in both groups (5 $mL.kg^{-1}.h^{-1}$ in both groups), urinary output was significantly higher in Control group (2.7 ± 1.2 vs 1.6 ± 0.7, $p = 0.014$).

Lactate and oxygenation data

There were significant increases in arterial lactate from 1.8 ± 0.6 (baseline) to 2.8 ± 0.8 $mmol.L^{-1}$ (LPS180) in the Control group and 2 ± 1.0 (baseline) to 3.25 ± 1.3 $mmol.L^{-1}$ (LPS180) in the Sildenafil group, with no difference between groups. The DO_2I increased significantly in all animals from LPS60 with no changes in VO_2I. The SvO_2 increased significantly in both groups but was significantly higher at LPS30 in the Sildenafil group. The intrapulmonary *shunt* increased

Table 1 Oxygenation data for all animals at baseline-180 min after LPS infusion.

	Baseline	LPS0	LPS30	LPS60	LPS90	LPS120	LPS150	LPS180	RM ANOVA
DO_2 ($mL.min^{-1}.m^{-2}$)									P1 = 0.952
CTL	484 ± 85	531 ± 103	469 ± 124	667 ± 77[a]	711 ± 57[a]	702 ± 85[a]	679 ± 133[a]	643 ± 127[a]	P2 < 0.001
SIL	511 ± 102	516 ± 70	528 ± 106	629 ± 104[a]	699 ± 120[a]	683 ± 109[a]	649 ± 107[a]	656 ± 127[a]	P3 = 0.648
VO_2I ($mL.min^{-1}.m^{-2}$)									P1 = 0.027
CTL	125 ± 22	122 ± 12	129 ± 33	129 ± 19	132 ± 21	128 ± 16	126 ± 41	135 ± 23	P2 = 0.336
SIL	125 ± 26	113 ± 24	99 ± 19	114 ± 19	108 ± 17	113 ± 13	119 ± 10	127 ± 19	P3 = 0.317
ERO_2 (%)									P1 = 0.084
CTL	26 ± 4	24 ± 3	29 ± 8	20 ± 3[a]	19 ± 3[a]	18 ± 2[a]	18 ± 5[a]	22 ± 7	P2 < 0.001
SIL	25 ± 3	22 ± 6	19 ± 4[b]	19 ± 5[a]	16 ± 3[a]	17 ± 4[a]	19 ± 5[a]	20 ± 5	P3 < 0.009
Qs/Qt									P1 = 0.521
CTL	5,3 ± 1,1	6,0 ± 1,4	6,0 ± 1,8	7,4 ± 1,2[a]	8,2 ± 1,8[a]	9,3 ± 2,6[a]	9,9 ± 2,5[a]	9,9 ± 3,3[a]	P2 < 0.001
SIL	5,6 ± 0,9	6,7 ± 1,7[a]	6,8 ± 1,0	7,7 ± 2,0[a]	9,1 ± 1,8[a]	8,6 ± 1,9[a]	7,9 ± 1,5[a]	8,0 ± 1,7[a]	P3 = 0.066
PaO_2/FiO_2									P1 = 0.364
CTL	411 ± 29	401 ± 32	369 ± 71[a]	389 ± 30	383 ± 32	365 ± 42[a]	348 ± 48[a]	334 ± 49[a]	P2 < 0.001
SIL	405 ± 26	392 ± 33	410 ± 34[b]	387 ± 39	380 ± 29	380 ± 28	379 ± 25	370 ± 33[a,b]	P3 < 0.001
Lactate ($mmol.L^{-1}$)									P1 = 0.427
CTL	1.8 ± 0.6	1.7 ± 0.5	1.6 ± 0.4	1.9 ± 0.4	2.1 ± 0.5	2.4 ± 0.7[a]	2.7 ± 0.8[a]	2.8 ± 0.8[a]	P2 < 0.001
SIL	2 ± 1.0	1.9 ± 0.9	1.8 ± 0.7	2.1 ± 0.7	2.2 ± 0.7	2.5 ± 0.7[a]	2.9 ± 1.1[a]	3.2 ± 1.3[a]	P3 = 0.942
SvO_2 (%)									P1 = 0.070
CTL	73.1 ± 3.9	75.7 ± 3.3	70.4 ± 8.2	79.5 ± 2.9[a]	80.4 ± 3.2[a]	80.4 ± 2.5[a]	80.4 ± 5.7[a]	76.6 ± 7.2[a]	P2 < 0.001
SIL	74.8 ± 3.1	77.0 ± 6.2	80.1 ± 4.5[b]	80.5 ± 4.8[a]	83.5 ± 2.6[a]	82.1 ± 3.8[a]	80.1 ± 4.6	79.0 ± 5.3	P3 < 0.008

CTL, Control group; SIL, Sildenafil group; DO_2I, oxygen delivery index; VO_2I, oxygen consumption index; ERO_2, oxygen extraction rate; Qs/Qt, intrapulmonary *shunt*; SvO_2, mixed venous oxygen saturation; RM ANOVA, Repeated measures ANOVA; P1, Group effect; P2, P Time effect; P3, interaction Group x Time.
Measurements are given as mean ± SD.
[a] $p < 0.05$ vs. baseline.
[b] $p < 0.05$ CTL vs. SIL.

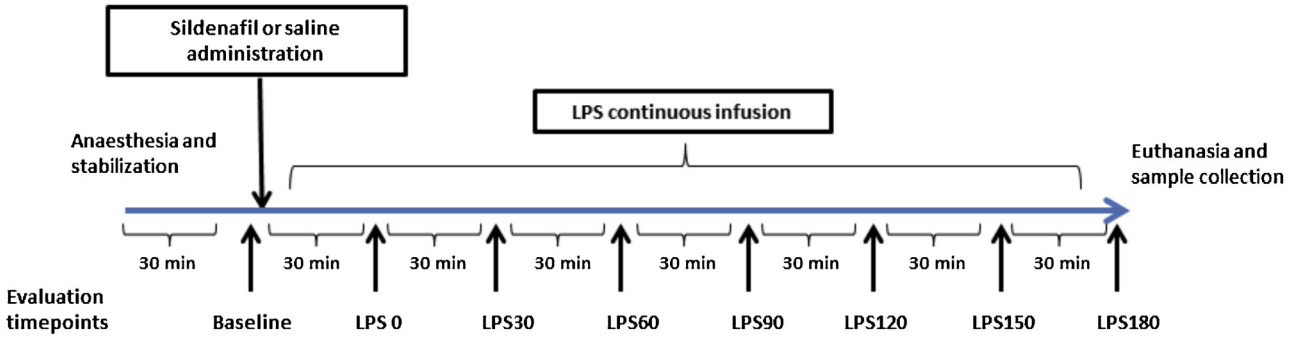

Figure 1 Timeline for interventions and measurements. LPS, lipopolysaccharide endotoxin.

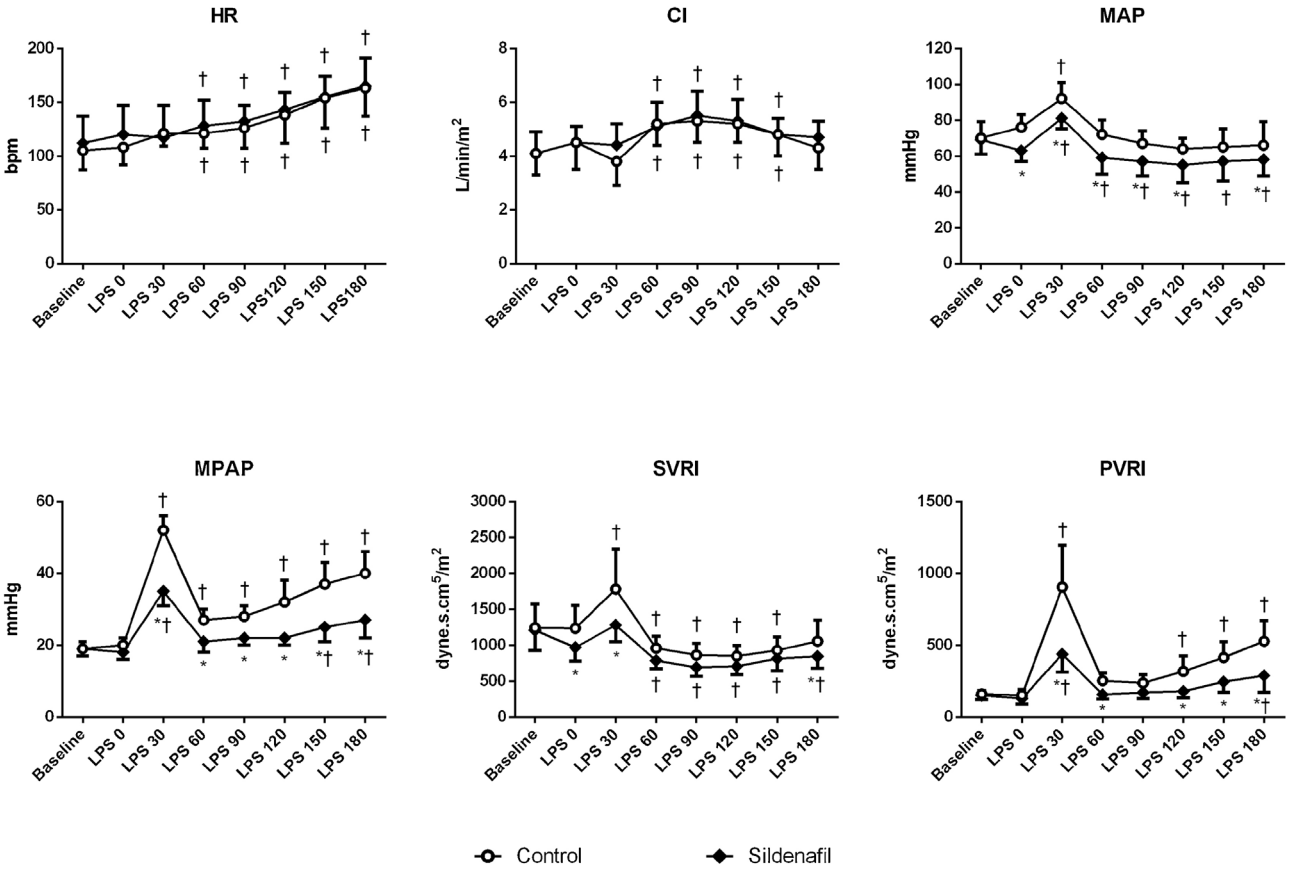

Figure 2 Hemodynamic variables in Control and Sildenafil group. HR, heart rate; CI, cardiac index; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.
† $p < 0.05$ vs. baseline.
* $p < 0.05$ CTL vs. SIL.

significantly over time in both groups, with no difference between groups. The PaO_2/FiO_2 decreased significantly in the Control group at LPS30, LPS 120, LPS 150 and LPS180 and was significantly lower than the Sildenafil group at LPS30 and LPS180. The O_2ER decreased in all animals from LPS60 to LPS150 with difference between groups at 30-minute of LPS infusion, in which the Sildenafil group showed lower values (Table 1).

Transesophageal echocardiography

There were no significant differences in the RVEDV in the Sildenafil group, but there were significant increases in the Control group with *post hoc* analyses identifying differences between groups at LPS30, LPS60, LPS120, and LPS180. LVEDV and LVESV decreased at LPS180 in both groups without differences between groups. For left ventricular ejection fraction,

Table 2 Echocardiography variables for all animals at baseline-180 min after LPS infusion.

	Baseline	LPS0	LPS30	LPS60	LPS120	LPS180	RM ANOVA
LV EF (%)							P1 = 0.719
CTL	62.6 ± 4.9	64.5 ± 6.5	61.6 ± 11.9	66.6 ± 7.5	62.9 ± 6.6	67.0 ± 6.4	P2 = 0.279
SIL	61.2 ± 3.2	63.8 ± 8.4	63.9 ± 8.5	66.1 ± 4.2	66.3 ± 4.8	63.0 ± 7.3	P3 = 0.391
LV EDV (mL)							P1 = 0.541
CTL	25.5 ± 6.1	26.6 ± 4.5	23.2 ± 4.5	27.6 ± 4.8	24.3 ± 5.8	21.4 ± 5.9[a]	P2 < 0.001
SIL	21.9 ± 4.8	22.0 ± 4.3	23.7 ± 6.5	21.4 ± 6.1	20.0 ± 2.7	17.4 ± 3.2[a]	P3 = 0.059
LV ESV (mL)							P1 = 0.512
CTL	9.8 ± 3.3	8.8 ± 2.5	9.0 ± 4.1	9.8 ± 3.7	9.2 ± 3.2	7.2 ± 2.8[a]	P2 = 0.002
SIL	8.4 ± 1.9	7.9 ± 2.1	8.0 ± 1.9	7.0 ± 1.4	6.8 ± 1.0	6.3 ± 1.6[a]	P3 = 0.691
RV EDV (mL)							P1 < 0.001
CTL	9.9 ± 2.1	10.7 ± 2.2	20.1 ± 3.3[a]	13.9 ± 3.6[a]	13.4 ± 3.0	13.6 ± 1.9[a]	P2 < 0.001
SIL	10.5 ± 1.7	10.7 ± 3.6	11.8 ± 4.4[b]	10.5 ± 3.6[b]	10.8 ± 2.3[b]	8.0 ± 1.7[b]	P3 < 0.001

CTL, Control group; SIL, Sildenafil group; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RVEDV, right ventricular end-diastolic volume; RM ANOVA, Repeated measures ANOVA; P1, Group effect; P2, P Time effect; P3, interaction Group x Time.
Measurements are given as mean ± SD.
[a] $p < 0.05$ vs. baseline.
[b] $p < 0.05$ CTL vs. SIL.

Table 3 Histological scores in Control and Sildenafil group. Median (min-max).

	Control	Sildenafil	*p*-value
Atelectasis	1 (3–0)	2 (3–0)	> 0.05
Overinsuflation	12 (10–12)	12 (12–12)	> 0.05
Inflammation	10 (7–12)	9.5 (7–12)	> 0.05
Edema	0 (0–0)	0 (0–0)	> 0.05
Hemorrhage	3 (0–6)	3.5 (0–6)	> 0.05

no differences were observed with time and between groups (Table 2).

Cytokines and troponin

Plasma TNFα, IL-1β, IL6 and IL10 increased significantly with time in both groups, with no differences between groups. Troponin I concentration also increased in all animals, again without difference between groups (Fig. 3).

Histology

Histological evaluation revealed a predominance of intense mononuclear infiltrates with thickening of the alveolar septum, overinflation, disrupted alveolar septum, congestion, and areas of atelectasis in both groups. There were no differences in the histological scoring system between groups (Table 3).

Discussion

The major findings of this study are that in an experimental model of septic shock, (a) sildenafil attenuated endotoxin-induced pulmonary hypertension preserving right heart function, (b) sildenafil decreased systemic blood pressure, (c) sildenafil-maintained oxygenation without effect in shunt fractioning, and (d) sildenafil did not influence lung morphology, plasma cytokines, and troponin.

The endotoxemia was successfully induced by LPS infusion, with significant increase in pulmonary arterial pressure, tachycardia, serum cytokines, and cardiac troponin. A hyperdynamic state was observed after 30 minutes of LPS infusion, with a marked increase in pulmonary and systemic blood pressure. These LPS infusion effects on PAP were already described in other studies and are associated with the great presence of macrophages in porcine lungs and massive release of thromboxane and endothelin-1.[13] The LPS infusion in our protocol was based on Lipcsey et al. (2008) investigation,[14] who described an endotoxemia model of hypoperfusion and organic dysfunction. One possible explanation for the absence of marked hypotension/hypoperfusion, aside low dose of LPS, could be the anesthetic protocol employed in this study. We used isoflurane for anesthesia maintenance. In contrast, Lipcsey used sodium pentobarbital well-known agent to provoke more hemodynamic instability. To corroborate this fact, Schaefer et al. (1987) showed the different hemodynamic effect comparing several anesthetic agents in an endotoxic model in rats.[15]

Higher doses of LPS could be used to promote hypotension and decreased cardiac output, but also require vasoactive drugs and fluids resuscitation to prevent high mortality. Also, in some studies, LPS infusion was titrated to avoid excessive PAP increase and consequent right ventricle failure.[16] We choose a LPS dose to promote lung injury and pulmonary hypertension with mild effect on blood pressure to preserve hemodynamics during sildenafil effects. Otherwise, the animals would present excessive hemodynamic instability needing vasoactive drugs and fluid resuscitation, which would confound the sildenafil effects.

Although the LPS did not promote acute lung injury according to the Berlin definition, LPS-induced histologic lung lesions similar to acute lung injury, with marked mononuclear infiltrates in lung tissues, over inflation, and atelectasis.[17,18]

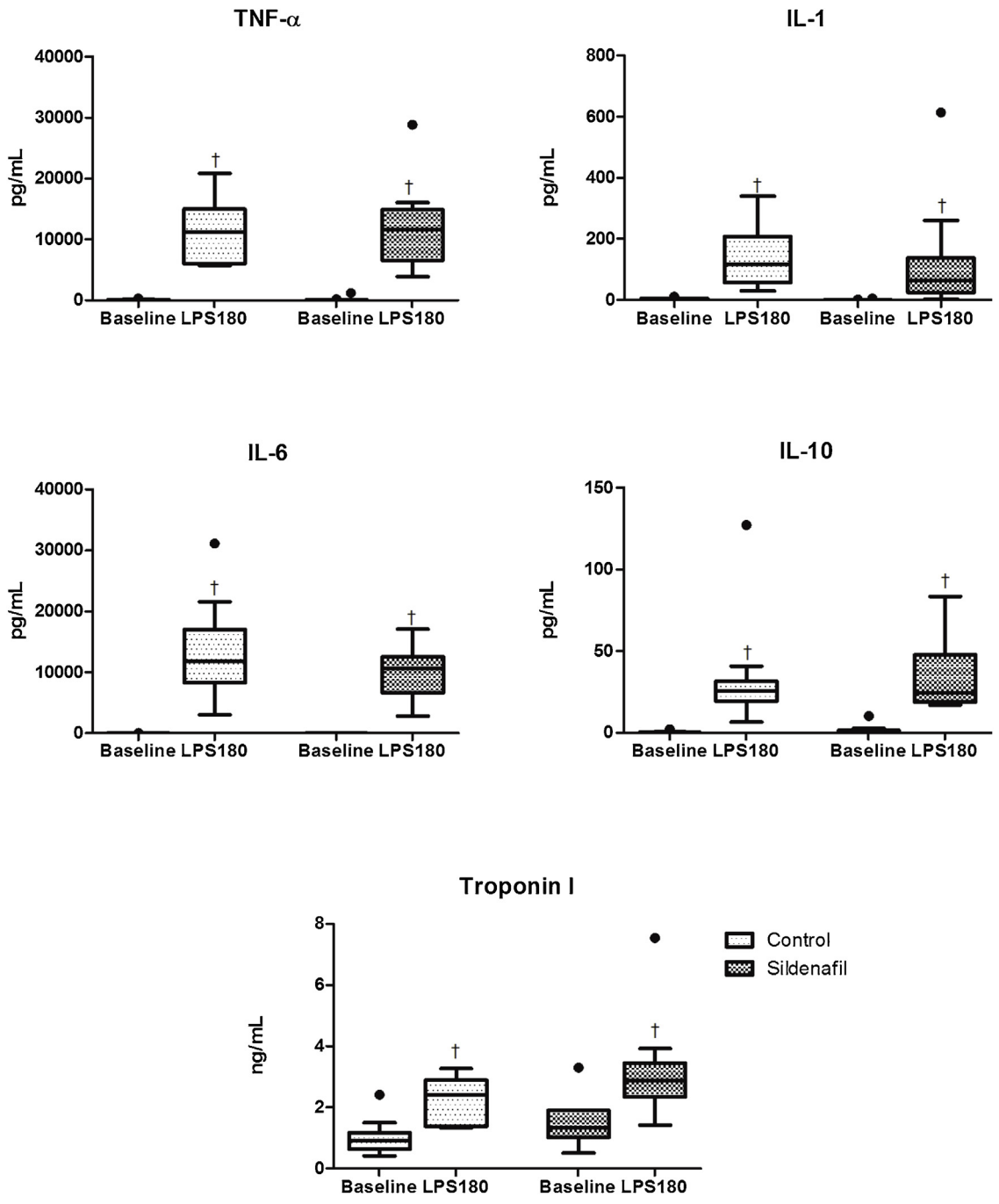

Figure 3 Cytokines and cardiac troponin in Control and Sildenafil group. * denotes significant intergroup differences ($p < 0.05$). • denotes outliers.

Sildenafil decreased pulmonary vascular resistance, pulmonary artery pressure, and RVSWI, decreasing afterload. Furthermore, animals that received sildenafil did not show changes in the end-diastolic volume of the right ventricle avoiding acute right heart dilation. The RV distention at end-diastole is a component of critical care echocardiography to diagnose RV failure as a potential cause of shock.[19] Sepsis-related myocardial dysfunction is not limited to only LV; the RV is also affected being present in about 30% of patients with severe sepsis[20]; by speckle tracking echocardiography, right ventricle dysfunction was detected in 72% of patients with severe sepsis or septic shock and was associated with high mortality.[21]

Several mechanisms lead to sepsis-related cardiac RV dysfunction. Anatomical characteristics and hypoxia due to low perfusion make it difficult to compensate RV afterload increases as we observe in acute pulmonary injury increased pulmonary vascular resistance.[3,22] Right ventricle dysfunction is associated with lower cardiac output, higher norepinephrine doses, higher troponin and lactate.[17] Therefore, sildenafil may play a role in attenuating the severity

of septic shock, avoiding RV dysfunction, but more studies are necessary.

The sildenafil effect in systemic arterial pressure has been previously reported and is dose-related.[5,10,23] In patients with primary pulmonary hypertension the decreased in MAP is clinically insignificant, but its effect in septic patients is probably deleterious[3,9] without a vasoactive support. In a porcine model of meconium-induced lung injury sildenafil reduced MAP even at the lowest dose used (0.4 $mg.kg^{-1}$), demonstrating a markedly systemic vasodilator effect in acute lung injury probably due to inflammation.[24] The decrease in MAP observed in this study might be explained by the high dose used or the presence of a significant systemic inflammation.

The DO_2I increased after LPS infusion in both groups as consequence of increase in cardiac index, resulting in greater supply of oxygen to tissues. In contrast to the report by Kleinsasser et al., where sildenafil caused increases in intrapulmonary shunt in anesthetized pigs which was reflected by marked decreases in PaO_2,[5] we found that sildenafil-maintained oxygenation without effect in shunt fractioning. In patients with pulmonary hypertension associated to lung fibrosis, sildenafil has shown to cause selective pulmonary vasodilation on well ventilated areas and improve gas exchange. It was proposed that sildenafil could amplify pulmonary vasoregulatory mechanisms, enhancing pulmonary nitric oxide effects.[25]

Sildenafil has demonstrated an anti-inflammatory effect in experimental models of acute lung injury and sepsis in rats.[12] We found no effect of sildenafil in cytokines in this porcine LPS model. Species differences, LPS dosage, and the short period of observation could explain the lack of differences in cytokines concentrations.

Troponin has been shown to be an early indicator of pulmonary hypertension related RV dysfunction.[26] All animals had higher troponin concentration at the end of the study. Our findings support that troponin increases in lung injury.[28] Elevated plasma levels of troponin are associated with poor outcomes in pulmonary hypertension and in acute lung injury.[26,27] Sildenafil has been shown to decreases myocardial leak of troponin in rat model of myocardial hypertrophy,[28] but this association in clinical settings of pulmonary hypertension is unknown. Although sildenafil was unable to reduce this cardiac marker in our study, further studies are necessary to evaluate this association.

In contrast to the report by Kiss et al.,[29] in which sildenafil presented a protective effect on lung morphology in monocrotaline (MCT)-induced rat pulmonary arterial hypertension model, we found no attenuation of endotoxin-induced lung lesions. One explanation for these divergent findings may be that sildenafil in this model of acute lung injury has no anti-inflammatory effect, thus cannot attenuate lung lesions. In a model of inhaled LPS airway injury model, sildenafil had shown no anti-inflammatory effects.[30]

There are limitations in our study. Because of the lack of information on the pharmacokinetics and pharmacodynamics of sildenafil in porcine model, the measurement of serum levels of sildenafil would be valuable. The oral administration prior to LPS infusion could be a limitation. Administration of sildenafil orally can cause differences in serum concentration and the injectable form would be more suitable for this purposed, but it is not available commercially. The chosen dose (100 mg) and time of administration were established based on Kleinsasser et al. (2001)[5] and our pilot study (25, 50 and 100 mg) data. Both in our preliminary study and Kleinsasser's, it was observed a decrease in MAP and MPAP 30 minutes after oral administration of sildenafil. Based on these findings we decide to administer sildenafil 30 minutes before LPS infusion to match sildenafil action onset and LPS endotoxemia. We believe that the same behavior would be observed in human patients, but additional studies are necessary to confirm our hypothesis. Finally, this was a model of acute porcine endotoxemia induced by bacterial LPS, and hence cannot be extrapolated to longer-term outcomes nor to clinical practices as it may not accurately reflect human septic shock physiopathology. Pigs show very important increase in pulmonary resistance in response to endotoxin, explained by the great presence of macrophages in porcine lung and the massive release of thromboxane A2.[12] Sample size and evaluation time could also be accounted for these negative results. However, considering the limitations of the study, it was possible to achieve the objective proposed to evaluate the effects of sildenafil in experimental endotoxemic shock in swine model, whose results may encourage future research with sildenafil in sepsis.

Conclusion

Sildenafil attenuated endotoxin-induced pulmonary hypertension, preserving right ventricle function and maintaining oxygenation without effecting shunt fractioning. However, sildenafil did not present an anti-inflammatory effect and did not attenuate lung lesions in this porcine model of endotoxemia. These data reinforce that sildenafil might be useful in patients with septic shock and cardiovascular and respiratory complications. However, more data are needed to determine the risk-benefit ratio of this drug in clinical practice.

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Conflicts of interest

The authors declare no conflicts of interest.

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SYSTEMATIC REVIEW

The effects of magnesium sulfate added to epidurally administered local anesthetic on postoperative pain: a systematic review

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Analgesia, epidural;
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Abstract
Background: This study evaluated the efficacy of epidurally administered magnesium associated with local anesthetics on postoperative pain control.
Methods: The study protocol was registered in PROSPERO as CRD42021231910. Literature searches were conducted on Medline, Cochrane, EMBASE, CENTRAL, and Web of Science for randomized controlled trials comparing epidural administration of magnesium added to local anesthetics for postoperative pain in elective surgical adult patients. Primary outcomes were the time to the first Postoperative (PO) Analgesic Request (TFAR), 24-hour postoperative opioid consumption, and Visual Analog Scale (VAS) scores at the first six and 24 postoperative hours. Secondary outcomes included Postoperative Nausea and Vomiting (PONV), pruritus, and shivering. Quality of evidence was assessed using GRADE criteria.
Results: Seventeen studies comparing epidural were included. Effect estimates are described as weighted Mean Differences (MD) and 95% Confidence Intervals (95% CI) for the main outcomes: TFAR (MD = 72.4 min; 95% CI = 10.22—134.58 min; $p < 0.001$; $I^2 = 99.8\%$; GRADE: very low); opioid consumption (MD = -7.2 mg (95% CI = -9.30 — -5.09; $p < 0.001$; $I^2 = 98\%$; GRADE: very low). VAS pain scores within the first six PO hours (VAS) (MD = -1.01 cm; 95% CI = -1.40—0.64 cm; $p < 0.001$; $I^2 = 88\%$; GRADE: very low), at 24 hours (MD = -0.56 cm; 95% CI = -1.14—0.01 cm; $p = 0.05$; $I^2 = 97\%$; GRADE: very low).
Conclusions: Magnesium sulfate delayed TFAR and decreased 24-hour opioid consumption and early postoperative pain intensity. However, imprecision and inconsistency pervaded meta-analyses, causing very low certainty of effect estimates.

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Introduction

Postoperative pain control is a critical component of anesthesia planning and management. Inadequate pain control causes patient dissatisfaction and increases perioperative morbidity, mortality, and hospital length of stay.[1,2]

Epidural Anesthesia (EA) has been considered the gold-standard technique for postoperative pain management in patients undergoing major thoracic, abdominal, pelvic, or orthopedic surgery, particularly for patients at increased risk of postoperative cardiac events, pulmonary complications, or prolonged ileus.[3,4] The implementation of Enhanced Recovery After Surgery (ERAS) protocols associated with a global shift from open to laparoscopic surgery have limited the indication of epidural analgesia to major abdominal, gynecological, urological, thoracic, or orthopedic surgeries.[5] For patients undergoing major surgeries, thoracic epidural anesthesia, and postoperative epidural analgesia are recommended to accelerate the recovery from surgery as an element of the ERAS protocol.[6] Epidural analgesia is obtained with local anesthetics, usually associated with adjuvant analgesics such as opioids, alpha-2 adrenergic agonists, ketamine, or magnesium.[7]

Magnesium inhibits calcium entry into dorsal horn neurons through non-competitive blockade of N-Methyl-D-Aspartate (NMDA) receptors, modulating the projection of nociceptive stimuli and preventing central pain sensitization.[8]

The effectiveness of intravenously administered magnesium sulfate in decreasing postoperative pain has been documented in several randomized controlled trials, systematic reviews, and meta-analyses.[9,10] The intravenous administration of magnesium sulfate as a single bolus (30–50 $mg.kg^{-1}$), a continuous infusion, or both has been associated with decreased postoperative opioid consumption, delayed time to the first postoperative analgesic request, and decreased prevalence of postoperative shivering.[11]

Magnesium as an adjuvant to local anesthetics in spinal anesthesia has been associated with increased duration of anesthesia without affecting the time to achieve sensory or motor blockade.[12] Moreover, intravenous magnesium sulfate attenuates opioid-related side effects (e.g., nausea, vomiting, and pruritus).[9–11] To date, a limited number of studies have addressed magnesium as an adjuvant to local anesthetics for postoperative epidural analgesia. A former systematic review of eleven studies found that magnesium sulfate added to bupivacaine was associated with a delayed first analgesic requirement, fewer patients requiring rescue analgesia, and smaller doses of postoperative analgesics.[13] This systematic review with meta-analyses aimed to estimate the pooled effects of randomized controlled trials addressing the effectiveness and safety of magnesium sulfate as an adjuvant to bupivacaine, levobupivacaine, or ropivacaine for postoperative epidural analgesia in adult surgical patients.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[14] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO)[15] under registration number CRD42021231910.

Sources of information and search strategy

Articles, theses, abstracts, and conference reports of Randomized Control Trials (RCT) were searched from databases: MEDLINE (from 1946), Web of Science (from 1945), EMBASE (from 1947), Scholar Google, and the Cochrane Central Register of Controlled Trials (CENTRAL) with no language restrictions. Filters were applied to searches to identify studies in human adults. Searches were conducted from December 2020 through January 2021.

The PubMed search included the following string: *(magnesium AND epidural anesthesia AND (humans [Filter])) AND ("randomized controlled trial" [Publication Type]) Filters: Humans*. Scholar Google search string was *"allintitle: magnesium epidural*. The string *"(('magnesium sulfate'/exp OR 'magnesium sulfate') AND ('epidural anesthesia'/exp OR 'epidural anesthesia') AND ([cochrane review]/lim OR [systematic review]/lim OR [meta-analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)) AND 'article'/it"* was used to search EMBASE. The Web of Science: was searched by using the following terms *"TI = (epidural AND magnesium)"*. The following terms were used to retrieve abstracts from CENTRAL: *"epidural OR intrathecal OR subarachnoid in Title Abstract Keyword AND magnesium sulfate in Title Abstract Keyword AND "postoperative pain" in Title Abstract"*.

Clinical questions

The clinical questions addressed the following PICOT elements: **Population**: adult patients undergoing general, epidural, or Combined Spinal-Epidural (CSEA) anesthesia scheduled for elective surgical procedures; **Intervention**: epidural administration of magnesium sulfate associated with local anesthetics solutions; **Comparison**: epidurally-administered local anesthetic alone or with placebo; **Primary outcome**: time to first analgesic request, opioid consumption, and visual analog pain scores; **Secondary outcomes**: prevalence of postoperative nausea or vomiting, pruritus, and shivering. **Time:** during the initial 24 postoperative hours.

Eligibility criteria and study selection

The three authors (GNB, AMJ, GROF) conducted independent literature searches and assessed titles, abstracts, and full papers of the selected references. The authors searched for Randomized Controlled Trials (RCT) on the adult (≥ 18 years old) surgical population, comparing the analgesic efficacy of magnesium sulfate added to epidurally administered local anesthetics solutions compared to local anesthetic alone or with a placebo. Studies were required to also provide data on at least one of the primary outcomes: the time to first postoperative request for rescue analgesics or the opioid consumption during the first 24 postoperative hours. No language restrictions were applied. The following were exclusion criteria: magnesium sulfate was administered via a route other than epidural (e.g., intrathecal, intravenous, or intramuscular); epidural magnesium sulfate

was associated with other adjuvants (e.g., opioid, ketamine, alpha-2 adrenergic agonists were added to the local anesthetic solution in the control group), the study was not a randomized controlled trial; the study was conducted in children or did not report any of the primary outcomes. Controversies about study inclusion were resolved by consensus among the authors.

Data extraction process and data items

Two investigators (GNB, AMJ) independently extracted data from the eligible studies on dedicated spreadsheets. Data presented as graphs in the original articles were extracted with the Engauge Digitizer software.[16] The following information was extracted from the studies included in meta-analyses: the number of patients in the intervention and control groups, type of surgery, anesthesia technique, anesthetic agents, epidural local anesthetic and dose, dose and concentration of the magnesium sulfate bolus and infusion, rescue analgesic and administration route, reported outcomes and the respective mean and standard deviation or frequency. The time to the first analgesic request was computed in minutes. Because distinct analgesics and routes of administration were used for rescue analgesia, their doses were transformed into intravenous morphine equivalents (mg) using converting factors provided elsewhere.[17–19] Average standard deviations of studies assessing the same outcome were imputed to studies that did not report the mean's standard deviation or standard error.[20] Outcome data were double-checked, consolidated, and included in the meta-analysis software.

Assessment of the risk of bias within studies

Individual within-study risk of bias was assessed according to the revised Cochrane risk-of-bias tool for Randomized Trials (ROB 2).[21] Studies were classified as "high risk" if a high risk of bias was assigned to any domain, or "some concerns" were assigned to multiple domains of the ROB 2.[21]

Summary measures

Weighted Mean Differences (MD) were used to summarize the effect sizes of outcomes measured on continuous variables: time to the first analgesic request, opioid consumption during the first 24 postoperative hours, and VAS pain scores at the sixth and 24th postoperative hours. The Risk Ratio (RR) was used to summarize results measured on categorical variables: postoperative nausea or vomiting, pruritus, and shivering. Ninety-five percent confidence intervals (95% CI) were estimated for effect size measures.

Synthesis of results

Random effects meta-analyses were used to estimate pooled effect sizes based on the following assumptions: the studies involved different treatment protocols (e.g., varying dose combinations of magnesium with local anesthetics in the intervention groups). Moreover, distinct time points were used to measure postoperative outcomes. Thus, variability among the different effect estimates could be attributed to within-study sampling error, between-study heterogeneity, or both. Cochrane Q tests and I^2 statistics were used to estimate statistical heterogeneity in effect sizes among the studies included in the meta-analyses,

Assessment of risk of bias across studies

The risk of publication bias was assessed by visual inspection of funnel plots based on the primary outcomes and quantified using Egger's test. Missing studies were filled, and the effect size was corrected using Duval & Tweedie's trim-and-fill method.[22,23] The standardized mean difference against its standard error was used to construct contour-enhanced funnel plots for the primary outcome, including filled studies and adjusted effect sizes from the trim-and-fill method.

Sensitivity analyses

Leave-one-out analyses were conducted to discard single-study dominance in effect sizes. Analyses were done by sequentially removing one study and estimating the effect size based on data from the remaining studies. Study dominance was ascribed to the removed study whenever pooled effect size *p*-values changed from significant to non-significant, or vice-versa.[24]

Different doses of magnesium sulfate were added to local anesthetics, intraoperative magnesium infusions followed bolus doses of magnesium sulfate in some studies, and effects were estimated on patients undergoing different types of surgery. These distinct characteristics might have affected the effect size estimates. Subgroup analyses and meta-regression were used to estimate the simultaneous influence of the abovementioned potential effect modifiers on the pooled effect sizes and the between-study heterogeneity. Random effects and Knapp-Hartung variance adjustment were used in meta-regression.[25]

Quality of evidence

The quality of evidence provided by the meta-analyses was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[26]

Software

Review Manager software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for meta-analyses. STATA 14/MP (StataCorp, College Station, TX, USA) was used to conduct Egger's tests (*metabias* module), Duval & Tweedie's trim-and-fill analyses (*metatrim* module), and meta-regression (*metareg* module).[22,25,27] The GRADEpro GDT software was used to construct a Summary of Findings (SoF) table and estimate evidence quality.[28]

Results

Study selection

Seventeen studies were included in the meta-analyses (Fig. 1). The complete list of retrieved references with reasons for rejection or acceptance are provided in e-component 1.

The seventeen studies[29–43] (1150 patients) used only magnesium as an adjuvant to local anesthetic in the intervention group. Only data applicable to the meta-analyses of the current study were extracted from these studies. The main characteristics of the studies are described in Table 1.

Primary and secondary outcomes of the included studies

Time to the first analgesic request was reported in 12 studies (790 patients).[29,31,33,34,36–42] Analgesic consumption during the first 24 postoperative hours was reported in six studies (416 patients).[30–32,34,37,44] Postoperative pain intensity was reported as visual analog pain scores during the first six postoperative hours in eight studies[31–34,37,39,41,43] (540 patients), and during the first 24 postoperative hours in five studies[30–32,34,37] (356 patients). Postoperative nausea and vomiting were reported in 12 studies[29–33,35,37,39–42] (818 patients), shivering was reported in ten studies[29,31,33,35,37,38,40–42] (640 patients), and pruritus was reported in five studies[31,32,35,37] (318 patients).

Types of surgery

Included studies were performed on patients undergoing the following surgical procedures: cesarean section (n = 2),[31,45] lower limb surgery (n = 6),[29,30,35,40,42,44] lower abdominal and pelvic surgeries (n = 5),[32,34,36,39,41] mixed lower limb and low abdominal surgery (n = 2),[33,38] spine surgery (n = 1),[43] and thoracotomy (n = 1).[37]

Type of anesthesia

Combined spinal-epidural anesthesia was used in one study,[45] combined epidural-general anesthesia was used in

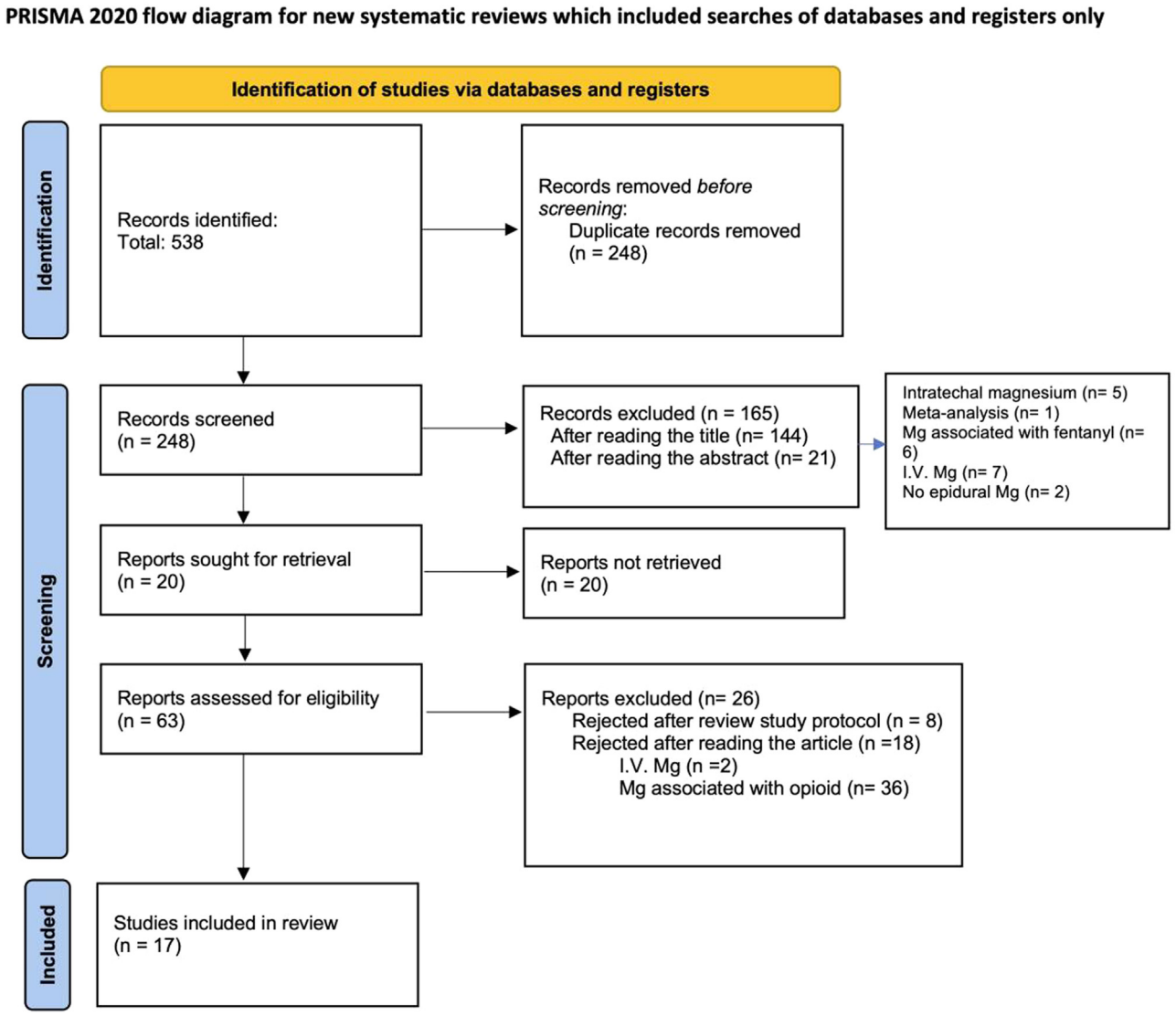

Figure 1 PRISMA study flow diagram.

Table 1 Characteristics of the studies.

Study ID	n $_{MgSO4}$	n control	Control group	Administration of $MgSO_4$	Language	Surgery	Type of anesthesia	Epidural local anesthetic (LA)	Dose (LA)	Epidural $MgSO_4$ Bolus	Epidural $MgSO_4$ infusion	Duration of infusion	Rescue analgesics	Outcomes of interest
Asha 2012[29]	30	30	Placebo (0.9% saline)	Bolus	English	Lower limb surgeries	Epidural	Ropivacaine	16 mL 0.75%	50 mg		Before surgery	Epidural 9 mL of 0.25% ropivacaine bolus	TFAR, adverse effects
Daabis 2013[30]	40	40	Placebo (0.9% saline)	Bolus + infusion	English	Knee replacement	Epidural	Bupivacaine	1 mL 0.5% per segment	50 mg	$MgSO_4$: 10 mg.h^{-1}	During the surgery	Epidural fentanyl 2 μg.mL^{-1} + LA 0.08% bolus	Analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects,
Elsharkawy 2018[31]	30	30	Placebo (0.9% saline)	Bolus	English	Cesarean section	Epidural	Levobupivacaine	20 mL 0.5%	500 mg		Before surgery	diclofenac 75 mg VO or fentanyl 0.5 1 μg.kg^{-1} IV bolus	TFAR, analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Farouk 2008a[32]	29	29	Placebo (0.9% saline infusion before anesthesia induction until the end of the surgery)	Bolus before induction of anesthesia + intraoperative infusion	English	Hysterectomy	General	Bupivacaine	None	50 mg	10 mg.h^{-1}	During surgery	Epidural lidocaine bolus on demand	Analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Farouk 2008b[32]	29	29	Placebo (0.9% saline infusion before anesthesia induction until the end of the surgery)	Bolus at the end of the				surgery + infusion	English				Hysterectomy	General
Bupivacaine	None	50 mg		During surgery	Epidural lidocaine bolus on demand	Analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects								
Ghatak 2010[33]	30	30	Placebo (0.9% saline)	Bolus	English	Lower abdominal and lower limb surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery	Epidural bupivacaine 0.25% 8 mL bolus	TFAR, analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Gupta 2013[34]	30	30	Placebo (0.9% saline)	Bolus	English	Hysterectomy	Epidural	Bupivacaine	9 mL 0.125%	50 mg		End of surgery	Epidural fentanyl 1 μg.kg^{-1} bolus	TFAR, 24h analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Kandil 2012[44]	30	30	Placebo (0.9% saline)	Bolus	English	Lower limb surgery	Epidural	Bupivacaine	0.5% 1 mL per segment	50 mg	10 mg.h^{-1}	During surgery	PCEA fentanyl + LA+ pethidine IM	24h analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Lakra 2015[35]	30	30	Placebo (0.9% saline)	Bolus	English	Lower limb surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery		PO adverse effects
Lenin 2012[36]	25	25	Placebo (0.9% saline)	Bolus	English	Lower abdominal surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery		TFAR
Mohamad 2015[37]	20	20	Placebo (0.9% saline)	Bolus	English	Thoracotomy	Epidural + general	Bupivacaine	8 mL 0.25%	50 mg		End of surgery	i.v. tramadol 50 mg	TFAR, analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects

Table 1 (*Continued*)

Study ID	n $_{MgSO4}$	n control	Control group	Administration of $MgSO_4$	Language	Surgery	Type of anesthesia	Epidural local anesthetic (LA)	Dose (LA)	Epidural $MgSO_4$ Bolus	Epidural $MgSO_4$ infusion	Duration of infusion	Rescue analgesics	Outcomes of interest
Munshi 2016[38]	30	30	Placebo (0.9% saline)	Bolus	English	Lower abdominal surgeries and lower limb surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery	Epidural tramadol 50 mg bolus	TFAR, PO adverse effects
Omar 2018[39]	50	50	Placebo (0.9% saline)	Bolus + epidural infusion levobupivacaine + magnesium infusion 5 $mL.h^{-1}$ until the end of the surgery	English	Lower abdominal and pelvic surgeries	Epidural + general	Levobupivacaine	14 mL 0.5%	50 mg	15 $mg.h^{-1}$	during surgery	i.v. pethidine 1 $mg.kg^{-1}$ + paracetamol 1g	TFAR, VAS pain scores, PO adverse effects
Radwan 2017[43]	22	22	Placebo (0.9% saline)	Bolus + infusion	English	Spine surgeries	Epidural + general	Levo-bupivacaine	14 mL 0.5%	50 mg	10 $mg.h^{-1}$ (LA 0.125%+ $MgSO_4$ 2 $mg.mL^{-1}$. 5 $mL.h^{-1}$)	During surgery	Para-cetamol 1g i.v. / 50 mg pethidine i.v.	Analgesic consumption (24 PO hours, VAS pain scores, PO adverse effects
Rekha 2020[40]	30	30	Placebo (0.9% saline)	Bolus	English	Lower limb surgeries	Epidural	Ropivacaine	16 mL 0.75%	50 mg		Before surgery	Epidural ropivacaine bolus	TFAR, analgesic consumption (24 PO hours), PO adverse effects
Roy 2015[41]	30	30	Placebo (0.9% saline)	Bbolus	English	Infra-umbilical surgeries	Epidural	Bupivacaine	19 mL 0.5%	50 mg		Before surgery	Epidural bupivacaine 0.5% bolus	TFAR, VAS pain scores, PO adverse effects
Shahi 2014[42]	40	40	Placebo (0.9% saline)	Bolus	English	Lower limb surgeries	Epidural	Bupivacaine	14 mL 0.5%	50 mg		before surgery	Epidural bupivacaine 12 mL 0.125% bolus	TFAR, analgesic consumption (24 PO hours), VAS pain scores, PO adverse effects
Sun 2012 [45]	50	50	Placebo (0.9% saline)	Bolus	English	Cesarean section	CSEA	Bupivacaine	10 mL 0.1%	500 mg		During surgery	Epidural 8 mL LA 0.1% bolus + FTN 1 $\mu g.mL^{-1}$ + $MgSO_4$ 1 $mg.mL^{-1}$	TFAR, analgesic consumption (24 PO hours, VAS pain scores, PO adverse effects

CSEA, Combined Spinal-Epidural Anesthesia; i.v., Intravenous; LA, Local Anesthetic; $MgSO_4$, Magnesium Sulfate; PO, Postoperative; TFAR, Time for the First Analgesic Request; VAS, Visual Analog Scale.

two studies.[39,37] Epidural anesthesia alone was used in 14 studies.[29–31,33–36,38,40–42,44]

Magnesium doses and regimens

All studies used epidural magnesium as a single bolus dose. The initial bolus dose of magnesium sulfate was 50 mg in 15 studies,[29,30,32–44] and 500 mg in two studies.[31,45] After the initial bolus, continuous epidural infusion of magnesium sulfate was used in five studies[30,32,39,43,44] at rates varying from 10–15 mg.h^{-1}, limited to the intraoperative period in four studies, and continued for 48 hours postoperatively in one study.[32]

Rescue medication modalities

In six studies, rescue analgesia was provided by epidural injections of plain Local Anesthetic (LA) solutions;[29,32,33,40–42] fentanyl was added to epidural LA in one study;[30] intramuscular pethidine was used in conjunction with epidural local anesthetic plus fentanyl in one study,[44] and magnesium sulfate was added to the local anesthetic fentanyl solution in one study.[45] Three studies reported only systemic analgesia with IV fentanyl, oral diclofenac, IV paracetamol or IV tramadol.[37,39,43] One study used epidural tramadol as a rescue analgesic.[6] Two studies did not report rescue medication.[7]

Synthesis of results

Primary outcomes

Epidural administration of magnesium sulphate added to local anesthetics delayed the first postoperative analgesic request as compared to placebo by 72.4 minutes (95% CI = 10.22–134.58 min; $p < 0.001$; I^2 = 99.8%; GRADE = very low) (Fig. 2). Postoperative opioid consumption during the first 24 postoperative hours (measured as IV morphine equivalents) was lower among patients who received epidural magnesium in combination with local anesthetics (MD = -7.2 mg; 95% CI = -9.30 – -5.09 mg; $p < 0.001$; I^2 = 98%; GRADE = very low) (Fig. 3). Pain intensity within the first six postoperative hours measured on 10-cm VAS was lower among patients who received epidural magnesium sulfate (MD = -1.01 cm; 95% CI = -1.40–0.64 cm; $p < 0.001$; I^2 = 88%). Comparisons between raw VAS pain scores at the 24 PO hours between magnesium and placebo yielded a borderline p-value (MD = -0.56 cm; 95% CI = -1.14–0.01 cm; $p = 0.05$; I^2 = 97%) (Fig. 4).

Secondary outcomes

Epidural magnesium alone did not differ from placebo regarding the probabilities of PONV (RR = 0.70; 95% CI = 0.34–1.14; $p = 0.15$; I^2 = 0%) or pruritus (RR = 1.23; 95% CI = 0.50–2.98; $p = 0.65$; I^2 = 0%) but reduced the risk of perioperative shivering (RR = 0.39; 95% CI = 0.21–0.71; $p = 0.002$; I^2 = 18%) (Fig. 5).

Sensitivity analyses

Leave-one-out procedures

One study was responsible for the significant p-value found in the meta-analyses of the time to first analgesic request outcome. The elimination of this study's results caused the weighted mean difference between groups move from 72.40 min (95% CI = 10.22, 134.58 min; $p = 0.02$) to 66.10 min (95% CI = -4.49, 136.69 min; $p = 0.07$). There was no study dominance among the postoperative opioid consumption meta-analysis studies.

Distinct doses of magnesium sulfate (50 or 500 mg) added to local anesthetics (t = 1.31; $p = 0.21$), bolus administration versus bolus dose followed by intraoperative magnesium infusions (t = 0.46; $p = 0.65$) or the types of surgery ($F_{(4,7)} = 0.45$; $p = 0.77$) were not identified as effect modifiers or inter-study heterogeneity at meta-regression of the time to first analgesic request outcome. However, magnesium sulfate added to levobupivacaine was associated with longer times to first analgesic request than bupivacaine or ropivacaine (t = 2.81; $p = 0.02$). Forest plots of subgroup analyses are shown in e-component 2. No subgroup analyses or meta-regression were conducted to assess the effect of the potential effect modifiers on the postoperative opioid consumption outcome because of the insufficient number of studies.

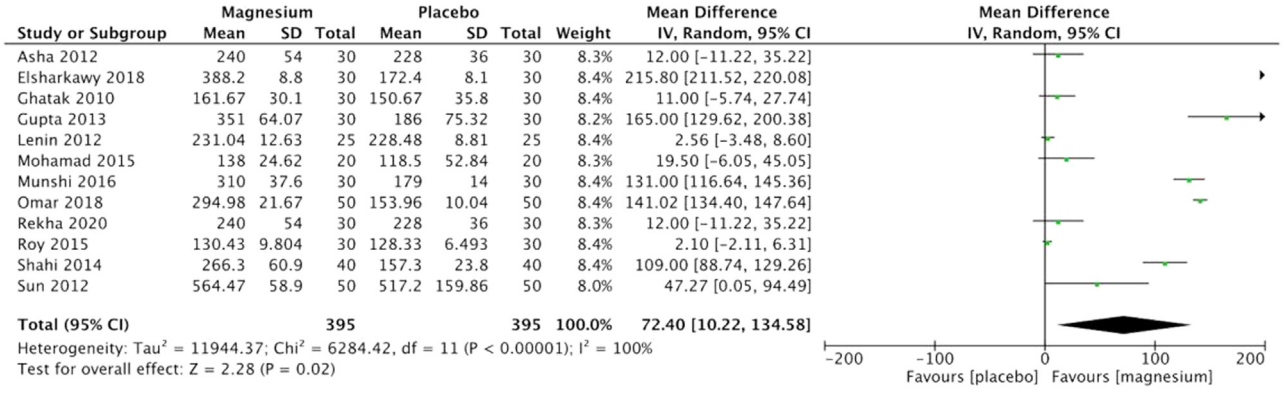

Figure 2 Forest plots of pooled comparisons of time to the first postoperative opioid request. Boxes represent the weighted mean difference between groups that received epidural magnesium sulfate (Magnesium) or 0.9% saline (Placebo). Black lines surrounding boxes represent the respective 95% Confidence Intervals (95% CI). The black diamond represents the pooled effect size, its middle point being the pooled averaged mean difference and the lateral extremes, the 95% confidence limits of the mean difference. IV, Inverse Variance Method; Random, Random-effects model; SD, Standard Deviation.

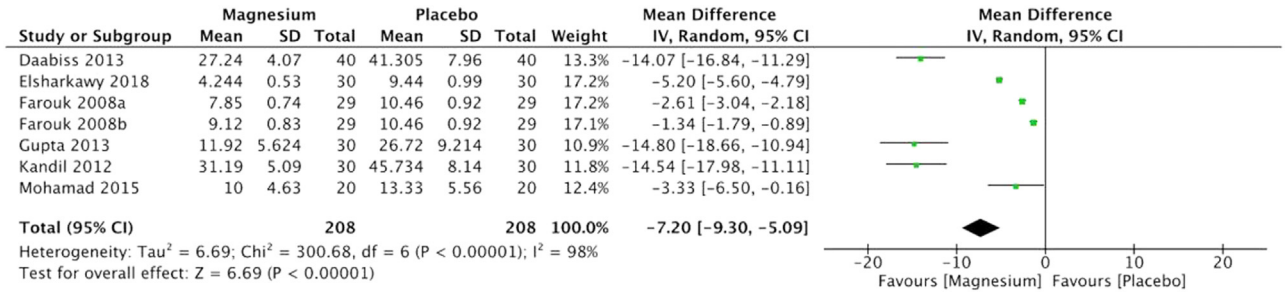

Figure 3 Forest plots of pooled comparisons of postoperative opioid consumption. Boxes represent the weighted mean difference between groups that received epidural magnesium sulfate (Magnesium) or 0.9% saline (Placebo). Black lines surrounding boxes represent the respective 95% Confidence Intervals (95% CI). The black diamond represents the pooled effect size, its middle point being the pooled averaged mean difference and the lateral extremes, the 95% confidence limits of the mean difference. IV, Inverse Variance method; Random, Random-effects model; SD, Standard Deviation.

Assessment of risk of bias within studies

Of the 17 studies included in meta-analyses, 15 raised some concerns about bias in at least one ROB 2 assessment tool domain, while 2 were classified as having a low risk of bias in all domains. No study was classified as having a high risk of bias (Fig. 6, e-component 3)

Assessment of risk of publication bias across studies

Eggers's test did not detect publication bias or small-study effects in meta-analyses of time to first analgesic request among studies that compared epidural magnesium to placebo (p = 0.75). Contour-enhanced funnel plots, including filled studies, are shown in e-component 3. Publication bias estimation based on the opioid consumption outcome was impossible given the insufficient number of studies available.

Quality of evidence

Very low confidence was assigned to the meta-analyses of the primary outcomes of the GRADE assessment, suggesting that the actual effect may be different from the estimated effect, driven by the within-study severe risk of bias, inconsistency, and imprecision issues that might have biased meta-analyses.[46] A GRADE summary of findings table is provided in e-component 4. A completed PRISMA checklist is provided in e-component 5.

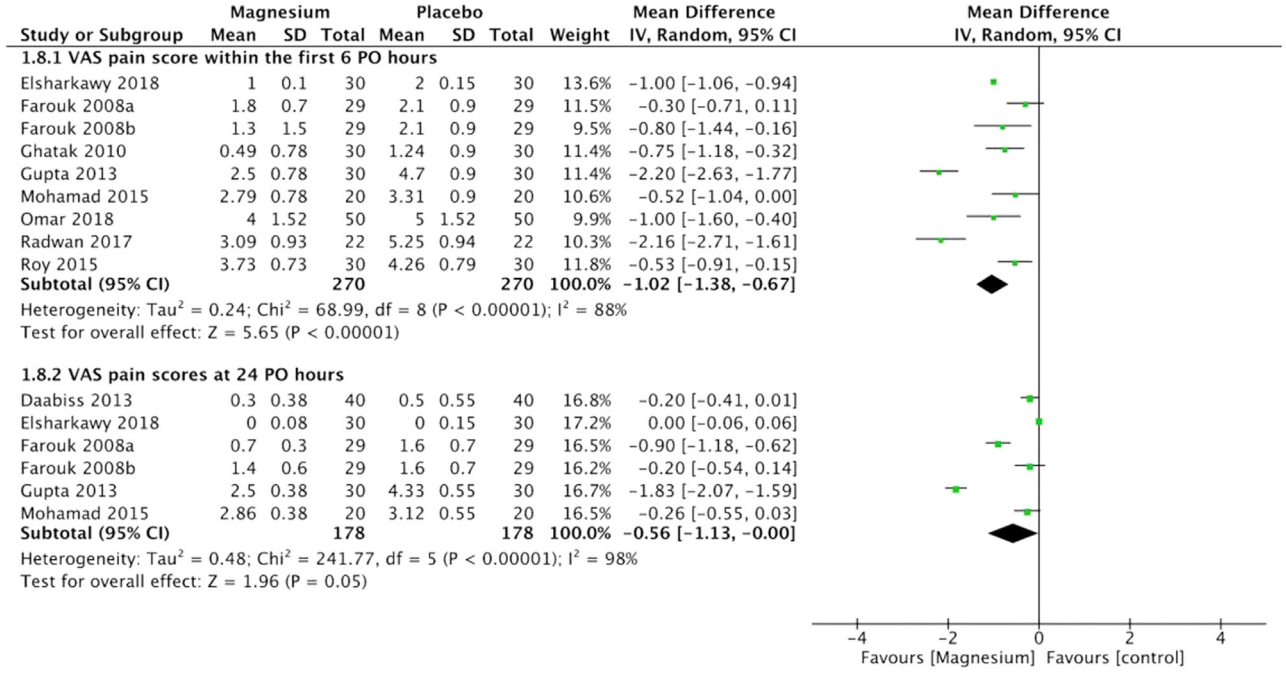

Figure 4 Forest plots of pooled comparisons of VAS pain scores within the first 6 and 24 postoperative hours. Boxes represent the weighted mean difference between groups that received epidural magnesium sulfate (Magnesium) or 0.9% saline (Placebo). Black lines surrounding boxes represent the respective 95% Confidence Intervals (95% CI). The black diamond represents the pooled effect size, its middle point being the pooled averaged mean difference and the lateral extremes, the 95% confidence limits of the mean difference. IV, Inverse Variance method; Random, Random-effects model; SD, Standard Deviation.

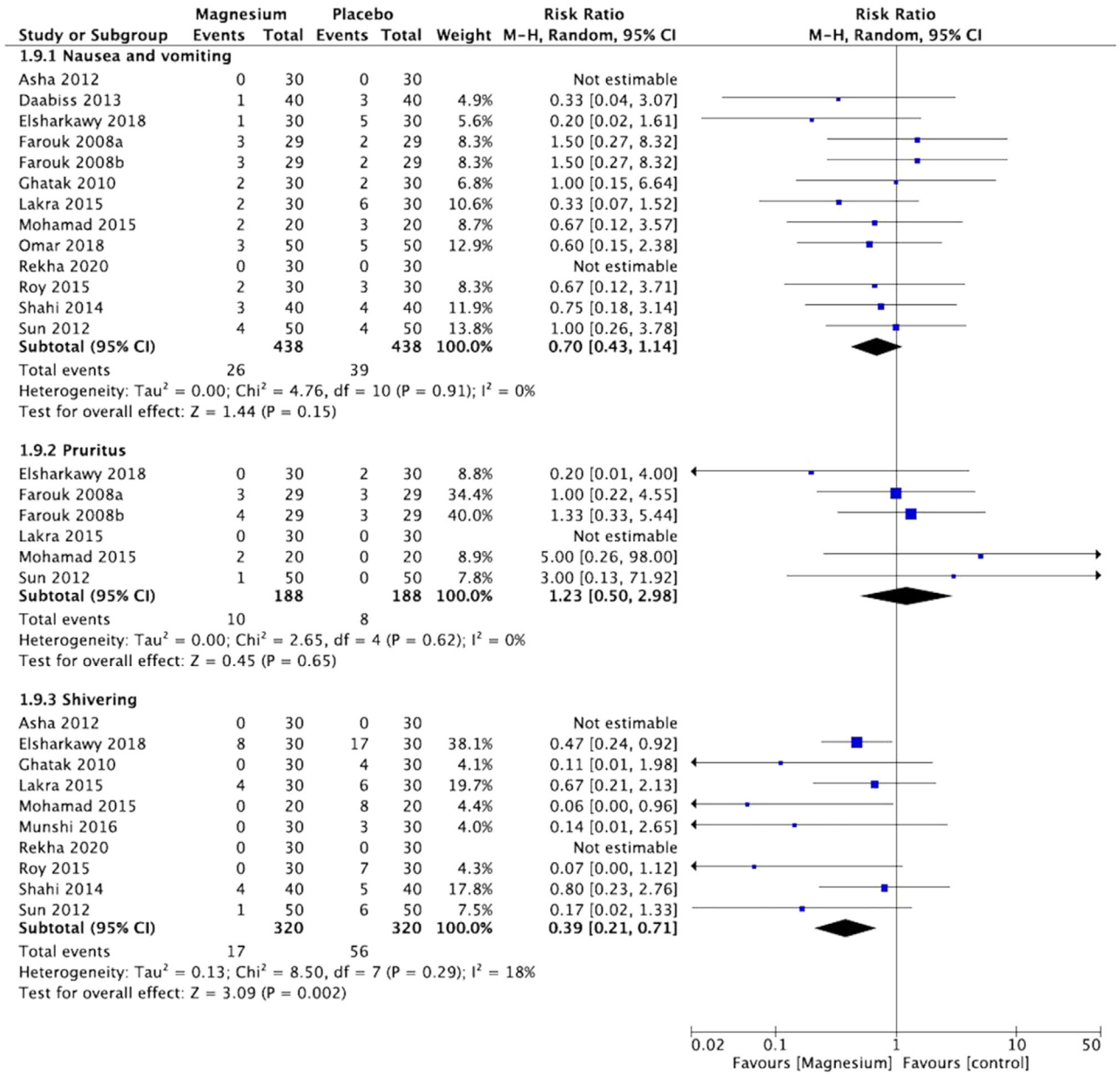

Figure 5 Forest plots of pooled comparisons of postoperative side-effects: PONV, pruritus, and shivering. Boxes represent the Risk Ratio (RR) between groups that received epidural magnesium sulfate (Magnesium) or 0.9% saline (Placebo). Black lines surrounding boxes represent the respective 95% Confidence Intervals (95% CI). The black diamond represents the pooled effect size, its middle point being the pooled risk ratio and the lateral extremes, the 95% confidence limits of the mean difference. IV, inverse variance method; Random, Random-effects model; SD, standard deviation.

Discussion

Mathematically, magnesium delayed the first postoperative analgesic request and decreased 24-hour postoperative opioid consumption compared to placebo. However, serious issues pervaded these meta-analyses. First, high statistical heterogeneity was found among studies' effect sizes. According to meta-regression, statistical heterogeneity was not due to between-studies methodological aspects, like the type of surgery, the use or not of an intraoperative magnesium infusion following the bolus dose, or even the doses (50 mg or 500 mg) used in the studies included in the meta-analyses. Consequently, systematic sampling errors may have contributed to differences among studies' effect sizes. Second, part of the data was extracted from graphs using a vector graph software, which may have introduced some imprecision in the extracted data. Moreover, because different analgesic and routes of administration were used, postoperative analgesic consumption was based on published equivalence ratios, which are not exact measures. Third, some concerns were raised about the critical aspects of randomized controlled trial methodology, mainly because most articles provided little information about randomization methods, allocation concealment, and participants' and investigators' blinding. Most studies did not report a clear *a priori* statistical plan or protocol registration, raising concerns about selective reporting bias.

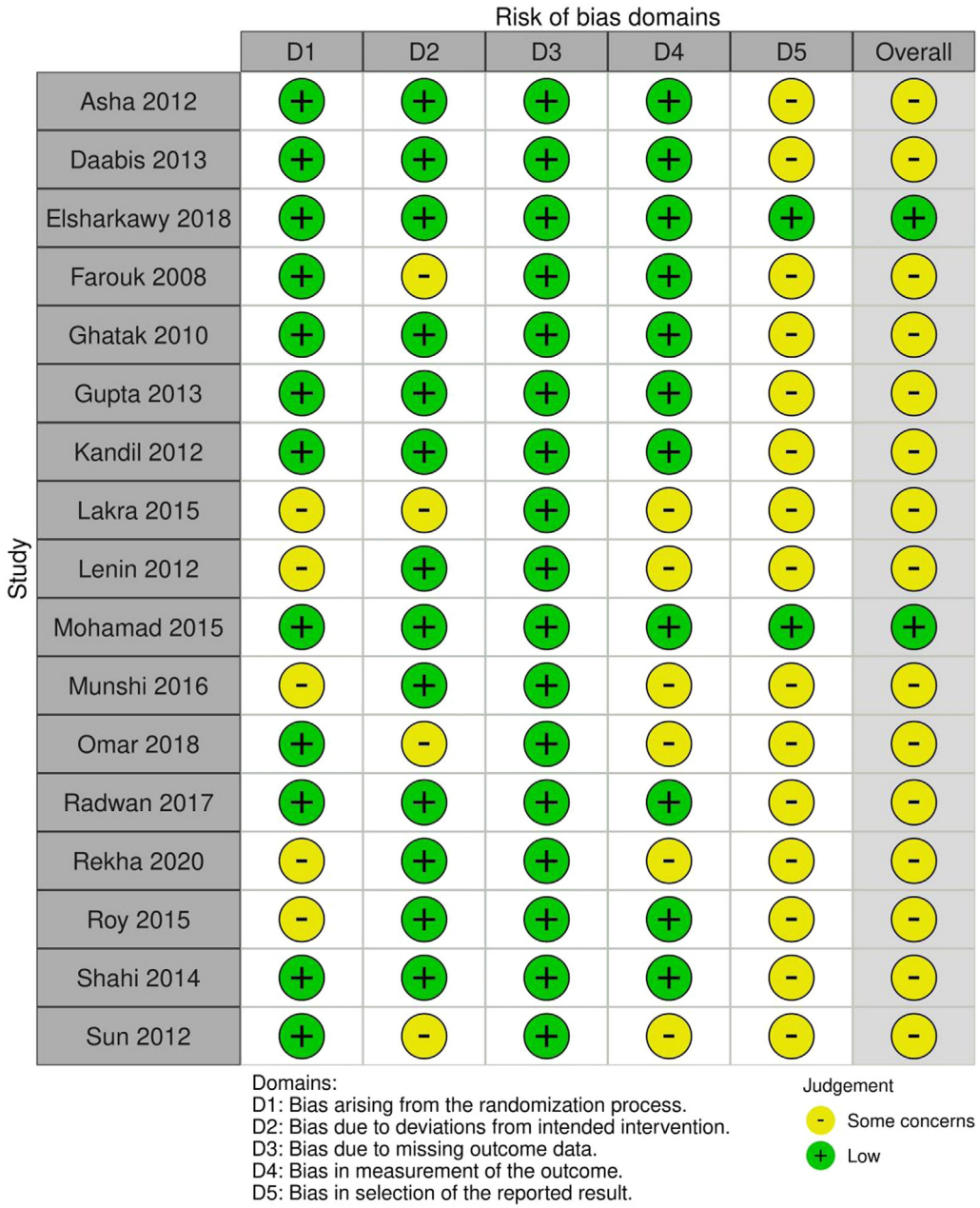

Figure 6 Rob 2 traffic-light plot showing results of within-studies risk of bias assessment. Although some concerns were raised on multiple aspects of most studies, no study showed reasons for assigning a high risk of bias in any domain of the RoB 2 tool.

Visual analog pain scores within the first six postoperative hours were lower among patients who received epidural magnesium. Still, they did not differ from the VAS scores of the placebo group at the 24-hour postoperative measurement occasion. Some studies did not report standard deviations for the mean VAS pain scores. Standard deviations were imputed to those studies to perform the meta-analyses according to the prognostic method proposed by Ma and colleagues.[20] Missing standard deviation imputation methods are acceptable alternatives to study data deletion during data extraction for meta-analyses and have been demonstrated to produce safe and informative estimates.[47]

Epidurally administered magnesium sulfate did not affect the incidence of postoperative nausea, vomiting, and pruritus but decreased the incidence of perioperative shivering. As suggested by the low statistical heterogeneity found in the separate meta-analyses, these findings were consistent across the available studies. Magnesium may affect hemodynamic stability, prolong neuromuscular block, and delay the awakening from anesthesia.[48,49] Insufficient data were present in the available studies. Furthermore, magnesium serum levels were not measured in any of the studies. The absence of such information prevents an appreciation of the safety profile of magnesium administered epidurally. Significant neurodegeneration has been reported after single or repeated intrathecal magnesium sulfate injections in rats.[50] However, data on the postoperative neurological status of patients were not present in the studies

included in this systematic review, further hindering conclusions about the neurological safety of epidurally administered magnesium sulfate.

According to GRADE criteria, this systematic review provided a very low quality of evidence for using epidural magnesium sulfate added to local anesthetics, suggesting that the actual effects may differ substantially from the estimated effects, that is very low certainty.

Besides the issues raised in the preceding paragraphs, additional methodological limitations of this study must be acknowledged. First, time to the first analgesic request, postoperative opioid consumption, and pain scores are imperfect surrogates for postoperative pain intensity because they are affected by factors dependent on the patients (e.g., culture, level of education, altruism, expectation, beliefs),[51] and on the mode of administration (e.g., patient- versus nurse-controlled analgesia or criteria for postoperative analgesia administration),[52] or the evaluator.[53] Second, readers must also consider that the small number of patients included in the limited number of available studies may have caused type II statistical error in meta-analyses and meta-regression. Combined spinal-epidural anesthesia was used in one study included in the time to first analgesic request meta-analysis.[45] Residual effect of spinal anesthetic might have affected the effect size estimator, but the elimination of this study during leave-one-out procedures did not affect the estimate, heterogeneity, or the meta-analysis' *p*-value.

This systematic review highlights caveats of mistrusting the mathematical results of small, low-quality studies and meta-analyses based on such studies. A meta-analysis by itself cannot fix the methodological issues of the included studies. However, systematic review methodology includes a critical appraisal of the data sources for the meta-analyses, helping readers to discern about relying or not on the numbers brought about by statistical calculations.[54]

Conclusion

Adding magnesium sulfate to local anesthetics is associated with a delayed first postoperative analgesic request and decreased opioid consumption during the first 24 postoperative hours. However, because of severe methodological issues in the available studies, the pooled effects found in the meta-analyses may have been seriously biased. Consequently, a very weak level of recommendation supports the use of magnesium sulfate as an adjuvant to epidural analgesia based on local anesthetics. In other words, the clinical use of magnesium sulfate as an adjuvant to epidural anesthetics lacks solid evidence and should be discouraged until large, well-designed clinical trials provide definitive evidence.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2022.08.005.

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SYSTEMATIC REVIEW

Analysis of the efficacy of prophylactic tranexamic acid in preventing postpartum bleeding: systematic review with meta-analysis of randomized clinical trials

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KEYWORDS
Postpartum hemorrhage;
Prophylaxis;
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Abstract

Background: Postpartum Hemorrhage (PPH) is one of the main causes of maternal mortality, mainly in the poorest regions of the world, drawing attention to the need for strategies for preventing it. This study aims to evaluate the efficacy of prophylactic administration of Tranexamic Acid (TXA) in decreasing blood loss in pregnant women in delivery, preventing PPH.

Methods: Systematic review of randomized clinical trials. We searched for publications in PubMed, EMBASE and Cochrane Library databases, with the uniterms "postpartum, puerperal hemorrhage" and "tranexamic acid", published between January of 2004 and January of 2020. The eligibility criteria were trials published in English with pregnant women assessed during and after vaginal or cesarean delivery about the effect of prophylactic use of TXA on bleeding volume. The random-effects model was applied with the DerSimonian-Laird test and the Mean Difference (MD) was calculated for continuous variables together with each 95% CI. This systematic review was previously registered in the PROSPERO platform under the registration n° CRD42020187393.

Results: Of the 630 results, 16 trials were selected, including one with two different doses, performing a total of 6731 patients. The intervention group received a TXA dose that varied between 10 $mg.kg^{-1}$ and 1g (no weight calculation). The TXA use was considered a protective factor for bleeding (MD: -131.07; 95% CI: -170.00 to -92.78; $p = 0.000$) and hemoglobin variation (MD: -0.417; 95% CI: -0.633 to -0.202; $p = 0.000$). In the subgroup analysis related to the cesarean pathway, the effect of TXA was even greater.

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Conclusion: The prophylactic use of tranexamic acid is effective in reducing the post-partum bleeding volume.
PROSPERO registration ID: CRD42020187393.

Introduction

The occurrence of post-partum hemorrhage is a leading cause of maternal morbidity and mortality. With an incidence that can reach 6%, Post-Partum Hemorrhage (PPH) is, according to the World Health Organization (WHO), responsible for almost one quarter of all maternal deaths in the world, and can reach one third in developing nations.[1-3] The difference in mortality related to socioeconomic indices reflects how the quality of the health structure and treatment are factors that might impact this outcome.[1] Thus, the development of actions that are not only effective, but also of reasonable cost, is essential to improving these numbers.

Classically, PPH is defined as a volume of postpartum blood loss higher than expected: ≥500 mL after vaginal birth or ≥1000 mL after cesarean delivery. However, this definition is criticized because bleeding may not be externally visible, or blood volume may be wrongly measured in a mixture with amniotic fluid. In addition, postpartum morbidity is relatively infrequent among women with blood loss from 500 to 999 mL.[4] The definition of PPH was revised by the American College of Obstetricians and Gynecologists (ACOG) in 2017, and a new one was proposed: cumulative blood loss ≥1000 mL or bleeding associated with signs/symptoms of hypovolemia within 24 hours of the birth process regardless of delivery route.[5] However, they kept the recommendation to consider abnormal a blood loss greater than 500 mL and proceed investigation in a vaginal delivery.

Several risk factors are associated with PPH, including a history of prior PPH, overdistended uterus (multiple gestations, polyhydramnios, and a macrosomic fetus), nulliparity, induction and augmentation of labor, placental abnormalities (placenta praevia, placenta accreta), coagulation disorders, and prolonged labor. Some studies even suggest epidural anesthesia as a risk factor.[6] Nevertheless, only one third of PPH cases have identifiable risk factors, and there is no isolated risk factor that helps to identify which patient is likely to respond to initial treatment, which is mostly based on the use of traditional uterotonics, such as oxytocin and methylergometrine, assuming that the main cause of PPH is uterine atony.[3]

Tranexamic Acid (TXA) is a synthetic lysine analogue that inhibits fibrinolysis. In recent years, due to its relatively low cost and ease of use, this drug started to be used in the treatment of acute bleeding in several situations, with low incidence of collateral effects.[7] Solid evidence recommends its use in some situations, and the best known examples are the CRASH-2 and WOMAN trials which, respectively, validated the use of TXA in situations like trauma and the treatment of PPH itself.[8,9] However, it is not yet defined whether the prophylactic use of TXA brings benefits, leaving open the possibility of its administration even before the diagnosis of PPH is established. Previous meta-analyses failed to define this question, and new clinical trials have been published since then.[10,11]

The aim of this systematic review and meta-analysis was to evaluate the effectiveness of the prophylactic use of TXA in reducing postpartum bleeding.

Methods

Eligibility criteria

This study is a systematic review with meta-analysis of blinded and randomized clinical trials about the effect of prophylactic use of TXA on bleeding volume in patients undergoing vaginal or cesarean delivery. The search included studies in English published between January of 2004 and January of 2020.

Information sources

The search was performed in the PubMed/Medline, EMBASE and Cochrane Library databases. PRISMA statement guidelines were followed for planning and preparing the study and the research protocol was previously registered on the PROSPERO platform under registration CRD42020187393.[12]

Data items

The primary outcome assessed was bleeding volume, in milliliters, in the peripartum period. As secondary outcomes, hemoglobin variation, incidence of side effects, use of uterotonics, and need of transfusion of blood products were evaluated. Sensitivity assessments were performed for type of delivery, presence of risk factors for PPH and time of drug administration.

Search strategy

The search in the database was carried out between March 10th and 12th, 2020. The search strategy consisted of the keywords "postpartum, puerperal hemorrhage" and "tranexamic acid" or synonyms, adopting AND and OR as interlocutors. The search strategies at EMBASE and Cochrane Library were as follows: *"postpartum hemorrhage" in Title Abstract Keyword AND tranexamic acid in Title Abstract Keyword - (Word variations have been searched)"* with filter for clinical trials. In PubMed/Medline, the search comprised: *((("postpartum period"[MeSH Terms] OR ("postpartum"[All Fields] AND "period"[All Fields]) OR "postpartum period"[All Fields] OR "postpartum"[All Fields]) OR ("postpartum period"[MeSH Terms] OR ("postpartum"[All Fields] AND "period"[All Fields]) OR "postpartum period"[All Fields] OR "puerperium"[All Fields])) AND ("tranexamic acid"[MeSH*

Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields])) AND (("hemorrhage"[All Fields] OR "hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields]) OR ("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleeding"[All Fields])) AND Clinical Trial [ptyp].

Selection process

Two independent researchers (IC and RF) made a preliminary assessment of the title and abstracts with the aid of the Rayyan© tool.[13] In this phase, all inaccessible studies, duplicates, only research protocols, in non-English language, or which used active control protocols were initially excluded. In a second phase, the articles were read in full text for inclusion consideration and the eligibility of each study was determined. In the case of a disagreement, a third researcher (CG) made the final assessment.

Study risk of bias assessment

As a way of assessing the risk of bias and the quality of the studies included in this meta-analysis, the Risk of Bias 2.0© tool was used.[14]

Data collection process, effect measures, and synthesis methods

The data regarding bleeding volume and the other secondary outcomes were recorded in a spreadsheet. A random effects model was used with the DerSimonian-Laird test. Mean Difference (MD) and 95% Confidence Intervals (95% CI) were calculated for continuous variables and a *p*-value of 5% was considered for statistical significance. Statistical heterogeneity was calculated using the Chi-Square method (X^2) and Higgins test (I^2).[15] The presence of heterogeneity was considered if $p < 0.05$ and $I^2 \geq 50\%$. Evaluation of potential publication bias was made through visual analysis of the funnel graph and by Begg[16] and Egger tests.[17]

Certainty assessment

To assess the impact of the study, the GRADE protocol (Grading of Recommendations, Assessment, Development and Evaluations) was applied to the GRADEpro GDT©[18] program, according to the GRADE System Methodological Guidelines.[19]

As for the secondary outcomes, in those in which there was not enough data to perform a meta-analysis, a qualitative analysis was performed.

Results

Results for study selection

The search in the databases resulted in 630 trials. Initially, 185 results were identified as duplicates. In addition to these, another 16 studies found through direct search were also included. Upon reading the abstracts of the 461 remaining results, only 39 studies were qualified for full text reading. Of these, two were excluded for not having or not reporting randomization,[20,21] nine for not using placebo in the control group,[22-30] four for not having or not reporting blinding,[31-34] five for not reporting neither blinding nor placebo,[35-39] one for using TXA as treatment and not as prophylaxis,[40] and one because only the abstract was written in English.[41] Thus, 17 trials were selected to comprise the systematic review, however, one of them could not be part of the meta-analysis, as the volume measurements did not report standard deviation[42] (Fig. 1)

Study characteristics

The 16 trials selected for the meta-analysis[11,43-56] included 6701 patients, with 3361 patients in the intervention group and 3340 in the control group. However, in the study by Goswami et al.,[49] two different doses of TXA were used in comparison with the control group (10 $mg.kg^{-1}$ and 15 $mg.kg^{-1}$); so, for the purposes of statistical analysis, each dose was regarded as an independent trial, but the control group was the same. As such, the final analysis considered the inclusion of 6731 patients from 17 trials,[11,43-56] with 3361 patients in the intervention group and 3370 in the control arm. Characteristics of each study are described in Table 1.

Regarding the trial countries, Turkey, Iran, India, and Egypt had three studies each. China, Pakistan, France, Thailand, and Nepal had one trial each.

Results of synthesis and qualitative assessment of individual studies

The assessment of peripartum bleeding in the 17 trials of the meta-analysis[11,43-57] showed a reduction in volume sufficient to consider TXA as a protection factor (MD: -131.70; 95% CI: -170.62 to -92.78; $p = 0.000$), as shown in Figure 2A.

Regarding secondary outcomes, seven of the total studies underwent hemoglobin variation assessment[11,43,46,48,51,53,55] allowing comparison of results. The TXA group also showed a lower variation in hemoglobin, expressed as $g.dL^{-1}$ (MD: -0.417; 95% CI: -0.633 to -0.202; $p = 0.00$) (Fig. 2B).

As for side effects, in the qualitative assessment, nine articles did not report or did not have side effects.[42-46,50,52,54,55] Two trials reported a rare occurrence of serious side effects,[11,48] such as Xu et al. who described two thromboembolic events in each arm of the study (RR = 0.98; 95% CI: 0.14 to 6.78; $p = 0.38$), and Sentilhes et al. who reported one event in TXA group and four in the control group (RR = 0.25; 95% CI: 0.03 to 2.24; $p = 0.37$). Only Sentilhes et al. described a case of seizure in the TXA group. The remaining studies only described mild side effects, with higher incidence of gastrointestinal symptoms such as nausea, vomiting, and diarrhea.

In the qualitative analysis of the use of different uterotonics, nine trials found a reduction in their need.[11,43-45,47,49,51,52,57] The highlights were Gungorduk et al. from 2013,[47] with a 69% reduction in the need for additional uterotonics ($p = 0.007$), and Sentilhes et al. with a reduction of 25% (RR = 0.75; 95% CI: 0.71 to 0.92; $p = 0.006$). The need to use blood products was assessed by eleven studies. However, only a few found statistical difference, such as Abbas et al.,[45] who observed a 76% reduction ($p = 0.0001$) in the need for blood transfusion in the TXA group, but this trial used a very small sample (n = 62) and evaluated patients with high risk of PPH (placental accretism).

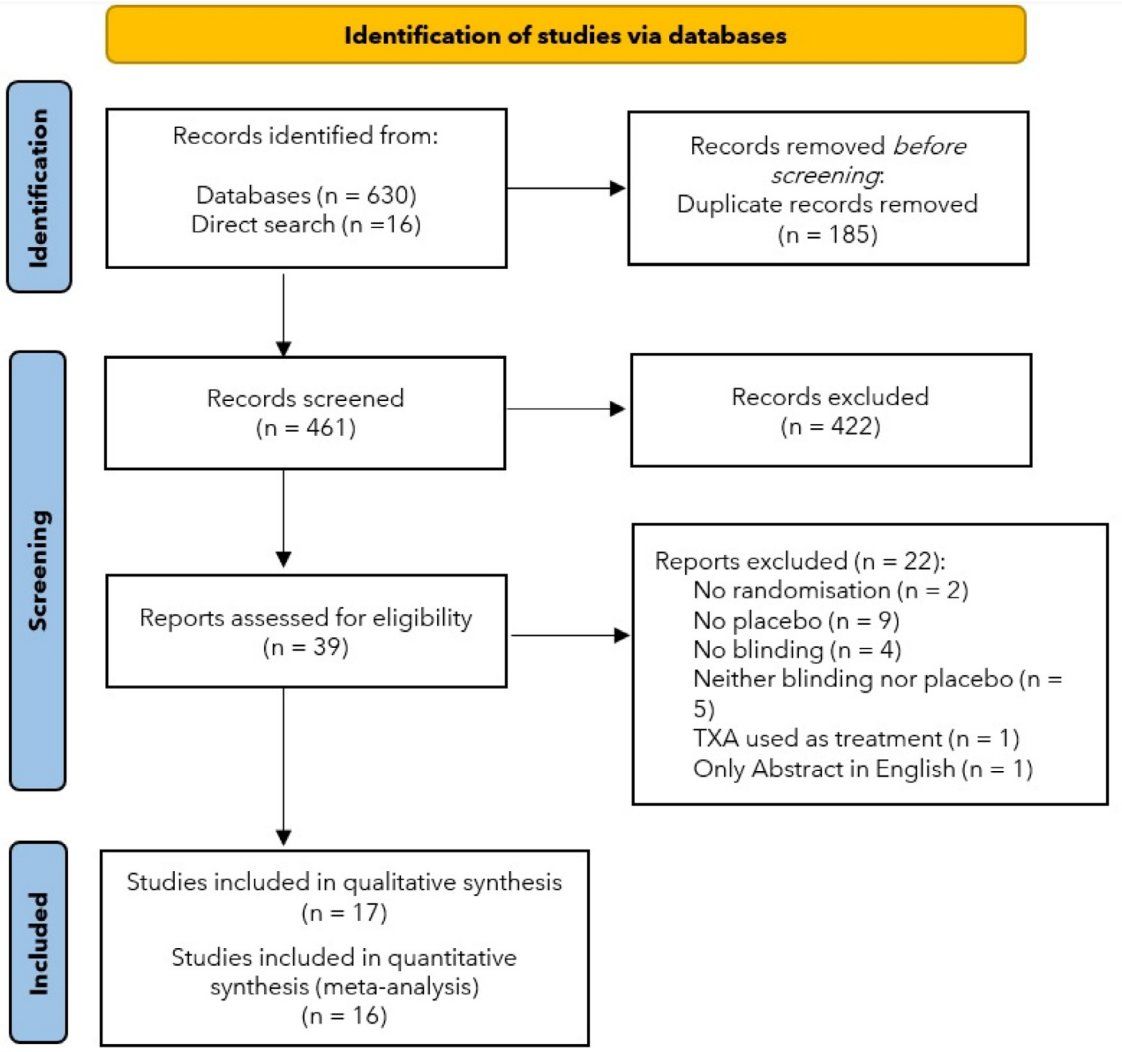

Figure 1 PRISMA 2020 flow diagram.

Considering only the 11 trials in which the cesarean delivery was studied, the quantitative subgroup analysis related to this type of birth showed that the effect of TXA is even greater on the reduction of bleeding (MD: -170.56; 95% CI: -218.84 to -122.29; $p = 0.000$) (Fig. 2C). Regarding the five trials that assessed vaginal delivery, a quantitative analysis in this restricted group showed a much smaller effect of TXA (MD: -48.99; 95% CI: -91.42 to -6.57; $p = 0.024$), with all the caveats that must be considered when conducting a meta-analysis in such a small group of trials.

The presence of risk factors for bleeding was an inclusion criterion in three trials, as in the study by Abbas et al., performed only in women with placental accretism, in the study by Goswami at al. that selected only patients with anemia, and in the trial by Sujata et al. that considered most risk factors as inclusion criteria.[42,45,47] The remaining articles considered these predisposing factors as exclusion criteria, with great variation in the quality and quantity of elements considered. The risk elements most used as exclusion criteria were coagulation disorders, being considered by 12 trials,[11,42,43,46,48,49,51-55,57] followed by factors that cause uterine hyperdistention, with 11 studies.[11,43,44,46,48,50-54,56] In third place, there were placental abnormalities[11,43,47,50,52,56] and anemia,[50-52,54,57] in six trials each. Even though some of the literature does not consider multiparity as risk factor, five studies used it as exclusion criteria.[11,44,50,53,57]

There was also heterogeneity of the time of drug administration; however, all trials were centered at some point between 20 minutes before incision and five minutes after fetus extraction.

Risk of bias in studies

In Figure 3, the funnel plot for the sixteen trials shows a smaller distribution of studies to the left of the summary effect, with a distribution mostly beyond the limits of the funnel. The Egger ($p < 0.001$) and Begg ($p < 0.001$) tests reinforce the presence of publication bias.

The evaluation with the Risk of Bias tool considered all trials in the systematic review. Two studies, the one from Maged et al. and the one from Sentürk et al.[46,52] were classified as "high risk" for bias in at least one of the domains analyzed. Another eleven trials presented "some concerns" in at least one of the domains. The remainders were classified as "low risk" (Fig. 5).

Table 1 Characteristics of the included studies.

Autor	Year	Country	Type of delivery	TXA Dose	Control	Patients TXA (n)	Patients Control (n)	Type of anesthesia (cesarean)
Gungorduk et al.	2011	Turkey	Cesarean	1g, 10 min before incision	30 mL glucose 5%	330	330	Non described
Movafegh et al.	2011	Iran	Cesarean	10 mg.kg^{-1}, 20 min before anesthesia	Saline IV	50	50	Spinal
Sentürk et al.	2012	Turkey	Cesarean	1 g, 5 min before incision	Dextrose 5%	101	122	Spinal
Gungorduk et al.	2013	Turkey	Vaginal	1 g, for 5 min after extracting the anterior shoulder	30 mL glucose 5%	220	219	–
Xu et al.	2013	China	Cesarean	10 mg. kg^{-1} + 200 mL saline	200 mL saline	88	86	Spinal
Goswami et al. A	2013	India	Cesarean	10 mg. kg^{-1} + 20 mL dextrose 5%	5 mL DW + 20 mL dextrose 5%	30	30	Spinal
Goswami et al. B	2013	India	Cesarean	15 mg. kg^{-1} + 20 mL dextrose 5%	5 mL DW + 20 mL de dextrose 5%	30	30	Spinal
Shahid et al.	2013	Pakistan	Cesarean	1g + 20 mL glucose 5%	10 mL DW + 20 mL glucose 5%	38	36	Spinal
Ghosh et al.	2014	India	Cesarean	1g	10 mL DW	70	70	Spinal
Maged et al.	2015	Egypt	Cesarean	1g	30 mL glucose 5%	100	100	Non described
Mirghafourvand et al.	2015	Iran	Vaginal	1g, after extracting the anterior shoulder	DW	60	60	–
Sujata et al.[a]	2016	India	Cesarean	10 mg.kg^{-1}	Saline IV	30	30	Non described
Ismail et al.	2017	Egypt	Vaginal	1g, soon after delivery	30 mL glucose 5%	100	100	–
Abbas et al.	2018	Egypt	Cesarean	1g before incision	Saline IV	31	31	General
Sentilhes et al.	2018	France	Vaginal	1g, 2 min after delivery	Saline IV	1931	1927	–
Sujita et al.	2018	Thailand	Vaginal	1g + 20 mL saline (30 mL total)	30 mL saline	72	69	–
Millani et al.	2019	Iran	Cesarean	1g + 20 mL of DW, 15 min before incision	Glucose 5% 10 mL + 20 mL DW	30	30	Spinal
Shah et al.	2019	Nepal	Cesarean	1g	10 mL saline	80	80	Non described

[a] This trial was not included in the meta-analysis because lack of data; IV, Intravenous; DW, Distilled Water; A and B, In Goswami et al. the analysis was divided into two groups because two different doses of TXA were used (10 mg.kg^{-1} and 15 mg.kg^{-1}).

Certainty of evidence

The analysis of the quality of evidence by GRADE protocol[17] indicates that the certainty of evidence is "moderate", both for the primary outcome of bleeding and for the secondary outcome of hemoglobin variation (Fig. 4).

Discussion

This meta-analysis carried out with 16 trials published between 2011 and 2019 showed a favorable result for the prophylactic use of TXA in the reduction of PPH.

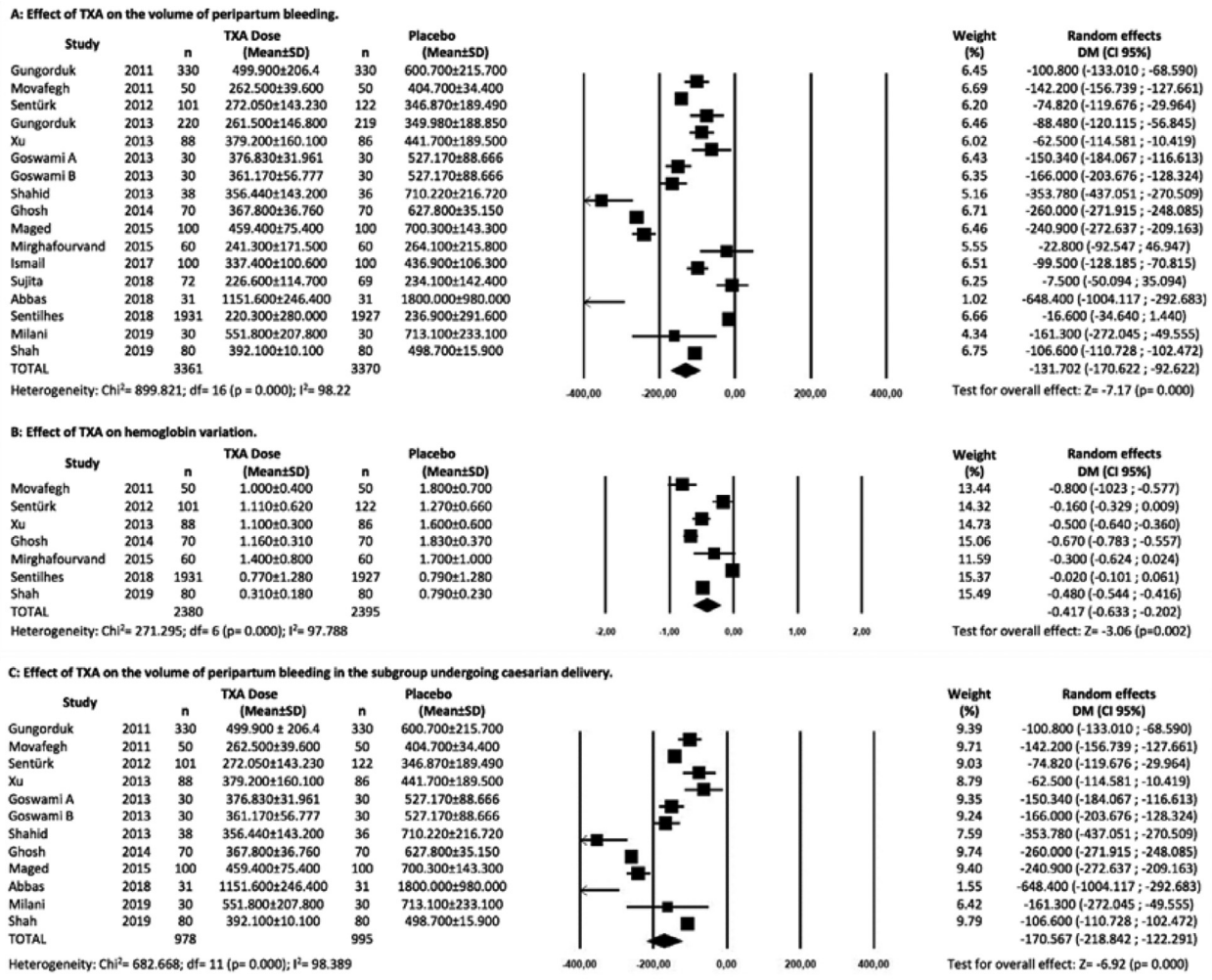

Figure 2 (A) Meta-analysis of the effect of TXA on the volume of peripartum bleeding in difference of means and 95% CI. (B) Meta-analysis of the effect of TXA on hemoglobin variation in difference of means and 95% CI. (C) Meta-analysis of the effect of TXA on the volume of peripartum bleeding in the subgroup undergoing cesarean delivery in difference of means and 95% CI.

There is plausibility for the use of TXA in this context, from a logic of the mechanism of action to its establishment as another option for the treatment of PPH after the WOMAN trial.[8] This famous multicenter and international RCT, with more than twenty thousand patients, was a milestone from which this medication started to be adopted in protocols for the control of PPH worldwide.[58]

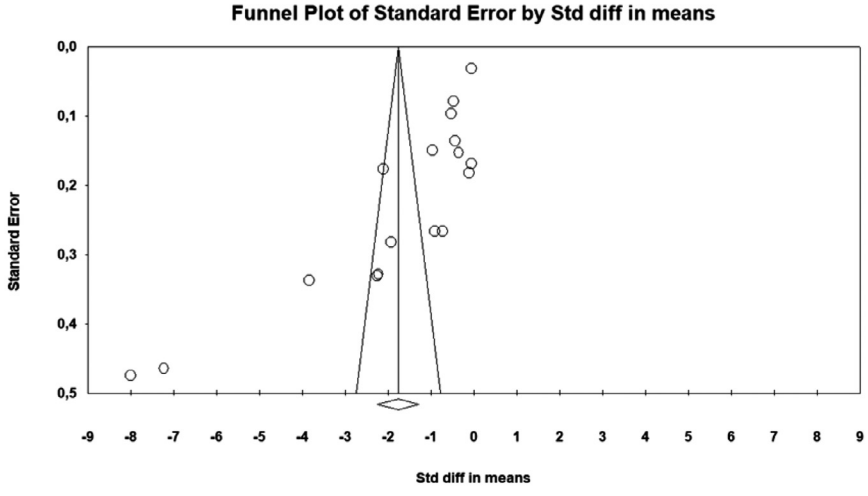

Figure 3 Funnel plot with publication bias analysis.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic Acid	Placebo	Relative (95% CI)	Absolute (95% CI)		
Peripartum bleeding (follow up: mean 2 horas; assessed with: bleeding volume; Scale from: 0 to infinito)												
16	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	3361	3340	-	MD **131.7 ml fewer** (170.62 fewer to 92.78 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Hemoglobin variation (follow up: mean 24 horas; assessed with: Hemoglobin variation; Scale from: 0 to 20)												
7	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	2380	2395	-	MD **0.417 g/dl fewer** (0.633 fewer to 0.202 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. The funnel plot, Begg and Egger tests strogly suggest publication bias

Figure 4 Graduation of the certainty of evidence by the GRADE protocol.

As with any disease, the idea of developing preventive strategies is more interesting than investing in the treatment itself, especially when it comes to a health problem like PPH. This condition demands a large amount of human and material resources for its treatment, and it is more prevalent precisely in regions where such resources are scarce. This systematic review shows that the TXA may indeed be one of the recommended strategies.

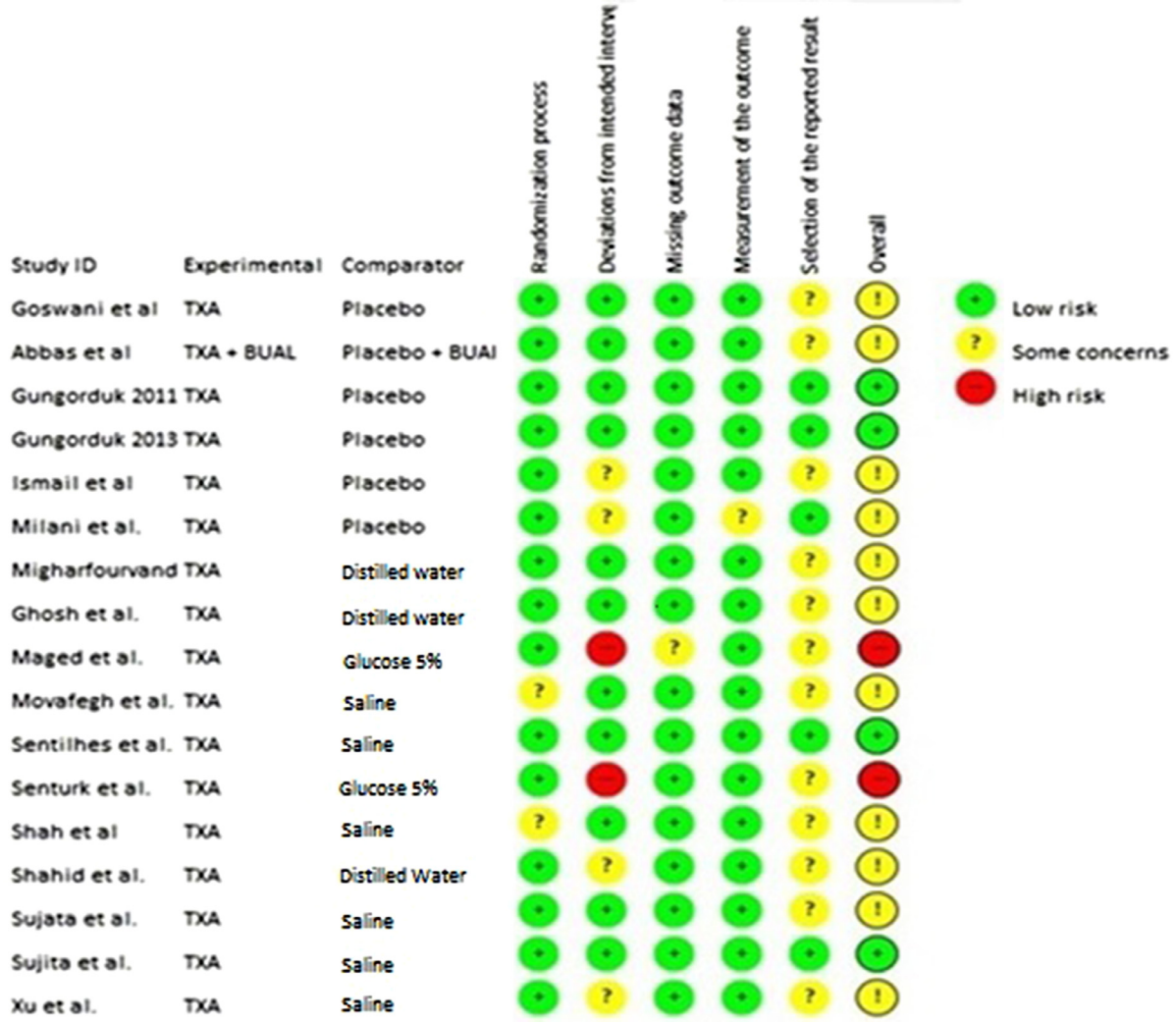

Figure 5 RoB 2.0 analysis framework.

The results of this study are in line with previous systematic reviews,[10,59] including a systematic Cochrane review conducted in 2015 with twelve trials and a total of 3285 patients, where the authors concluded that the TXA decreased postpartum bleeding prevented PPH, and reduced the need for blood components. Since then, other RCTs have been published, including the study by Sentilhes et al.,[11] a large multicenter RCT performed in France, with almost four thousand patients who underwent vaginal delivery and is, by far, the RCT with the highest weight of this meta-analysis. However, this study failed to identify a statistically significant reduction in the diagnosis of PPH between the two groups (RR = 0.83; 95% CI 0.68 to 1.01; $p = 0.07$), despite the reduction in the use of uterotonics (RR = 0.75; 95% CI 0.61 to 0.92; $p = 0.04$). It was important that a new meta-analysis showed the effect that these new clinical trials would have on the results of the prophylactic use of TXA.

This meta-analysis showed high heterogeneity ($I^2 = 98.22$), which can be attributed to several factors. One of them is related to the different intervals during which the bleeding was recorded. While some trials measured bleeding after the removal of the placenta up to hours after the delivery,[51] others measured it from the beginning of the cesarean section,[53] and some only after the fetus extraction.[11,48] The different TXA dosages administered, always within usual clinical range and with small differences in the administration technique, may also have influenced. There were also differences in populations, as already mentioned, with some trials including patients with recognized risk factors for PPH and others considering its presence as an exclusion criterion. In addition to the different routes of delivery, even differences in the methods of measuring volume can be embroiled as causes of heterogeneity (calculation based on hematocrit, weighting surgical dressings, aspirated contents, etc.).

The statistical analysis of the hemoglobin variation showed a significant effect in favor of the TXA administration, corroborating and being consistent with the result of the main outcome.

Overall, there was no increase in serious adverse events, with only two trials reporting a low incidence of serious complications.[11,48] When it comes to TXA, thromboembolic events are the most worrying complication, but in this systematic review this concern does not represent an impediment to the adoption of the intervention. It is important to remember that many of the trials did not aim to identify these events and even establish risk factors for thromboembolic episodes as exclusion criteria. It is also important to consider that pregnancy and postpartum represent, by themselves, risk factors for thromboembolic events, due to the physiological prothrombotic state of these conditions.

Regarding the use of uterotonics and blood products, there was a reduction in the incidence of needs of both interventions in the patients receiving TXA in the qualitative analysis, which, as well as the variation of hemoglobin, is consistent with the main outcome.

The specific analysis of the cesarean delivery showed an enhanced effect of TXA in this subgroup, which is consistent with the nature of a procedure in which major bleeding is expected. In a context of prevention, such a result could justify the use of TXA in this particular group instead of the entire universe of patients. However, it should be noted that this result may have been influenced by the fact that the trial by Sentilhes et al., which had the largest population in the meta-analysis and studied only vaginal delivery, did not show significant effect and its simple withdrawal from any analysis would tend to favor the intervention group. Due to heterogeneity in the other sensitivity analyses, regarding the time of administration, it was not possible to perform specific statistical analysis. However, it is believed that the variation between trials is too small to affect the outcome in this matter in any way.

Several strategies have been adopted to minimize bias; however, even so, due to the very nature of the meta-analysis, there is no way to rule out its presence. The evaluation by the RoB 2.0 tool showed that almost all trials had at least one domain with some problem, mainly in the "selection of reported results" domain, which assesses the bias that may arise because the result is selected among the various measures of effect that were initially evaluated by the clinical trial. This is due, in large measure, to the fact that few trials have previously registered their research protocols on independent platforms, corroborating the finding. The evaluation with the GRADE protocol indicated that the certainty of the evidence is moderate. However, this analysis also shows that the study has no inconsistency bias, because even with such different trials, the result tended to the same direction, that is, the conclusion of the intervention was consistent.[60]

Finally, the present systematic review helps to make it clear that the use of this medication can indeed be beneficial for the prevention of PPH and that the evidence is robust in favor of its effectiveness. The inclusion of prophylactic TXA in the active management of the third stage of vaginal delivery (along with oxytocin administration and controlled traction of the umbilical cord) may be considered, as well as it may be even more beneficial in cesarean sections, considering the higher blood loss expected during this procedure. Even so, more studies are still necessary, mainly under a more adequate design for detecting adverse effects and considering what would be the effective dose with the lowest incidence of adverse events, in addition to what would be the most appropriate administration form.

A general recommendation for the prophylactic use of TXA in preventing postpartum bleeding still lacks more weight of evidence, not because of efficacy, which was present in this study, but because of its cost-effectiveness. The widespread adoption of medication in such a common event around the world, even if relatively inexpensive, would mean a significant increase in the cost and complexity of healthcare. Perhaps clinical outcomes that really represent an improvement in care, such as mortality and morbidity, should be the focus of the next clinical trials.

Conclusion

The prophylactic use of tranexamic acid is effective in reducing the bleeding post-partum volume.

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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.2022.08.002.

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SYSTEMATIC REVIEW

Oral preanesthetic medication in children – comparison between midazolam alone and in combination with ketamine: a systematic review and meta-analysis

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Abstract

Background: Up to 60% of pediatric surgical patients develop high levels of preoperative anxiety. This study compared the effects of oral combinations of midazolam and ketamine with oral midazolam alone for pediatric preanesthetic medication.

Methods: The study protocol was registered in PROSPERO as CRD42020172920. A systematic literature search was conducted using Medline, Cochrane, EMBASE, CENTRAL, and Web of Science for randomized controlled trials comparing oral combinations of midazolam and ketamine with midazolam alone as preanesthetic medication in elective surgical pediatric patients. Meta-analyses included the following outcomes: anxiety and sedation levels, child's behavior during separation from parents, face mask acceptance, and venipuncture. The quality of evidence was assessed using GRADE criteria.

Results: Twenty studies were included. The following effects (RR (95% CI)) were observed for combinations of ketamine and midazolam relative midazolam alone: anxiolysis (1.2 (0.94–1.52); $p = 0.15$; I2 = 80%; GRADE = very low); satisfactory sedation (1.2 (1.10–1.31); $p < 0.001$; I2 = 71%; GRADE = very low); behavior during parental separation (1.2 (1.06–1.36); $p = 0.003$; I2 = 88%; GRADE = very low); facial mask acceptance (1.13 (1.04–1.24); $p = 0.007$; I2 = 49%; GRADE = very low); behavior during venipuncture (1.32 (1.11–1.57); $p = 0.002$; I2 = 66%; GRADE = very low).

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Conclusions: While similar probabilities of obtaining anxiolysis were found, adequate sedation, calm behavior during child's separation from parents, low levels of fear during face mask adaptation, and cooperative behavior during peripheral venous cannulation were more likely with midazolam-ketamine combinations.

Introduction

Up to 60% of children undergoing anesthesia and surgery develop high levels of preoperative anxiety.[1] Preoperative high-anxiety levels are associated with emergence delirium, increased postoperative pain, analgesic consumption, general anxiety, sleeping problems and postoperative eating disorders, and maladaptive behavior.[2,3] For these reasons, managing preoperative anxiety and fear is of utmost clinical relevance.

The effectiveness of the preanesthetic medication has been measured as a composite outcome that includes the child's levels of anxiety[4] and sedation in the preanesthesia holding area and her behavior during critical events that precede the anesthetic induction: the separation from parents, the adaptation of the face mask during preoxygenation or induction of inhalational anesthesia, and the venipuncture for peripheral vein cannulation.[5]

An ideal preanesthetic medication agent should exhibit consistent, predictable results, good patient acceptance, and be free of significant side effects (e.g., hemodynamic instability, respiratory obstruction, or delayed recovery).[6] Midazolam and ketamine fulfill many of such characteristics. Midazolam, a GABA-A agonist, is among the most commonly used drugs for preanesthetic medication. Good or excellent sedation, however, is observed only in 60 to 80% of cases.[7] Ketamine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, has also been administered orally as preanesthetic medication to pediatric patients. Doses of 3 or 6 $mg.kg^{-1}$ produce adequate sedation with no prolongation of recovery time, time to discharge, or increased incidence of postoperative nausea and vomiting (PONV), although nystagmus occurs frequently.[8] The rationale for combining midazolam and ketamine rests on the assumption of maintaining the anxiolysis provided by midazolam while adding the sedative and analgesic properties of ketamine without increasing side-effects.[5] To date, only small studies have investigated the efficacy of orally-administered combinations of midazolam and ketamine compared to midazolam alone as preanesthetic medication in children. This systematic review with meta-analysis aimed to estimate the pooled effect sizes of the currently available studies that compared oral combinations of midazolam and ketamine relative to oral midazolam alone used for preanesthetic medication of pediatric surgical patients according to the adequacy of the outcomes of anxiolysis and sedation, behavior during separation from parents, facial mask acceptance during preoxygenation or anesthesia induction, and behavior at venipuncture for intravenous cannulation.

Methods

The study complied with Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA).[9] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42020172920.[10]

Sources of information and search strategy

MEDLINE (from 1946), Web of Science (from 1945), EMBASE (from 1947), Scholar Google, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles, abstracts, theses, and conference reports of randomized controlled trials (RCTs). Filters were applied to identify studies performed on humans and children with no language restriction. Searches were conducted from November 2019 through January 2020. The following keywords and index terms were used: "midazolam," "ketamine," "preanesthetic medication," "premedication," "randomized clinical trial," "pediatric," and "children."

The search string used on the PubMed engine was ''((((ketamine[MeSH Terms]) AND midazolam[MeSH Terms]) AND preanesthetic medication[MeSH Terms])) Filters: Clinical Trial; Humans; Child: birth-18 years''.

The EMBASE search was done with the following string: "children:ab AND 'oral midazolam' AND 'ketamine'/exp AND 'midazolam'/mj AND 'sedation'/exp AND ('randomized clini' OR 'premedication'/exp).

The CENTRAL search string was: "midazolam" AND "ketamine" in Record Title AND ("preanesthetic" OR "preanesthesia" OR "premedication") in Title Abstract Keyword AND "oral" NOT "intranasal" NOT "transmucosal" in Title Abstract Keyword AND ("children" OR "pediatric") in Title Abstract Keyword AND "randomized control trial" in Publication Type.

Scholar Google was searched with the following terms: "allintitle: midazolam ketamine children oral preanesthetic OR premedication OR oral -intranasal -transmucosal -intramuscular -rectal."

The Web Of Science search terms were: "TS = (midazolam AND ketamine) AND TS = (preanesthesia medication OR preanesthetic medication) AND TS = child* Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years."

The reference lists of the selected articles were manually screened for additional relevant articles. Study protocols, unpublished studies, conference abstracts, or unpublished theses were also searched. Abstracts, conference proceed-

ings, and theses were included if providing complete data. Clarifying information or study data were requested from authors when necessary.

Eligibility criteria

The studies eligible for inclusion in quantitative analyses were randomized clinical trials. The clinical question addressed the following PICOT elements: P, pediatric patients scheduled for elective surgical procedures; I, ketamine combined with midazolam administered orally; C, midazolam administered orally; O, scoring of anxiolysis, sedation, emotional status, behavior during separation from parents, facemask acceptance, and behavior at venipuncture; T, in the immediate preanesthetic period.

Study selection

Three authors conducted independent literature searches (GROF, CMC, JPK). All authors (GROF, CMC, JPK, and GNB) screened titles, abstracts, and full papers of the retrieved references. Studies were rejected at title screening, after reading abstracts, or after reading the full articles. Reasons for exclusion for individual studies included: not being a prospective randomized trial; both oral midazolam and oral ketamine groups were not included in the same study; other than oral administration routes were used; study samples did not include pediatric surgical patients; study outcomes did not include at least one of the primary outcomes of this systematic review (anxiety and sedation levels, child's behavior during separation from parents, face mask acceptance, or behavior at venipuncture). Controversies about the inclusion of studies were resolved by consensus among the authors (GROF, CMC, JPK, GNB).

Data extraction process and data items

The authors independently extracted data from the included studies on dedicated forms consolidated for inclusion in the analysis software. The software Engauge Digitizer was used to extract data presented as graphs in the original articles.[11]

Assessment of the risk of bias within studies

Within-study risk of bias was assessed according to the revised Cochrane risk-of-bias tool for randomized trials (ROB 2).[12] Studies were considered to have a high risk of bias if a high risk of bias was assigned to any domain or ''some concerns'' were assigned to the ROB 2 tool's multiple domains.[12]

Summary measures

Effect-sizes were summarized as relative risks (RR) because outcomes were reported as categorical, dichotomized variables in the included studies. Ninety-five percent confidence intervals (95% CI) were estimated for summary measures.

Synthesis of results

Random effects meta-analyses were used to estimate pooled effect sizes based on the following assumptions: the included studies comprised distinct treatment protocols (e.g., varying dose combinations of midazolam and ketamine in intervention groups), and different scales were used to measure outcomes. Consequently, variability among the different effect estimates could be attributed to both within-study sampling error and between-study heterogeneity in real effects. Cochrane Q tests and I^2 statistics were used to assess statistical heterogeneity in effect sizes across the studies included in the meta-analyses.

Assessment of risk of bias across studies

Potential publication bias was evaluated through visual inspection of contour-enhanced funnel plots and quantified by Harbord's zero-slope regression asymmetry test. Duval & Tweedie's trim-and-fill method was used to identify missing studies and adjust the effect size[13,14] if publication bias was detected. Fixed-effects meta-analyses were performed on the log-transformed RR and standard errors to apply the trim-and-fill method.[13,15] Contour-enhanced funnel plots incorporating the trim-and-fill method results were constructed plotting the log-transformed RR against the log-transformed standard error. Additionally, filled studies were included in the funnel plots whenever indicated by the trim-and-fill procedures, and the predicted log-transformed effect-size was presented beside the observed log-transformed effect size.[15]

Sensitivity analyses

The pooled estimates' robustness was assessed by sequentially removing each study's data and re-analyzing the remaining data (leave-one-out analysis) to confirm that the pooled effect-sizes did not result from single-study dominance.

The studies included in meta-analyses differed regarding the dosing regimens of midazolam and ketamine. Such methodological differences might affect the clinical effectiveness of the different dosing regimens. Therefore, subgroup analyses were conducted to explore the different dosing regimens' effect on the primary outcomes. Chi-square tests were used to assess subgroup differences. The quality of evidence provided by the meta-analyses was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[16]

Software

Review Manager software 5.3 (Review Manager (RevMan), Copenhagen) was used for meta-analyses. STATA 14/MP (StataCorp, College Station, TX, USA) was used to conduct Harbord's tests (*metabias* module) and Duval & Tweedie's trim-and-fill analyses (*metatrim* module).[13,17] The GRADEpro GDT software was used to construct a summary of findings (SoF) table.[18]

Results

Study selection

Twenty studies were included in the meta-analyses (Fig. 1). Twelve of them were published in the English language, two articles in the Persian language, and one article in the Russian language. The search strings used to identify studies in each database and the complete list of retrieved articles and abstracts with reasons for rejection or acceptance are provided in e-component 1.

Characteristics of the studies

The 20 studies included in the meta-analyses provided data relative to 1540 patients, 834 received orally administered combinations of midazolam and ketamine, and 706 received midazolam alone. The main characteristics of the studies included in quantitative analyses are shown in Table 1 and detailed below.

Primary outcomes of the included studies

Anxiolysis was reported in 5 studies (436 patients), sedation was reported in 18 studies (1556 patients); behavior at separation from parents was reported in 16 studies (1302 patients); mask acceptance was reported in 11 studies (832 patients); behavior at venipuncture was reported in 9 studies (735 patients).

Midazolam and midazolam ketamine combination dosing regimens

Several dosing combinations of midazolam and ketamine (MIKE) were used in the intervention groups. The combination of midazolam 0.25 $mg.kg^{-1}$ with ketamine 3 $mg.kg^{-1}$ was used in 4 studies.[6,19–21] Midazolam 0.5 $mg.kg^{-1}$ with ketamine 3 $mg.kg^{-1}$ was used in 5 studies.[5,22–25] Midazolam 0.25 $mg.kg^{-1}$ with ketamine 2.5 $mg.kg^{-1}$ was used in 3 studies.[26–28] Midazolam 0.3 $mg.kg^{-1}$ with ketamine 1 $mg.kg^{-1}$ was used in 2 studies.[29,30] Midazolam 0.3 $mg.kg^{-1}$ with ketamine 2 $mg.kg^{-1}$ was used in 2 studies.[29,30] Midazolam 0.3 $mg.kg^{-1}$ with ketamine 3 $mg.kg^{-1}$, midazolam 0.5 $mg.kg^{-1}$ with ketamine 6 $mg.kg^{-1}$, midazolam 0.25 $mg.kg^{-1}$ with ketamine 1 $mg.kg^{-1}$ midazolam 0.25 $mg.kg^{-1}$ with ketamine 4 $mg.kg^{-1}$, and midazolam 0.2 $mg.kg^{-1}$ with ketamine 5 $mg.kg^{-1}$ were used in one study each.[19,31–34] Except for two studies in which the dose of midazolam was 0.75 $mg.kg^{-1}$ in the midazolam groups (MDZ),[22,35] 0.5 $mg.kg^{-1}$ was used in the remaining eighteen studies.

Types of surgery

The studies included patients undergoing urologic,[29] ophthalmologic,[19,20,28,29] cardiac,[21] CT imaging,[31,33] neurosurgery,[22] tonsillectomy,[34] or miscellaneous elective pediatric surgical procedures lasting 20 through 180 minutes.[5,23–27,30,32,35,36]

Measurements

Measurement of sedation. Three or four-point categorical scales were used in the included studies to measure anxiolysis level (e.g., 1 = panicky, 2 = moaning, 3 = composed, 4 = friendly); sedation (e.g., 1 = alert and active, 2 = awake, 3 = drowsy, but responds to verbal command, 4 = asleep); behavior at separation from parents (e.g., 1 = combative and clinging, 2 = anxious, 3 = calm, 4 = sleeping); facial mask acceptance (e. g., 1 = terrified, crying with mask, 2 = fear of mask, not reassured, 3 = slight fear of mask, reassured; 4 = unafraid, accepts face mask), and behavior at venipuncture (e.g., 1 = crying and uncooperative, not able to start IV line, 2 = withdraw for painful stimulus, but allows IV cannulation; 3 = calm, awake not crying, no withdrawal for IV cannulation, 4 = asleep, no response to painful stimulus).[6,24,25] Results were presented in the included studies as dichotomized categories ''satisfactory'' or ''unsatisfactory'' anxiolysis, sedation, behavior at separation from parents, facial mask acceptance, and behavior at venipuncture, according to criteria established by the respective authors.

Side-effects attributable to preanesthetic medication. Six studies reported postoperative nausea and vomiting (PONV).[6,21,23,29,32,34] Three studies reported excessive salivation.[6,23,35] Two studies reported[6,23,35] hallucination or diplopia or nystagmus.[23,29] Excessive sedation and peripheral oxygen desaturation,[23] and headache[29] were reported in one study each.

Synthesis of results

Primary outcomes

There was no difference between the treatments regarding RR of anxiolysis (RR = 1.2 (0.94–1.52; p = 0.15; I^2 = 80%; GRADE = very low) (Fig. 2). The probabilities of obtaining a ''satisfactory rating'' were higher among patients who received combinations of ketamine and midazolam relative to patients who received midazolam alone as preanesthetic medication for the following outcomes: sedation (RR = 1.20; 95% CI = 1.10–1.31; p < 0.001; I^2 = 71%; GRADE = very low) (Fig. 3), behavior during parental separation (RR = 1.2; 95% CI % = 1.06–1.36; p = 0.003; I^2 = 88%; GRADE = very low) (Fig. 4), facial mask acceptance (RR = 1.13; 95% CI = 1.04–1.24; p = 0.007; I^2 = 49%; GRADE = very low) (Fig. 5), and venipuncture (RR = 1.32; 95% CI = 1.11–1.57; p = 0.002; I^2 = 66%; GRADE = very low) (Fig. 6).

Adverse effects

Treatments did not differ regarding the probabilities of PONV (RR = 1.37; 95% CI = 0.59–3.18; p = 0.46; I^2 = 0%), hallucinations (RR = 4.54; 95% CI = 0.53–38.89; p = 0.17; I^2 = 0%), excessive salivation (RR = 1.90; 95% CI = 0.71–5.08; p = 0.20; I^2 = 0%), diplopia/nystagmus (RR = 1.77; 95% CI = 0.58–5.41; p = 0.31; I^2 = 0%), or oxygen desaturation (RR = 1.36; 95% CI = 0.10–19.39; p = 0.82; I^2 = 33%). The following adverse effects were extracted from one study each, so that the I^2 statistic was not applicable: excessive sedation (RR = 5; 95% CI = 0.25–99.95; p = 0.29); headache (RR = 2.72; 95% CI = 0.11–64.85; p = 0.54), tachycardia (RR = 2; 95% CI = 0.38–10.43; p = 0.31), bradycardia (RR = 0.33; 95% CI = 0.001–7.99; p = 0.50), involuntary movements (RR = 5; 95% CI = 0.25–101.58; p = 0.29), hiccoughs (RR = 0.20; 95% CI = 0.01–3.97; p = 0.29), and delayed recovery (RR = 0.20; 95% CI = 0.01–3.97; p = 0.29).

Table 1 Characteristics of the studies.

Study	Source	Country	Language	n MIKE[1]	n MDZ[2]	Age range	Type of surgery	MIKE Doses	MDZ dose	Vehicle	Volume	Timing	Reported outcomes
Astuto 2002	Article	Italy	English	MK1 = 40; MK2 = 42	38	2–6 years	Urologic	Group MK1: M 0.3 + K 1 $mg.kg^{-1}$ and Group MK2: M 0.3 + K 2 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Glucose syrup	1–2 teaspoons	30 min before induction	sedation, anxiolysis, parental separation, face mask acceptance, adverse events: PONV, headache, diplopia, hallucinations
Darlong 2004	Article	India	English	24	24	1–9 years	Eye surgery	M 0.25 + K 3 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	50% dextrose	Up to 0.3 $mL.kg^{-1}$	30 min before induction	sedation, parental separation, face mask acceptance, adverse events: PONV, salivation, irrelevant talking, breath holding
Darlong 2011	Article	India	English	MKL = 29; MKH = 29	29	1–10 years	Eye surgery	Group MKL M 0.25 + K 3 $mg.kg^{-1}$ and Group MKH: M 0.5 + K 6 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Honey	Up to 0.5 $mL.kg^{-1}$	30 min before induction	sedation, parental separation, face mask acceptance, adverse events: PONV, salivation, irrelevant talking breath holding
Foroutan 2007	Article	Iran	English	50	59	2–8 years	Cardiac	M 0.25 + K 3 $mg.kg^{-1}$ + atropine 0.02 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Apple juice	Up to 5–8 mL	45 min before induction	parental separation, behavior at venepuncture, face mask acceptance
Funk 2000	Article	Germany	English	39	38	2–10 years	Elective surgery more than 30 minute-expected duration	M 0.5 + K 3 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Strawberry-flavored glucose syrup	Up to 12.5 mL	30 min before induction	Sedation, anxiolysis, parental separation, behavior at venepuncture; PONV, vertigo,psychodelic symptoms, salivation

Table 1 (*Continued*)

Study	Source	Country	Language	n MIKE[1]	n MDZ[2]	Age range	Type of surgery	MIKE Doses	MDZ dose	Vehicle	Volume	Timing	Reported outcomes
Ghai 2005	Article	India	English	49	48	10 months–6 years	Elective surgery	M 0.25 + K 2,5 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Honey	Not reported	20 min prior to induction	sedation, anxiolysis, parental separation, face mask acceptance, adverse events: PONV
Hasani 2000	Article	Iran	Persian	50	50		Elective surgery	M 0.25 + K 2,5 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Not reported	Not reported	30 min before induction	sedation, parental separation, face mask acceptance.
Jain 2010	Article	India	English	31	29	1–5 years	CT imaging	M 0.25 + K 1 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Honey	5 mL	20–30 min before venepunc-tion	behavior at venepuncture, sedation, parental satisfaction
Kulikov 2010	Article	Russia	Russian	80	20		Elective neuro-surgery	M 0.5 + K 3 $mg.kg^{-1}$	0.75 $mg.kg^{-1}$	Honey or thick syrup (e.g.haw-thorn)	10 m L	40 min before induction	sedation, behavior at venepuncture
Kumar 2009	Article	India	English	20	20	3–10 years	Elective surgery	M 0.3 + K 3 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Apple juice	Up to 0.5 $mL.kg^{-1}$	30 min before induction	Sedation, anxiolysis, parental separation, behavior at venepuncture; facial mask acceptance PONV
Lin 1993	ASA Meeting Abstract	USA	English	15	15	under 8 years	Ambulatory surgeries	M 0.5 + K 3 $mg.kg^{-1}$	0.75 $mg.kg^{-1}$	Apple juice	3 mL	20–30 min before induction	Sedation, parental separation, face mask acceptance, behavior at venepuncture adverse events: salivation, nistagmus.
Magar 2016	Article	India	English	30	30	3–10 years	Surgeries under general anesthesia	M 0.5 + K 3 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Midazolam syrup (2 $mg.mL^{-1}$) / parenteral preparation of ketamine dissolved in 5% dextrose	According to the total dose of midazolam for each group.	30 min before surgery	Sedation, anxiolysis, parental separation, behavior at venepuncture; Face mask acceptance hallucinations, salivation, excessive sedation

Table 1 (*Continued*)

Study	Source	Country	Language	n MIKE[1]	n MDZ[2]	Age range	Type of surgery	MIKE Doses	MDZ dose	Vehicle	Volume	Timing	Reported outcomes
Majidinejad 2015	Article	Iran	English	33	33	6 months–6 years	Brain CT	M 0.2 + K 5 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Sugar syrup	5 mL	40 min before the scheduled procedure	sedation. PONV
Mithun 2018	Article	India	English	50	50	2–10 years	Elective surgeries between 20 minutes to 2 hours	M 0.5 + K 3 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Orange syrup	0.5 $mL.kg^{-1}$ up to a maximum of 10 m L	30 min before induction	Sedation, anxiolysis, parental separation, PONV, nystagmus, salivation, tachycardia, bradycardia, exitement, involuntary movements, respiratory depression
Rabie 2005	Article	Egypt	English	30	30	3–8 years	Tonsillectomy with or without adenoidectomy	M 0.25 + K 4 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Cherry or orange syrup	5 mL	20 min prior to induction	sedation, parental separation, face mask acceptance, adverse events: PONV
Ramakrishna 2018	Article	India	English	50	50	2–10 years	Surgeries lasting more than 30 minutes	M 0.5 + K 3 $mg.kg^{-1}$ + atropine 0.02 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$ + atropine 0.02 $mg.kg^{-1}$	Honey	Up to 0,5 $mL.kg^{-1}$	30 min before induction	Sedation, anxiolysis, parental separation, behavior at venepuncture.
Sajedi 2014	Article	Iran	Persian	68	68	6 months–6 years	Outpatient eye surgery	M 0.25 + K 2.5 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Strawberry-flavored juice	Up to 0,5 $mL.kg^{-1}$	30 min before induction	Sedation, anxiolysis, parental separation, behavior at venepuncture. PONV

Table 1 (*Continued*)

Study	Source	Country	Language	n MIKE[1]	n MDZ[2]	Age range	Type of surgery	MIKE Doses	MDZ dose	Vehicle	Volume	Timing	Reported outcomes
Sathyan 2006	Doctoral thesis	India	English	25	25	1–12 years	Surgeries lasting at least 30 minutes	Group A - M 0.3 + K 1 $mg.kg^{-1}$; Group B- M 0.3 + K 2 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Solution mixed with sugar crystals + 2-3 g of sugar crystal to chew	Not reported	30 min before induction	Sedation, parental separation, behavior at venepuncture, face mask acceptance. Hiccoughs, delayed recovery
Walia 2017	Article	India	English	30	30	1–8 years	Elective surgeries lasting less than 3 hours	M 0.25 + K 3 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$	Acetaminophen syrup (5 mL = 120 mg)	Up to 0,4 mL. kg^{-1}	30 min before induction	Sedation, parental separation, face mask acceptance, emergence score. Hiccoughs, delayed recovery
Warner 1995	Article	USA	English	20	20	1.5–7 years	Minor outpatient surgeries	M 0.4 + K 4 $mg.kg^{-1}$ + atropine 0.02 $mg.kg^{-1}$	0.5 $mg.kg^{-1}$ + atropine 0.02 $mg.kg^{-1}$	Cherry syrup	1 - 2 teaspoons	20–30 min before surgery	Sedation, anxiolysis, parental separation, facial mask acceptance

[1] MIKE, Group that received the combination of midazolam and ketamine.
[2] MDZ, Group that received the combination of midazolam and ketamine; M, Midazolam; K, ketamine.

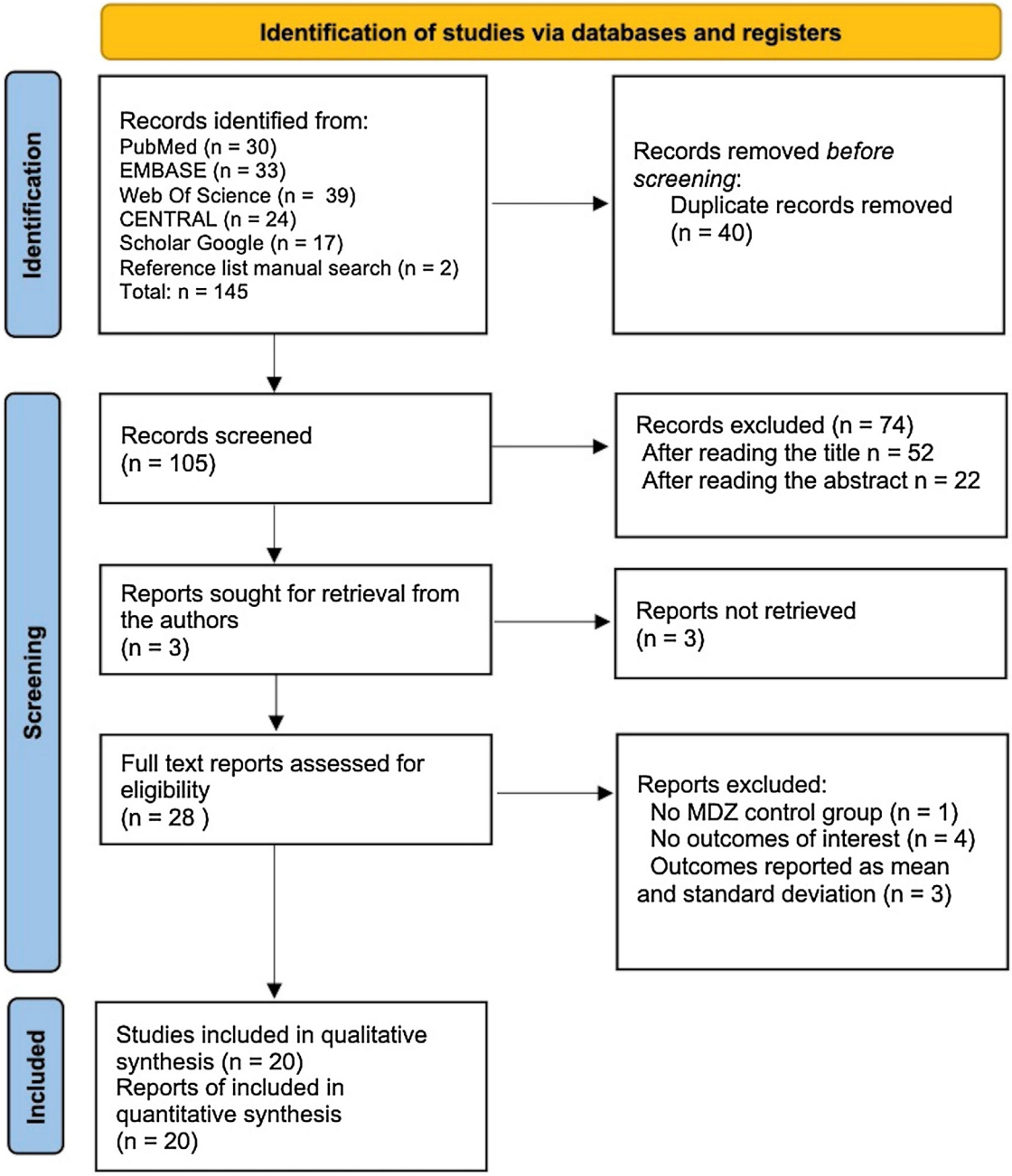

Figure 1 Study flow diagram.

Sensitivity analyses

Leave-one-out procedures

No changes in *p*-values of the z-tests for overall effects were observed during leave-one-out procedures conducted on the studies included in the primary outcomes' meta-analyses.

Subgroup analyses

Subgroup analyses disclosed significant differences in effect sizes attributable to the dose combinations of the midazolam and ketamine in the MIKE treatment regarding sedation (chi^2 = 22.38, df = 9; p = 0.008); I^2 = 59.8%) and behavior at separation from parents (chi^2 = 19.73; df = 8; p = 0.01; I^2 = 59.4%). No significant differences across dose combinations of the midazolam and ketamine subgroups were found for the outcomes anxiolysis (chi^2 = 2.81; df = 2; p = 0.24; I^2 = 28.9%), face mask acceptance (chi^2 = 10.76; df = 7; p = 0.15; I^2 = 34.9%), and behavior at venipuncture (chi^2 = 10.87; df = 6; p = 0.09; I^2 = 44.8%) (e-component 2).

Assessment of risk of bias within studies

Because ''high risk'' or ''some concerns'' grade was assigned to one or more domains of the Cochrane Collaboration ROB 2 tool, 11 studies (55%) were classified as having a high overall risk of bias.[6,20,22,23,27,29,30,32,33,35,36] The ''some

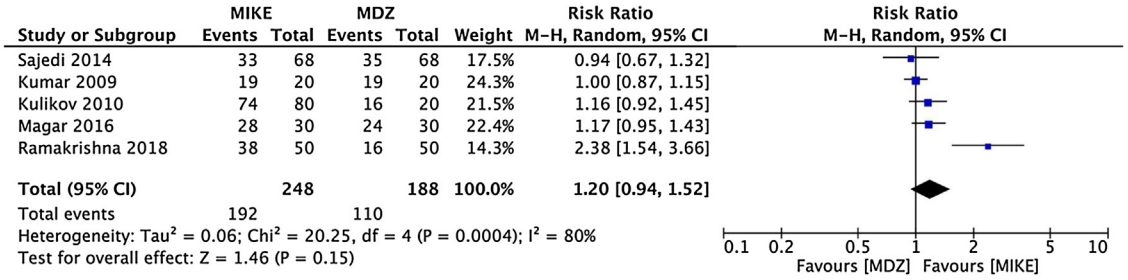

Figure 2 Forest plots of pooled comparisons of the frequency of satisfactory anxiolysis. Black boxes relative risks (RR). Black lines surrounding boxes represent the respective 95% CI. The black diamond represents the combined RR estimate, and its width corresponds to the 95% CI bounds. MDZ, midazolam; MIKE, Combinations of midazolam and ketamine; M-H, Mantel-Haenszel.

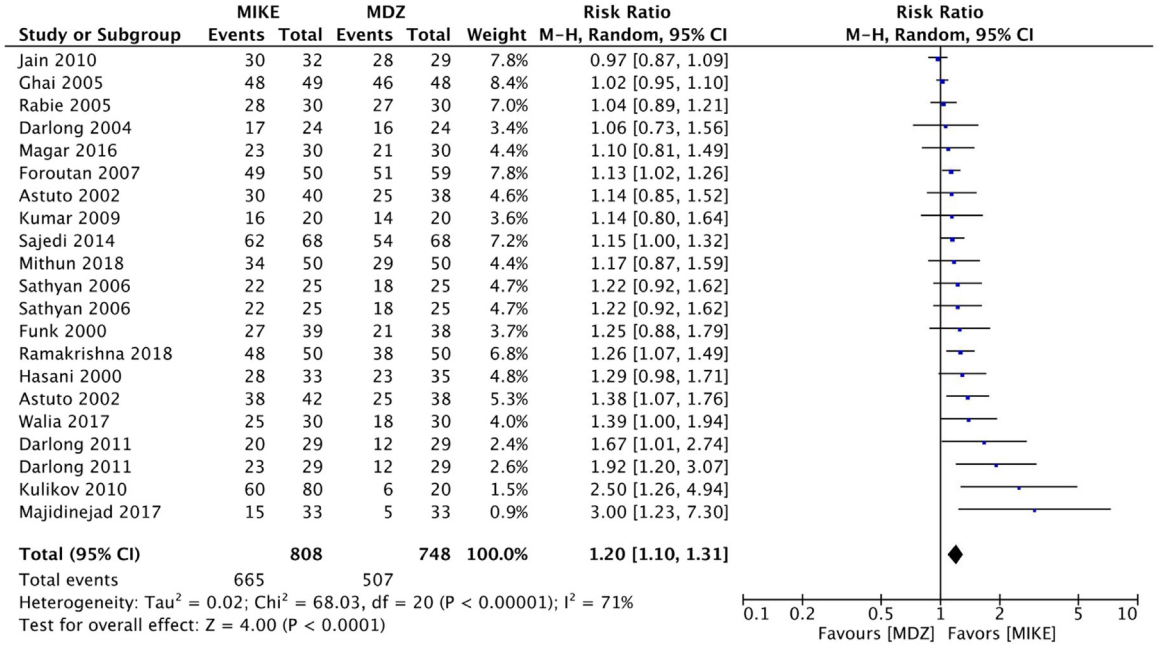

Figure 3 Forest plots of pooled comparisons of the frequency of satisfactory sedation. Black boxes relative risks (RR). Black lines surrounding boxes represent the respective 95% CI. The black diamond represents the combined RR estimate, and its width corresponds to the 95% CI bounds. MDZ, midazolam; MIKE, Combinations of midazolam and ketamine; M-H, Mantel-Haenszel.

concerns'' class was assigned to the overall risk of bias of 9 studies (45%).[5,19,21,24–26,28,31,34] (e-component 3).

Assessment of risk of publication bias across studies

Harbord's test detected evidence of publication bias or small-study effects in meta-analyses of sedation ($p < 0.001$), behavior at separation from parents ($p < 0.001$), and behavior at venipuncture ($p = 0.04$). No evidence of publication bias or small-study effect was detected for the face mask acceptance ($p = 0.07$) and anxiolysis ($p = 0.30$) meta-analyses.

As a result of the trim-and-fill method, the sedation meta-analysis produced ten filled studies, seven of which in the region of $p > 0.10$, and three filled studies in the region of $0.05 < p < 0.1$ of the contour-enhanced funnel plot. The adjusted intervention effect, that is, the risk ratio that would have been found in the absence of publication bias, was estimated as 1.07 (95% CI = 0.99–1.55; $p = 0.057$; $I^2 = 79.07\%$). Despite the lack of evidence of small-study or publication bias produced by the Harbord's test, applying the trim-and-fill method, the mask acceptance meta-analysis produced five filled studies, two of which in the region of $p > 0.10$, two filled studies in the region of $0.05 < p < 0.1$, and one study in the $p < 0.01$ region of the contour-enhanced funnel plot. The adjusted risk ratio was 1.043 (95% CI = 0.945–1.151; $p = 0.40$; $I^2 = 62.2\%$). The separation from parents meta-analysis produced eight filled studies, five of which in the region of $p > 0.10$, and three studies in the region of $0.05 < p < 0.1$ of the contour-enhanced funnel plot. The adjusted risk ratio was 1.075 (95% CI = 0.987–1.171; $p = 0.096$; $I^2 = 62.5\%$). The behavior at venipuncture meta-analysis produced four filled studies, two of which in the region of $p > 0.10$, and two studies in the region of $0.05 < p < 0.1$ of the contour-enhanced funnel plot. The adjusted risk ratio was 1.14 (95% CI = 0.946–1.340; $p = 0.16$; $I^2 = 73.8\%$). No filled studies resulted from apply-

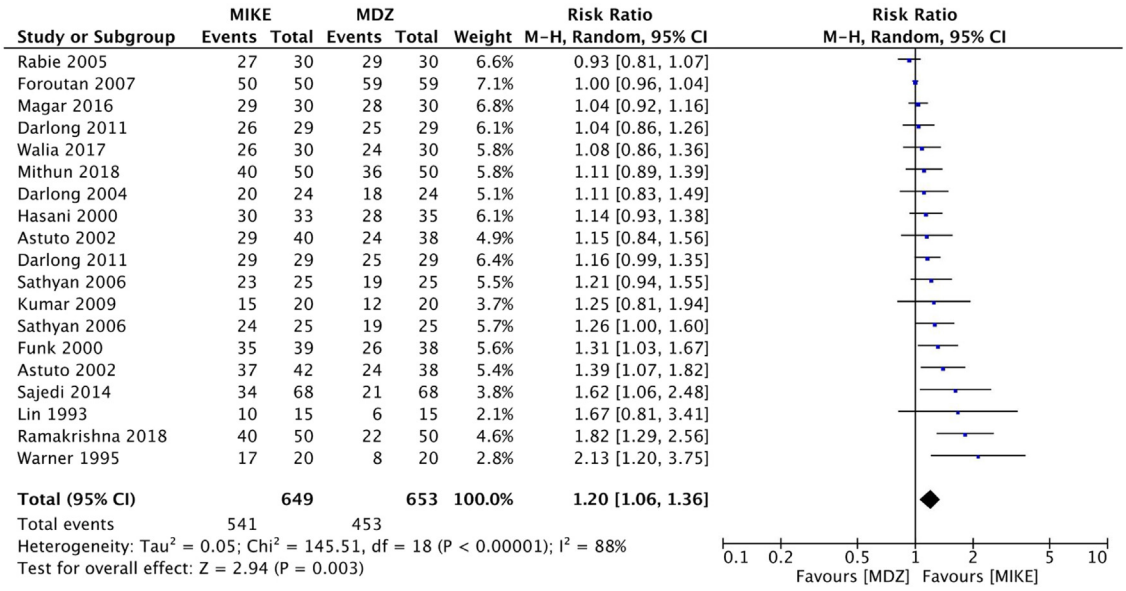

Figure 4 Forest plots of pooled comparisons of the frequency of satisfactory behavior during separation from parents. Black boxes relative risks (RR). Black lines surrounding boxes represent the respective 95% CI. The black diamond represents the combined RR estimate, and its width corresponds to the 95% CI bounds. MDZ, midazolam; MIKE, Combinations of midazolam and ketamine; M-H, Mantel-Haenszel.

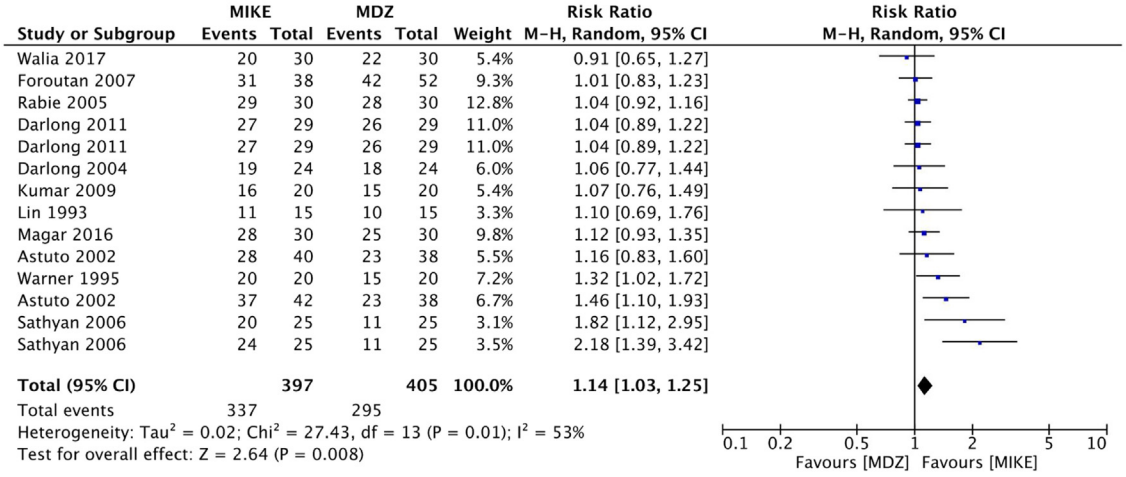

Figure 5 Forest plots of pooled comparisons of the frequency of satisfactory facial mask acceptance. Black boxes relative risks (RR). Black lines surrounding boxes represent the respective 95% CI. The black diamond represents the combined RR estimate, and its width corresponds to the 95% CI bounds. MDZ, midazolam; MIKE, Combinations of midazolam and ketamine; M-H, Mantel-Haenszel.

ing the trim-and-fill method to the anxiolysis meta-analysis. Contour-enhanced funnel plots, including filled studies, are shown in e-component 4.

Quality of evidence

Very low confidence was assigned to the meta-analyses of all primary outcomes at GRADE assessment, driven by the high statistical heterogeneity, the severe risk of bias within the included studies, and the high risk of publication bias (e-component 5).

A completed PRISMA checklist is provided in e-component 6.

Discussion

This systematic review with meta-analyses pooled the results of 20 studies that addressed preanesthetic medication effects with combinations of midazolam and ketamine compared with midazolam alone orally administered to surgical pediatric patients 20 to 45 minutes before anesthetic induction. The primary outcomes were satisfactory anxiolysis and sedation, satisfactory behavior at separation from parents, satisfactory facial mask acceptance, and satisfactory behavior at venipuncture, as defined by each study's authors.

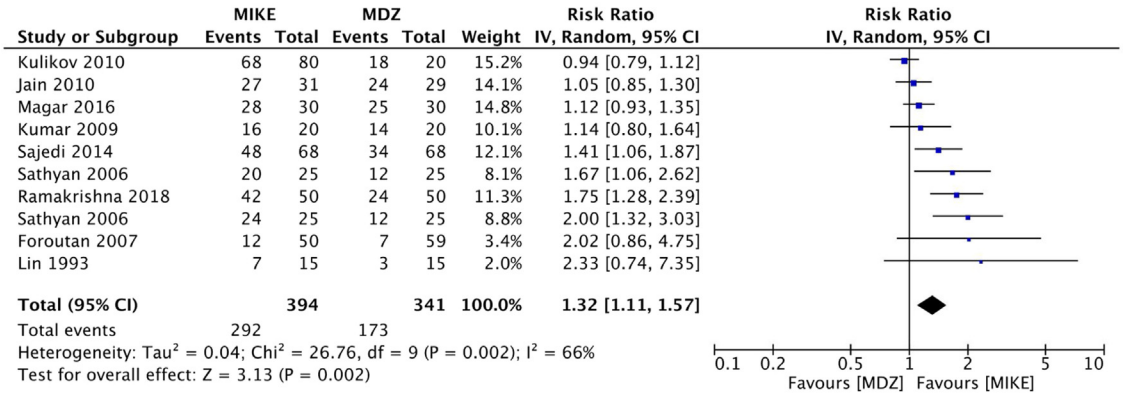

Figure 6 Forest plots of pooled comparisons of the frequency of satisfactory behavior during venipuncture. Black boxes relative risks (RR). Black lines surrounding boxes represent the respective 95% CI. The black diamond represents the combined RR estimate, and its width corresponds to the 95% CI bounds. MDZ, midazolam; MIKE, Combinations of midazolam and ketamine; M-H, Mantel-Haenszel.

The main results were that oral combinations of midazolam and ketamine were associated with a similar probability of achieving satisfactory anxiolysis and higher probabilities of satisfactory sedation, calm behavior during parental separation, no fear during facial mask adaptation, and cooperative behavior during venipuncture relative to oral midazolam alone.

Midazolam is a water-soluble benzodiazepine and the most commonly used sedative in pediatric surgical patients. After orally-administered doses of 0.5–0.75 $mg.kg^{-1}$ (maximum of 20 mg), sedation and anxiolysis are achieved within 20 minutes, and an elimination half-time of 2.2 to 6.8 hours.[37] Because of the injectable form's bitter taste, several vehicles such as honey, glucose, apple juice, and paracetamol syrup have been used to increase palatability and acceptance. Currently, a cherry-flavored syrup formulation is available for oral use (2 $mg.mL^{-1}$).[38] However, oral midazolam may fail to produce sedation in 20–40% of patients.[7,37]

Intramuscular ketamine has long been used for preanesthetic medication in children.[39] Less painful routes have been studied, including the oral transmucosal,[40,41] the intranasal,[42,43] and the rectal routes.[44,45] Orally administered ketamine undergoes significant first-pass effects that result in the formation of norketamine and dehydronorketamine. Norketamine crosses the blood-brain barrier and has about one-fifth to one-third the potency of ketamine, contributing to prolonging its analgesic effect.[46]

The rationale for using combinations of oral midazolam and ketamine was not consistent across the studies included in this systematic review. While some studies used lower doses of midazolam in the group that received the drug combination compared to the control group,[6,19–21,26–34,36] others used the same doses of midazolam in the control group and in the group that received the drug combination,[5,19,22–25,35] suggesting that while the former sought to study the effectiveness based on the synergism between midazolam and ketamine, the later based their hypotheses on additive effects. Although these different rationales could have been associated with differences in side effects related to the potentiation of midazolam effects, such as excessive sedation, respiratory depression, and prolonged awakening from anesthesia,[47] the scarcity of data regarding those outcomes prevented comparisons.

The variety of dosing regimens was associated with variations in effect sizes larger than those expected by chance, as suggested by the highly significant heterogeneity measures associated with meta-analyses of all primary outcomes and confirmed in subgroup analyses.

Some concerns and/or high suspicion of methodological biases were found in critical aspects of randomized controlled trials methodology, mainly because little information was provided in most articles about randomization methods, allocation concealment, and participants and investigators' blinding. Because no study had a clear statistical plan or protocol registration, biases in selecting reported results could not be discarded. Moreover, except for the anxiety outcome, the high risk of publication bias and small-study effects pervaded the included studies.

The trim-and-fill method assumes that publication bias is the only cause of funnel plot asymmetry and performs poorly whenever high within-studies heterogeneity exists. By combining contour-enhanced funnel plots with the trim-and-fill method, it is possible to assign other causes to funnel plot asymmetry depending on the location of the imputed missing studies on the funnel plot regions plot. Missing studies in the region of $p > 0.10$ indicate that publication bias is a plausible cause of the observed asymmetry, whereas missing studies in the region of $0.05 < p < 0.1$ or $p < 0.1$ suggest that other causes may have also contributed to the funnel-plot asymmetry, e.g., high heterogeneity or the effects of one-sided comparisons.[15] Accordingly, both publication and high within-studies heterogeneity are plausible causes of funnel plot asymmetry in meta-analyses of all primary outcomes, except anxiolysis. Moreover, caution must be exercised in interpreting the adjusted risk rates produced by the trim-and-fill meta-analyses because they are based on imputed intervention effect estimates.[48]

According to GRADE, this systematic review provides a very low quality of evidence (certainty) for the preanesthetic use of oral combinations of the ketamine/midazolam relative to oral midazolam alone for providing anxiolysis, sedation, or calm and cooperative behavior during separation from parents, facial mask acceptance, or venipuncture,

suggesting that the actual effect is probably markedly different from the estimated effect.

In conclusion, based on this study's relative risks that pooled the effect sizes of studies included in the meta-analyses, similar probabilities of obtaining satisfactory anxiolysis were found for the midazolam-ketamine combinations relative to midazolam alone. However, the probabilities of obtaining satisfactory sedation, calm behavior during the child's separation from parents, low levels of fear during face mask adaptation, and cooperative behavior during peripheral venous cannulation were higher for the midazolam-ketamine combinations administered orally 20 to 45 minutes before induction of anesthesia compared to oral midazolam alone. However, because of the small effect sizes, high within-studies risk of bias, high methodological and statistical heterogeneity, and high risk of publication bias found in meta-analyses, a weak level of recommendation is provided for replacing oral midazolam alone with oral combinations of midazolam and ketamine for the preanesthetic medication of pediatric surgical patients.[49,50]

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2021.07.026.

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SYSTEMATIC REVIEW

Predictive performance of thyromental height for difficult laryngoscopies in adults: a systematic review and meta-analysis

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KEYWORDS
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Laryngoscopy;
Intubation, intratracheal;
Systematic review;
Meta-analysis;
Sensitivity and specificity

Abstract
Background: Thyromental height (TMH) was first reported as a great single test for prediction of difficult laryngoscopies, although further studies have shown variable estimates of its accuracy. We thus performed this meta-analysis to summarize the predictive values of TMH mainly for prediction of difficult laryngoscopies.
Methods: A search in PubMed, EMBASE, LILACS, and Scielo was conducted in June 2020. We included prospective cohorts fully reported with patients ≥ 16 years old, providing data on predictive values of TMH for prediction of either difficult laryngoscopies or difficult intubations. Diagnostic properties and association between TMH and Cormack and Lehanes's classification by direct laryngoscopy were evaluated. A random-effects meta-analysis using hierarchical models was performed.
Results: Eight studies evaluating 2844 patients were included. All included studies had high risk of bias and low concern regarding applicability. There was significant heterogeneity among the studies. The pooled diagnostic odds ratio (DOR) and positive (LR+) and negative (LR-) likelihood ratios were as follows: DOR, 57.94 (95% CI: 18.19–184.55); LR+, 11.32 (95% CI: 4.28–29.92); and LR-, 0.23 (95% CI: 0.15–0.35). Summary sensitivity and specificity for studies with common threshold were 82.6 (95% CI: 74–88.8%) and 93.5 (95% CI: 79–98.2%), respectively. The estimated AUC was 81.1%.
Conclusion: TMH arises as a good predictor of difficult laryngoscopies in adult patients from diverse populations presenting better predictive values than most previously reported bedside tests. However, the high risk of bias throughout the studies may have skewed the results of the individual research as well as the summary points of the present meta-analysis.

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Introduction

Managing an unanticipated difficult airway usually comes with suboptimal care, which may take patients to a life-threatening scenario.[1–3] Physicians have then searched for a way of predicting difficult airways in order to build an appropriate approaching strategy. However, the predictive performance of most tests available so far is unreliable, their role in airway prediction is unclear, and anticipating difficult airways still remains challenging.[4–6]

Although it is unclear the extent of the value of airway assessment for airway prediction, anesthesia organizations around the globe recommend performing a physical examination in search for factors that might suggest possible difficult airways.[1,2,7–9] The upper airway assessment is supposed to take multiple features into account since a comprehensive examination is assumed to improve airway prediction and enhance sensitivity as compared to the use of a single test.[7,10,11] Nonetheless, despite the use of multivariable approaches, airway prediction still lacks accuracy to segregate easy and difficult airways.[6,12]

On the other hand, a novel and promising bedside test was recently described by Etezadi et al. It is the thyromental height (TMH) – an easily performed measure, drawn by a ruler with patient in supine position and defined as the height from the anterior border of thyroid cartilage to the notch of mentum.[13] Its predictive threshold for difficult laryngoscopies is regarded by initial research as TMH $\leq$ 5 cm. This measure works as an estimate of the antero-posterior position of larynx, which the authors have reported to present surprising predictive values – higher than most known single tests and multivariable scores.[4,5] However, the relatively small sample size of the study as well as the airway manipulation by training anesthesiologists, and the lack of prespecified threshold may bring some concern regarding the precision of the predictive values as well as the validity and generalizability of their results.[13]

Additionally, other studies have been conducted since the original one with variable estimates of its diagnostic test accuracy, what makes unclear the usefulness of this measure.[14–20] As no systematic review has been found by authors over the role of TMH to predict either difficult laryngoscopies or difficult intubations, the current meta-analysis was designed to better understand the summary performance of the TMH to anticipate both difficult laryngoscopies and difficult orotracheal intubations by direct laryngoscopies in apparently normal patients undergoing general anesthesia.

Methods

Protocol and registration

The current review was designed and prepared according to recommended standards and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[21–28] A review protocol was prepared and registered before commencing the screening steps (PROSPERO registration number: CRD42020184439) and followed during the study. Search strategy was designed according to the PRISMA guidelines.

Eligibility criteria

Inclusion criteria were as follows: 1) prospective cohorts or clinical trials in full reports; 2) patients aging 16 years or older; 3) data available on thyromental height for prediction of difficult laryngoscopies or endotracheal intubation that was measured in the same manner for all patients in each individual study; 4) endotracheal intubation by direct laryngoscopies under general anesthesia. Exclusion criteria were as follows: 1) studies published in language other than English, Spanish, or Portuguese; 2) inability to abstract relevant data.

Literature search

We conducted a computerized search (11/05/2020) through PubMed, LILACS, EMBASE, and Scielo, updated on August 8, 2020. The search strategy used was (''thyromental height'' [all fields]) OR (''altura tir?omentoniana'' [all fields]) without any limitation. We also searched the reference lists of included studies. The title and abstract of each citation were reviewed in duplicate by two of the reviewers (CC and JSN), with full-text retrieval of any citation that either reviewer considered potentially relevant for assessing the predictive performance of thyromental height for prediction of both difficult laryngoscopy and difficult intubation.

Study selection

Two reviewers (CC and JSN) independently assessed the full text of each retrieved citation. The selection was based on the eligibility criteria. Disagreements were resolved by consensus among all authors.

Data-collection process and data items

We collected or calculated data in duplicate by independent reviewers through a standardized form on author, year of publication, type of study, age, sex, height, weight, body mass index (BMI), true positive, false negative, false positive, true negative, sample size of difficult airway groups, sample size of easy airway groups, and threshold used. Where data was missing, the corresponding author was e-mailed. Where relevant data was not presented or data was conflicting and the corresponding author did not reply our contact after one month, the study was excluded. Duplicated datasets were compared, and disagreements were resolved by consensus among all authors.

Diagnostic accuracy measures

Primary outcome was sensitivity and specificity for difficult laryngoscopies classified according to Cormack and Lehane's grading system. The best view achieved during the manipulations was used for definition of difficult laryngoscopies. Secondary outcome was the sensitivity and specificity for difficult intubation classified according to definition used by

authors from each study other than Cormack and Lehane's classification. We alternatively evaluated diagnostic odds ratio, and positive and negative likelihood ratios.

Risk of bias in individual studies

Two authors (CC and JSN) assessed risk of bias and generalizability using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for diagnostic tests.[29] Studies were evaluated for risk of bias with signalling questions for (1) patient selection; (2) index test; (3) reference standard; and (4) patient flow and timing between the index test and reference standard (coded 'yes', 'no' or 'unclear'), with the first three domains also considered in terms of applicability (representativeness), which was coded 'high', 'low' or 'unclear'. Disagreements were resolved by discussion and consensus of all authors.

Summary measures and synthesis of results

Analyses were conducted in Review Manager[30] (RevMan, London, UK, v5.3.5), and R software[31] tools (R Foundation for Statistical Computing, Vienna, Austria), as appropriate. For R analyses, we used the ''mada'', the ''meta'', the ''metafor'', the ''metaviz'', and the ''dmetar'' packages.[32] The R code for such analyses is available in https://rpubs.com/clistenescarvalho/753921. Diagnostic properties of thyromental height for difficult laryngoscopy were extracted or calculated. Forest plots were constructed for OR, LR+, and LR- (Fig. 1), as well as for sensitivity and specificity (Fig. 2) of thyromental height for diagnostic of difficult laryngoscopies. Summary ROC (SROC) plot with confidence regions for primary study estimates was built (Fig. 3). Heterogeneity was evaluated qualitatively and quantitatively by Cochran's Q-test along with correlation test by Spearman method to assess presence of ''threshold effect''. A Baujat plot (Supplement Fig. 1) was also built to identify the contribution of each study to both overall heterogeneity and results. Pooled estimates based on DerSimonian and Laird random-effects models were calculated where heterogeneity was present. SROC curves were also generated using a bivariate random-effects approaching through a linear mixed model (Supplement Fig. 2).[23,32] Summary sensitivity and specificity were estimated for studies with the same threshold (5 cm).

We performed sensitivity analyses to explore the impact of two features on our results: performance of external laryngeal manipulation, and risk of bias.

Risk of publication bias across studies

Publication bias was investigated using funnel plots and the Durval and Tweedie trim-and-fill approach, a method that first identifies potentially unpublished estimates based on funnel plot asymmetry and then includes these unpublished estimates in a revised pooled value. We employed the Egger's weighted regression method with precision (1/standard error) and log odds ratio plotted (Supplement Fig. 3). The intercept value in Egger's regression method provides an estimate of asymmetry of the funnel plot, with positive values indicating a trend towards higher levels of test accuracy in studies with smaller sample size. The threshold of significance was set at $p < 0.100$ for this method as this test has low power.

Results

Study selection

Our initial electronic search identified 26 articles with 17 remaining after deduplication. These 17 papers had their full text assessed and after applying eligibility criteria, nine articles were thoroughly read. One of these nine articles presented conflicting data and then a total of 8 studies were included in the analysis (Fig. 4). Studies were not included or excluded mainly for the following reasons (Fig. 4): pediatric population (2); diverse language (1); letter (1); full report not available (4); duplicate data (9); and conflicting data[33] (1).

Study characteristics

Of these 8 studies, all presented data on difficult laryngoscopies according to CL grading system (n = 2844). Only one paper reported data on difficult intubation by definition other than CL classification (n = 120)[20] (Table 1), preventing us of undertaking the meta-analysis over this outcome. The studies were prospective cohorts conducted in Iran, Turkey, India, Bangladesh, Australia, Japan, and Egypt. Studied patients were recruited from those schedules for surgical procedures under general anesthesia in tertiary centers. All studies included only apparently normal patients, judged not to be at high risk of difficult airways by the attending anesthesiologists. One study included only patients undergoing coronary artery bypass surgery,[15] and another one included only elderly patients.[20] Two studies did not use digital, but regular, rulers for TMH.[16,20] The type of blade used was reported in 7 studies.[13–15,17–20] Macintosh's blade was used in all these studies. Four of them used either sizes 3 or 4[15,17–19]; one used only size 4[13]; one used either sizes 4 or 5[14]; and one did not mention the size used.[20] Miller's blade was used in one study when no laryngeal view was achieved with Macintosh's.[13] Seven studies reported direct laryngoscopies were performed by experienced anesthesiologists,[14,18–20] whilst one, by residents.[13] One study did not report if the airway manager was aware of the index test.[15] Four studies classified glottic view supported by external manipulation of larynx,[13,15,18,20] two did not applied it,[14,17] and two did not mention it.[16,19] Seven studies used CL grades 3 or 4 as difficult laryngoscopies and one[17] used CL 2b or higher to define difficulty. Two studies[17,18] reported measures of neuromuscular blockade depth, whilst six[13–16,19,20] did not report it. Sniffing position was employed in six studies,[13,15,17–20] whilst two[14,16] did not report data on it.

Risk of bias within studies

According to QUADAS-2 tool, all eight included studies had low applicability concerns. All studies were also at risk of

Table 1 Baseline characteristics of individual studies.

Author	Year	Design	Mean age; y	Sex	Height	Weight	BMI	DL; n (%)	Total sample size	Threshold; cm
Mostafa	2020	Cohort	68	Male: 57% Female: 43%	NA	NA	27.08	15 (12%)	120	5.7
Panjiar	2019	Cohort	37.19	Male: 43.6% Female: 56.4%	158.4	61.07	24.52	55 (10%)	550	5.1
Yabuki	2019	Cohort	50.6	Male: 18% Female: 82%	159.6	58.6	22.9	6 (1%)	609	5
Rao	2018	Cohort	43.4	Male: 47% Female:53%	162.6	62	23.4	26 (8.2%)	316	5
Nurullah	2018	Cohort	45.4	Male: 50.4% Female: 49.6%	NA	NA	NA	43 (31%)	139	5
Jain	2017	Cohort	56.7	Male: NA Female: NA	162.6	65.3	24.72	32 (9.3%)	345	5
Selvi	2017	Cohort	48.49	Male: 51% Female: 49%	NA	77.65	NA	37 (8.2%)	451	5
Etezadi	2013	Cohort	44.5	Male: 47.5% Female: 52.5%	166.1	72	25.8	23 (7.3%)	314	5

y, years of age; BMI, body mass index; DL, difficult laryngoscopy; NA, not available.

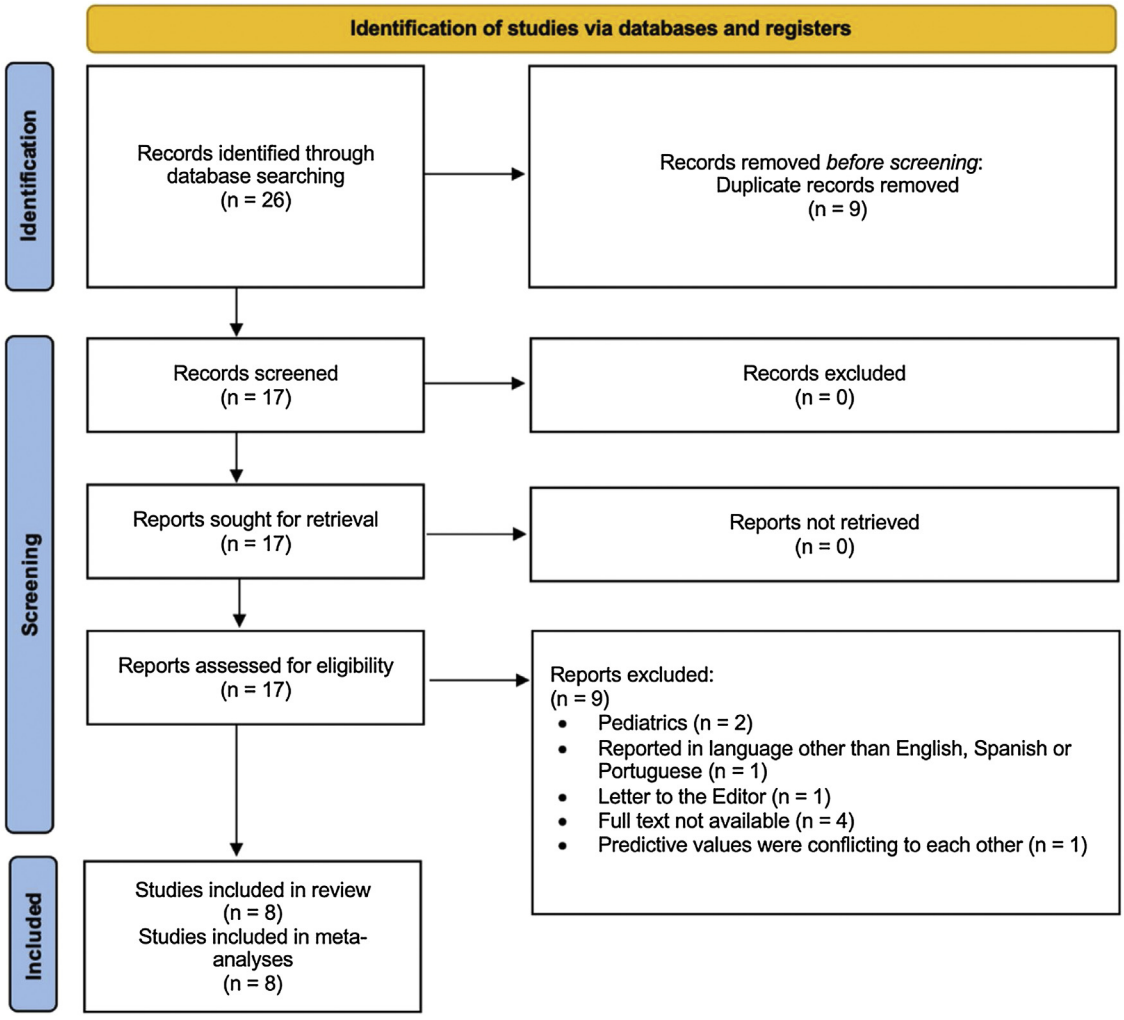


Figure 1 Systematic review flow diagram (PRISMA flow chart).

bias mainly due to concerns over patient's selection and the reference standard (Fig. 5). Six studies[14–19] were assumed to present inappropriate patient selection with exclusion of patients difficult to define THM such as obese and those with anatomic alterations as well as known to be at high risk of difficult airways, thus skewing the test accuracy. Four studies were at high risk of bias regarding index test, two[13,19] because of non-prespecified threshold (overestimating the test accuracy), and two[16,20] due to diverse and non-objective ways of measures. Only one single study was considered at low risk of bias regarding reference standard.[18] The main concerns over the reference standard were performer experience, standardization and measure of neuromuscular blockade depth, application of external manipulation over the larynx, performance of sniffing position, threshold of Cormack and Lehane's classification for difficulty, and awareness of index test. These features may have made studies heterogeneous for this domain.

Results of individual studies

Summaries of individual studies characteristics are presented in Table 1 and Figs. 1–3.

Synthesis of results

Sensitivity and specificity ranged from 50%[18] to 95%,[16] and 52%[14] to 99%,[13,17] respectively (Fig. 2).

Summary sensitivity and specificity for studies with the same threshold[13–19] were 82.6 (95% CI: 74–88.8%) and 93.5 (95% CI: 79–98.2%), respectively. Summary sensitivity and specificity for studies with prespecified threshold (5 cm)[14–18] were 84.1% (95% CI: 68.3–92.9%) and 90.4% (65–98%), respectively.

Only one paper[20] presented data on difficult intubation by classification other than Cormack and Lehane's grade system, preventing us of performing the meta-analysis over this outcome.

For difficult laryngoscopies, the frequency ranged from 1%[18] to 31%.[16] A summary of studies' patients baseline characteristics as well as further studies information are presented in Table 1.

Only one study did not present significant association between TMH and difficult laryngoscopies, when supported by external laryngeal manipulation (Fig. 1).[18] When laryngoscopy view was graded without laryngeal manipulation, the association was present.[18]

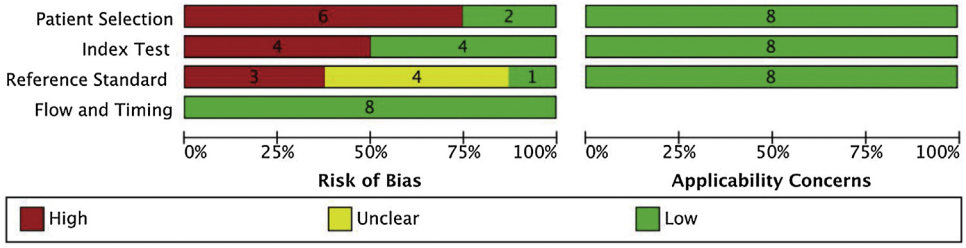


Figure 2 Risk of bias and applicability concerns graph for difficult laryngoscopy: summary of review authors' judgment about each domain presented as percentages across included studies.

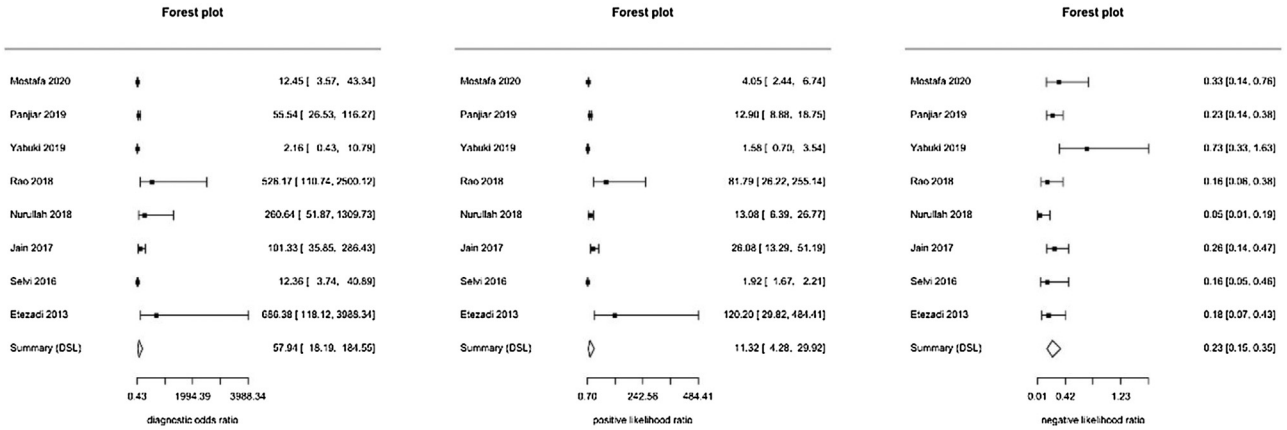
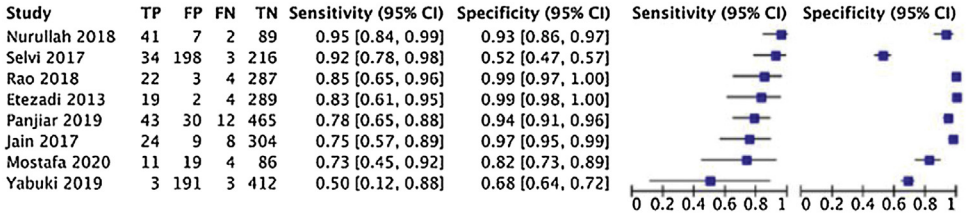


Figure 3 Forest plots for univariate analyses with summary measures of diagnostic odds ratio, positive and negative likelihood ratios.



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nurullah 2018	41	7	2	89	0.95 [0.84, 0.99]	0.93 [0.86, 0.97]
Selvi 2017	34	198	3	216	0.92 [0.78, 0.98]	0.52 [0.47, 0.57]
Rao 2018	22	3	4	287	0.85 [0.65, 0.96]	0.99 [0.97, 1.00]
Etezadi 2013	19	2	4	289	0.83 [0.61, 0.95]	0.99 [0.98, 1.00]
Panjiar 2019	43	30	12	465	0.78 [0.65, 0.88]	0.94 [0.91, 0.96]
Jain 2017	24	9	8	304	0.75 [0.57, 0.89]	0.97 [0.95, 0.99]
Mostafa 2020	11	19	4	86	0.73 [0.45, 0.92]	0.82 [0.73, 0.89]
Yabuki 2019	3	191	3	412	0.50 [0.12, 0.88]	0.68 [0.64, 0.72]

Figure 4 Forest Plot of thyromental height for difficult laryngoscopy, sorted by descending sensitivity. TP, true positive; FP, false positive; FN, false negative; TN, true negative.

The positive and negative likelihood ratios ranged from 1.58[18] to 120.20[13] and 0.05[16] to 0.73,[18] respectively. The summary points for univariate analyses were as follows: DOR, 57.94 (95% CI: 18.19–184.55); LR+, 11.32 (95% CI: 4.28–29.92); and LR-, 0.23 (95% CI: 0.15–0.35). Further information about univariate analyses are presented in Figure 1.

The estimated area under ROC curve for all 8 studies was 81.1% (Supplement Fig. 2).

Heterogeneity and risk of publication bias across studies

There was significant heterogeneity in both sensitivity ($p = 0.038$) and specificity ($p < 0.001$) of thyromental height for difficult laryngoscopies. It may have limited the robustness of pooled estimates, which therefore must be regarded with caution. The hypothesis of threshold effect as a possible reason for the caught heterogeneity was tested and rejected (Spearman correlation estimate 0.119; $p = 0.793$). A single study[18] was most implicated in the heterogeneity (Supplement Fig. 1).

In a visual inspection of the funnel plot (Supplement Fig. 3) used to check for publication bias in this meta-analysis, studies were distributed asymmetrically around the pooled estimate, suggesting a possibility for publication bias. It was confirmed by a regression test with p-value < 0.0148. The trim-and-fill method also suggested that there were possible unpublished studies (Supplement Fig. 3).

Sensitivity analysis

We conducted four separate sensitivity analyses to investigate if any of the following features significantly altered the pooled results: external laryngeal manipulation and risk of bias regarding patient selection, index test, and reference

standard. The only variable that affected the results was the high risk of bias regarding reference standard (ML false positive rate, fixed-effect coefficient -3.15; 95% CI: -5.59 to -0.71; $p = 0.011$; 3 studies; 1180 participants).

Discussion

The present systematic review showed quite good diagnostic accuracy of TMH for difficult laryngoscopies, according to the pooled sensitivity and specificity, along with other predictive values (sensitivity, 82.6%; specificity, 93.5%; LR+, 11.32; LR-, 0.23; bal acc, 88%). However, relevant imprecision was in place – with large 95% confidence intervals, significant heterogeneity, and scarcity of well-designed studies to validate its performance.

The predictive performance of TMH found in our meta-analysis was better than those from all predictors recently evaluated in other systematic review.[4] Roth et al. assessed the diagnostic accuracy of seven tests for difficult laryngoscopies: Mallampati test, modified Mallampati test, Wilson risk score, thyromental distance, sternomental distance, mouth opening, and upper lip bite test. The test with highest sensitivity was upper lip bite test (sensitivity, 67%; specificity, 92%; LR+, 8.37; LR-, 0.36; balanced accuracy [bal acc], 79.5%), whilst the test with highest specificity and LR+ was Wilson risk score (sensitivity, 51%; specificity, 95%; LR+, 10.2; LR-, 0.52; bal acc, 73%). The single test with highest specificity was mouth opening (sensitivity, 22%; specificity, 94%; LR+, 3.66; LR-, 0.83; bal acc, 58%). Thus, as compared to our results for TMH, most predictors presented close specificity, but all showed considerably lower sensitivity and balanced accuracy. Our result for LR+ of TMH was higher than that of most predictors, and similar to that of Wilson risk score. Also, TMH presented lower LR- than all seven predictors. Therefore, TMH performed better in our series of studies than other seven predictors did in a different meta-analysis. As in our analysis, few studies included in the systematic review of Roth et al. were at low risk of bias.[4]

Another meta-analysis evaluated 12 bedside tests for airway prediction: upper lip bite test, Wilson score, hyomental distance, retrognathia, impaired mandibular protrusion, ratio of height to thyromental distance, impaired neck mobility, sternomental distance, modified Mallampati, impaired mouth opening, thyromental distance, and palm print. The test with highest sensitivity was the palm print (sensitivity, 77%; specificity, 84%; LR+, 3; LR-, 0.28; bal acc, 80.5%). The test with highest specificity was retrognathia (sensitivity, 19%; specificity, 98%; LR+ 6; LR-, 0.85; bal acc, 58.5%). The test with highest LR+ was upper lip bite test (sensitivity, 60%; specificity, 96%; LR+ 14; LR-, 0.42; bal acc, 78%). Wilson risk score presented sensitivity of 43%, specificity of 95%, LR+ of 9.1, LR- of 0.6, and balanced accuracy of 69%, which was comparable to the results of Roth et al. As before, the predictive values of TMH in our meta-analysis also were better than that of all predictors in the meta-analysis of Detsky et al.[5] This superior TMH predictive performance draw our attention to what seems to be a major role of antero-posterior larynx position for the occurrence of difficult laryngoscopies.

Despite the great performance shown by TMH as a single test, some studies have demonstrated that multivariable assessments are superior for airway prediction, mainly by enhancing sensitivity values.[11,34,35] It makes sense since there are a multitude of factors determining the emergence of a difficult airway and has led authors to recommend the assessment of multiple features during the physical examination.[7,10,35] It is in accordance with the findings of Selvi et al., who encountered higher sensitivity for Mallampati and thyromental height when combined as compared to each one alone.[14] This way, a multivariable approach including TMH might be a good alternative for airway prediction and further studies investigating predictive scores and models with TMH would be worthwhile.

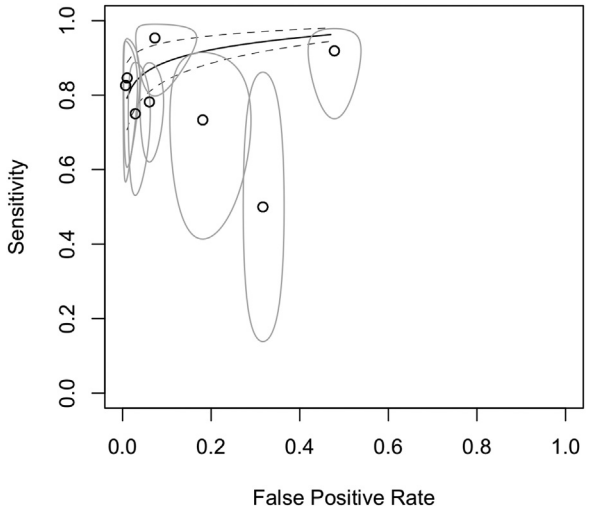


Figure 5 Summary receiver operating curve (SROC) plot along with SROC curve by proportional hazard model approach. Open circle (o) represents false positive rate (x-coordinate) and sensitivity (y-coordinate) of individual studies. Size of bubbles reflects precision of estimate. AUC = 95.2%.

It is important to state that in the present meta-analysis, the largest study[18] was also the only one regarded as at low risk of bias for direct laryngoscopies. In this study, the frequency of difficult laryngoscopies was the lowest (1%) and the performance of the TMH was the worst, with no significant association being presented between TMH and DL when applying external laryngeal manipulation. The best predictive performance of TMH, on the other hand, was presented in a study with uncommon high frequency of difficult laryngoscopies (31%)[16] – which by the way was not the one conducted with residents. This behavior is in accordance with the well-known dependence of a test accuracy on the prevalence of disease in the population.[36] These aspects along with the remaining risk of bias and heterogeneity across the studies bring further concern over the validity of our pooled results.

Another intriguing characteristic was how largely the frequency of difficult laryngoscopies ranged (1–31%) among studies. It raises some concern about the reliability of Cormack and Lehane's classification as a tool to define difficulty of laryngoscopy. Many instances may have been responsible for this variability such as some tool subjectivity and the non-standardized use of external laryngeal manipulation, patients' positioning, threshold for difficult laryngoscopy, and depth of neuromuscular blockade as well as the use of

different types of laryngoscope blades. On the other hand, manipulator experience did not seem to be a major concern in this regard since the only study conducted with non-experienced anesthetists – residents – showed second to the lowest frequency (7.3%).[13]

Notwithstanding, the association between TMH and difficult laryngoscopies was consistent and replicable throughout most studies. Furthermore, the overall predictive performance of the test was great and promising, even when compared to either single or composite scores. From these findings, TMH might be regarded at least as a risk factor for difficult laryngoscopies, while larger and more well-designed studies are yet not available.

Apart from the weaknesses discussed so far for the present meta-analysis, such as significant heterogeneity and high risk of bias across individual studies, other limitations should be taken into account. We excluded four studies not fully reported and one due to language, what reduced the total number of patients evaluated. The results were based on a small set of small studies, what also led to a large 95% CI and further compromised the reliability of our pooled results. Since there was no threshold effect, the estimated AUC should be regarded with caution. We did not assess the role of TMH in particular scenarios and populations such as in obese or elderly patients, in the emergency setting during anesthesia, in the ICU, in the emergency departments, and outside hospitals. Therefore, caution should be exercised in translating our results to these clinical settings. Also, we did not distinguish performance differences between different types of rulers for measuring TMH as well as between different types of laryngoscopy blades.

Conclusion

We found great predictive values of TMH for difficult laryngoscopies in adult patients submitted to general anesthesia for elective procedures. The pooled estimates of both sensitivity and specificity were higher than the estimates of all other predictors performed in different meta-analyses. It gives support to the use of TMH during routine airway assessment. However, our summary results originated from a small set of small and heterogeneous studies with high or unclear risk of bias in many domains. This way, further studies with larger sample sizes and more well-designed methods would be necessary to better understand the actual predictive performance of TMH.

Conflicts of interests

The authors declare no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2021.06.015.

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CASE REPORT

Anesthetic management of a patient with acquired angioedema submitted to broncofibroscopy: a case report

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KEYWORDS
Angioedema;
C1 Esterase Inhibitor;
Airway Management;
Bronchoscopy

Abstract Acquired angioedema with C1 inhibitor deficiency (AAE-C1INH) is a very rare condition of bradykinin-mediated angioedema. One of its major complications is potentially life-threatening, laryngeal edema. We report a 53-year-old woman with AAE-C1INH proposed for an elective broncofibroscopy. The direct stimulation caused by broncofibroscopy poses a high risk of angioedema, thus presenting an anesthetic challenge. Due to the risk of death, it is essential to adopt preventive measures. Short-term prophylaxis was performed, and the acute treatment was readily available. A well-structured multidisciplinary periprocedural plan makes it possible to safely approach the airway, in a remote area of the hospital.

Introduction

Acquired angioedema with C1 inhibitor deficiency (AAE-C1INH) is a very rare condition of angioedema with a prevalence in the general population estimated to be 1:10 that of the hereditary form, that is, around 1:50.000.[1]

It is characterized by an increase in vascular permeability and vasodilation, resulting from an overproduction of bradykinin, due to C1 esterase inhibitor (C1-INH) deficiency or dysfunction.[2,3] C1-INH plays an important role in the complement cascade, fibrinolysis, and contact activation (Fig. 1).[2] It is usually associated with rheumatologic disorders and B-cell lymphoproliferative diseases.[2,4] This condition usually appears after the fourth decade with no family history.[1,4] It manifests with acute, localized, non-pitting, nonpruritic, non-erythematous, and demarcated angioedema.[1,3] It typically lasts for 2—5 days and resolves spontaneously.[3] Edema predominantly involves the face, tongue, uvula, and upper airways.[1] Laryngeal edema incidence is approximately 70% during the disease course and can be fatal in 15—33% of the cases.[3] Although the edema can be spontaneous, there are several triggers such as (1)

Abbreviations: AAE-C1INH, Acquired angioedema with C1 inhibitor deficiency; C1-INH, C1 esterase inhibitor; HAE, Hereditary angioedema; PdC1INH, Plasma-derived C1-INH concentrate.

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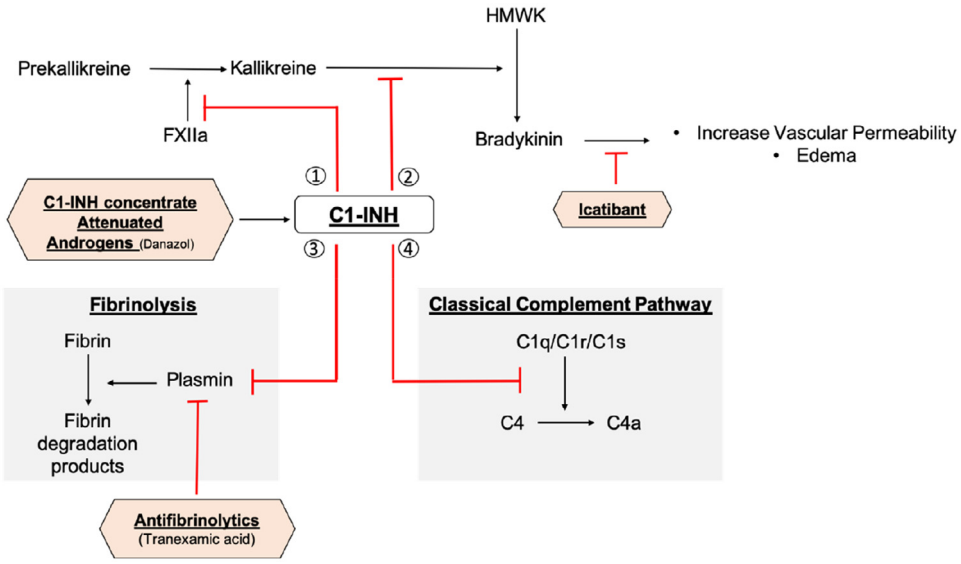

Figure 1 The function of C1 esterase inhibitor (C1-INH) includes inhibition of (1) activated factor XII (FXIIa)-mediated cleavage of prekallikrein to kallikrein; (2) kallikrein-mediated conversion of highmolecular-weight kinin (HMWK) to bradykinin; (3) plasmin-mediated fibrinolysis; (4) C1 esterase-mediated activation of C4 in the classical complement pathway. In the presence of C1-INH disfunction or deficiency, there is no inhibition of the contact activation, fibrinolysis and complement cascade, leading to overproduction of bradykinin and consequently edema. Management of bradykinin-mediated angioedema can include increasing C1-INH levels with C1-INH concentrate and attenuated androgens (e.g., danazol) and inhibition of bradykinin with Icatibant and plasmin with antifibrinolytics (e.g., tranexamic acid). C1-INH, C1 esterase inhibitor; FXII, Factor XII; HMWK, highmolecular-weight kinin. Figure redrawn based on "MacBeth LS, Volcheck GW, Sprung J, Weingarten TN. Perioperative course in patients with hereditary or acquired angioedema. J Clin Anesth. 2016;34:385-91." with authors' permission.

anesthetic and surgical trauma, (2) dental procedures, and (3) psychological and physiological stress. Triggers may vary between and within patients, thus it is not possible to predict complications, making the management of this disorder especially challenging.[2]

Distinguishing between AAE-C1INH and hereditary angioedema (HAE) can be difficult as clinically these two entities are indistinguishable.[3,4] Both conditions have usually Low C1-INH and C4 levels.[3,4] By contrast, C1q levels are often depressed in patients with AAE-C1INH, but nearly always normal in patients with HAE.[3,4] Clinical history can also provide important clues. Family history and onset of symptoms in the first or second decade of life favors HAE, and the presence of malignancy or auto-immune diseases favors AAE-C1INH.[3,4]

The following clinical case is presented after informed consent was obtained.

Clinical case

We report a case of a 53-year-old woman, with obesity grade I, hypertension, anxiety, and AAE-C1INH associated with systemic lupus erythematosus. She was never submitted to general anesthesia with airway manipulation.

She was proposed for broncofibroscopy, in the bronchoscopy suite, with bronchoalveolar lavage due to suspicion of interstitial lung disease.

The patient was diagnosed with AAE-C1INH nine years ago, after recurrent episodes of angioedema (lip, eye, and hand). Two previous episodes required stay in an intermediate care unit and the last one was seven years ago, triggered by an infection. At the time of diagnosis, C4 and C1q were decreased. The patient has been on Danazol since then, currently in a dose of 100 mg every 3 days, prescribed by the attending immunoallergologist.

After multidisciplinary evaluation by by the anesthesiologist, pulmonologist and immunoallergologist, short-term prophylaxis was performed with Danazol 200 mg each 8 hours 5 days prior and maintained 3 days after the procedure. Plasma-derived C1-INH concentrate (PdC1INH) 2 doses of 1500 U and subcutaneous Icatibant 30 mg were readily available for acute treatment of AAE-C1INH.

Prior to anesthetic induction, standard ASA (American Society of Anesthesiologists) monitoring and a peripheral venous access were obtained. Emergency equipment was readily available, and a second anesthesiologist was within reach. Broncofibroscopy was performed under deep sedation with fractionated boluses of intravenous propofol, total dose of 290 mg. The patient remained on spontaneous ventilation with oxygen supply through a fiberoptic face mask. Anesthetic procedure lasted 20 minutes and was uneventful. The patient was transferred to the Postanesthesia Care Unit for recovery and surveillance during 24 hours. Drugs for acute treatment were not needed.

Discussion

Despite being a very rare disease, AAE-C1INH poses a great anesthetic challenge due to the high risk of angioedema caused by airway manipulation. Broncofibroscopy directly

stimulates the airway, increasing the risk of upper airway angioedema in these patients. Angioedema can be fatal, so it is important to consider it pre-, intra-, and post-procedure, and anesthesiologists must be familiar with prevention and treatment strategies.

Management of patients with AAE-C1INH is still not well defined. There are no specific guidelines for AAE-C1INH. Its treatment has been extrapolated from HAE with some particularities.[1] Treatment of the underlying disease may lead to resolution of angioedema.[1]

To treat acute crises, PdC1INH and newer treatments such as Icatibant, a bradykinin receptor antagonist, are available.[2,5] Replacement therapy with PdC1INH has been effective with most patients responding, however some are resistant or require higher doses, because of rapid C1-INH catabolism mediated by autoantibodies. Those patients may respond to Icatibant.[1,5] For this reason, PdC1INH and Icatibant were available, although the probability of using both was very low. PdC1INH is used in a dose of 20 $U.kg^{-1}$ IV (intravenous), usually 1500 U repeated if ineffective. Icatibant is used in a dose of 30 mg subcutaneously and can be repeated every six hours twice if needed.[5]

Long-term prophylaxis to prevent angioedema has been used in AAE-C1INH.[1] It is indicated when patients have more than one exacerbation monthly if rescue therapy is not effective or is unavailable.[5] Antifibrinolytics (such as tranexamic acid 20—50 $mg.Kg^{-1}.day^{-1}$ split 2 to 3 times daily), attenuated androgens (such as Danazol up to 200 $mg.day^{-1}$), or PdC1INH are recommended for this approach.[1,5] Attenuated androgens were considered to be more effective and best tolerated for long-term prophylaxis of HAE[1,5] and were traditionally used.[4] PdC1INH is currently the preferred long-term prophylaxis in HAE patients.[4] Antifibrinolytic agents are not recommended for long-term prophylaxis. They are primarily used when PdC1INH is not available and androgens are contraindicated.[4] However, in AAE-C1INH, antifibrinolytic agents tend to be more effective than in the hereditary form and experts recommend this as the drug of choice for prophylaxis in AAE-C1INH.[1,4] Our patient was already medicated with danazol and has her disease well controlled free of crisis for 7 years. For this reason, no modifications in her long-term prophylaxis were made.

Short-term prophylaxis has only been described for HAE and mainly necessary when planning an elective dental extraction or other surgical procedures with manipulation of the airway.[4,5] PdC1INH and attenuated androgens are available. Due to possible refractoriness of AAE-C1INH patients to C1-INH concentrate, it is reserved for acute treatment and not for prophylaxis.[4] For this reason, our patient did short-term prophylaxis by increasing the dose of danazol in the periprocedural period, instead of PdC1INH.

For any procedure, acute treatment of bradykinin-induced angioedema should be readily available.[4,5]

Since the principal mediator is bradykinin, and not histamin, agents such as epinephrine, steroids, antihistamines will be ineffective to treat AAE-C1INH.[2,5]

Even with short-term prophylaxis and having acute treatment readily available, there is the possibility of an acute periprocedural crisis. Accordingly, it is desirable to minimize any laryngeal trauma which may trigger later angioedema and continue to monitor the patient in a Postanesthesia Care Unit.

The role of the anesthesiologist becomes essential to emergently manage a difficult airway and its particularities in the out of the room setting. Emergency airway equipment and help must be readily available. So far, no anesthetic drugs have been contraindicated in patients with bradykinin-mediated angioedema.[2,3] Drugs that are known to potentially worsen this disease are estrogen contraceptives, hormone replacement therapy, and angiotensin-converting enzyme inhibitors.[4,5]

In this case, sedation with propofol was chosen, maintaining spontaneous ventilation. In the case of acute angioedema, direct laryngoscopy may be difficult or even impossible due to the possibility of distorted airway anatomy. Awake fiberoptic intubation with spontaneous ventilation may be an alternative. However, it is important to be prepared for urgent cricothyrotomy.[3]

Although AAE-C1INH is a very rare disease, its life-threatening risk makes it essential that the patients and their families are informed and are aware of the importance of informing health providers when reaching a health facility. A multidisciplinary approach is extremely important, and it is essential that anesthesiologists become familiarized with the disease, its management, and preventive measures. Prophylactic and acute treatment drugs should be available throughout the procedure.

A well-structured multi-disciplinary periprocedural plan makes it possible to safely approach the airway in a patient with AAE-C1INH, in a remote area of the hospital. In this case, all the preventive measures contributed to a positive outcome.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Spinal cord ischemia as intraoperatory complication in shoulder surgery positioned in beach chair: case report

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KEYWORDS
Spinal cord ischemia;
Sitting position;
Postoperative complication;
Shoulder

Abstract Spinal cord infarction is an uncommon phenomenon, which can be caused by different etiologies, constituting a real diagnostic challenge which can lead to devastating consequences. General anesthesia in beach chair positioning with intraoperative hypotension in order to avoid surgical bleeding are associated with hypoperfusion and potential neurological ischemia-related complications. We present a case of spinal cord ischemia in the context of shoulder surgery in a beach chair position.

Introduction

Spinal cord infarction is a rare disorder, characterized by bilateral flaccid paralysis in the acute phase, caused by reduced perfusion of a nutritional artery, or even the aorta. Depending on the topography of the infarction, patients may suffer different types transverse spinal cord syndromes with several types of sensation deficits and bladder and bowel dysfunctions.

The beach chair surgical position has been widely used in shoulder surgery, mainly in arthroscopy. However, this vertical position is associated with a series of hemodynamic variations worsened by general anesthesia, which contribute to a series of physiological conditions that can cause hypoperfusion leading to intraoperative ischemic events further aggravated by permissive hypotension, frequently demanded by the surgeon to operate on a bloodless surgical field. In the last decade, there have been reports of catastrophic neurological sequelae secondary to neurological ischemia[1] during shoulder surgery in patients positioned in a beach chair and operated under general anesthesia. Spinal cord ischemia, unlike cerebral infarction (more frequently reported in the medical literature after shoulder surgery), accounts for less than 1% of all strokes,[2] one of the reasons being the extensive network of vascular collaterals of the spinal cord. However, it should be kept in mind that occlusion of a single spinal artery can also affect border-

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ing territories, which are sensitive to sudden hypoperfusion, and not only the directly irrigated tissues.

It is likely that the occurrence of ischemic neurological complications in this surgical population is multifactorial, however, we must know that sitting a patient under general anesthesia is not entirely harmless.[3]

We present the case of a middle-aged patient with cardiovascular risk factors, who presented spinal ischemia during a shoulder surgery intervention which underwent in beach chair position.

Written consent was obtained from the patient's son after the patient deceased.

This manuscript adheres to the applicable EQUATOR guideline.

Clinical case

We present a 56-year-old male (weight 90 kg and height 187 cm) with medical history of dyslipidemia and hypertension, with poor treatment adherence, former smoker, former alcohol abuse until the previous 4 months, former consumer of benzodiazepines for 10 years and former cannabis consumer for 9 months, that requires elective surgery to treat a proximal humerus fracture.

Upon arrival to the operating room (OR), standard monitoring was performed with noninvasive blood pressure (BP) measurement in the calf. The patient showed significant anxiety, maintaining high blood pressure figures 160/110 mmHg that decreased after the administration of 3 mg of midazolam.

An uneventful ultrasound-guided regional blockade of the brachial plexus was performed, using an interscalenic approach with bupivacaine 0.25% (20 ml) and mepivacaine 1.5% (8 mL). After confirming the blockage and the absence of complications, anesthesia was induced with 3 mcg/kg of fentanyl, 2.5 $mg.kg^{-1}$ of propofol, and 0.6 $mg.kg^{-1}$ of rocuronium. A number 8 flexometallic endotracheal tube was placed, and the patient was placed in beach chair surgical position with the corresponding abdominal, cranial, cervical, and limb fixations. The anesthetic maintenance was carried out with sevoflurane ensuring a minimum alveolar concentration (CAM) of 1. The patient remained hemodynamically stable with mean arterial pressures around 70 mmHg, without the need for intraoperative vasopressors, being extubated after reversal of the neuromuscular blockade. Blood loss was less than 300 milliliters. The procedure was performed without surgical or anesthetic complications.

During his stay in the Postanesthetic Recovery Unit, the patient reported inability to mobilize lower limbs. On examination he was conscious, oriented, and with stable blood pressure, neurologically the presence of flaccid paraplegia without movement in the horizontal plane and absence of both patellar and aquilear reflexes in both lower limbs but with preserved sensitivity, as well as hypotonia of the anal sphincter with abolished bulbocavernosus reflex. With the suspicion of spinal infarction, an urgent magnetic resonance imaging (MRI) was requested. The main findings in the spinal cord included a signal alteration of probable ischemic origin in the thoracic segments that fundamentally affected the grey substance (Figs. 1 and 2), therefore diagnosed as acute arreflexic flaccid paraplegia of probable ischemic origin without confirmed etiology.

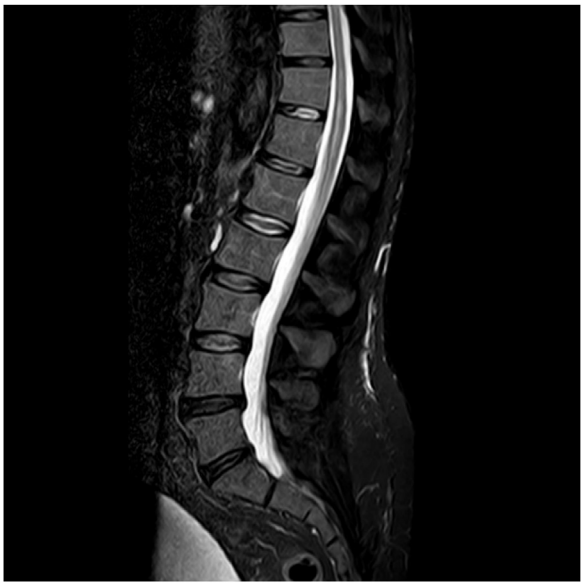

Figure 1 T2-weighted thoracolumbar spine MRI sagittal section showing hyperintense image in the lower segments of the dorsal medulla compatible with ischemic vascular process.

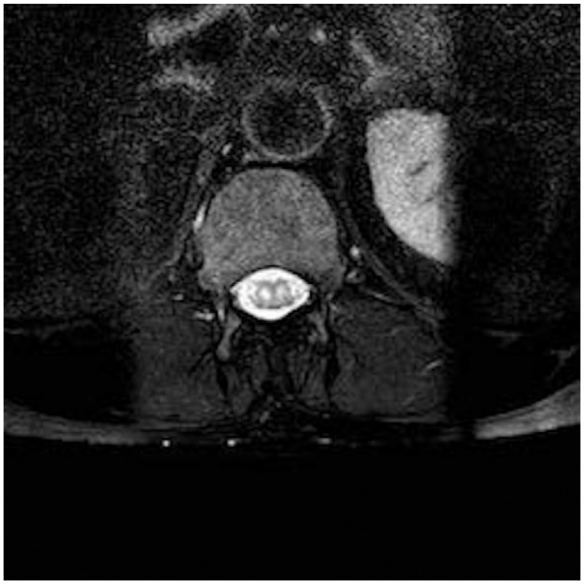

Figure 2 T2-weighted dorsal spine MRI axial section demonstrating signal alteration in the anterior horns of the medullary gray matter, which produces an ''owl eyes'' image. Finding compatible with acute spinal cord ischemic injury.

During his 23-day admission, the patient presented clinical improvement of distal muscle tone, recovered achilles reflexes and both anal sensibility and sphincter tone, but did not recover proximal muscle function. The patient was transferred to a paraplegic center, with no improvement in the neurological examination. Finally, the patient died of cardiovascular causes two years after the intervention.

Discussion and conclusions

Beach chair surgical positioning provides advantages in shoulder surgery; however, in relation with general anesthesia, it can lead to ischemic neurological events. The vertical position entails a series of hemodynamic changes that, in non-anesthetic conditions or in an awake patient under regional anesthesia, are compensated by an increase in sympathetic activity.[3] In patients under general anesthesia, the sympathetic response is inhibited, to which is added the vasodilator and myocardial depressant effect of anesthetics; causing a redistribution of venous flow, especially affecting the lower extremities, it causes a drop in preload, cardiac output, systemic blood pressure, and cerebral perfusion pressure.[4] Moreover, we must add another factor that accentuates the decrease in venous return, which is the increase in intrathoracic pressure caused by mechanical ventilation.[1]

We must bear in mind that shoulder surgery includes a rather heterogeneous group of patients, which ranges from young healthy athletes to elderly patients with varying degrees of limitation of their physiological reserve. With this last group we must have special consideration when positioning them, being rigorous in hemodynamic monitoring and less tolerant with hypotension. This is also valid for healthy patients, since among the reported cases there are patients without risk factors.[5]

In this case, the necessary tests (brain MRI, computed aortic angiotomography, eye fundus, and transthoracic echocardiogram) were performed to clarify the etiology by making a differential diagnosis that allowed to rule out fat embolism, air embolism, cholesterol embolism, and aortic pathology among other pathologies. It is interesting to find in the MRI a diffuse microangiopathy of the central nervous system and four older lagoon strokes that suggested a chronic arteriopathy background. No spinal cord angiographic study was carried out given the high risk of this technique and the low therapeutic profitability. After ruling out different medical causes and specifically anesthetic complications derived from interscalenic blockade; the most plausible explanation for this clinical case is that the decrease in systemic blood pressure (underestimated by its measurement in the lower limb) may have significantly compromised perfusion in the circulation of the spine this hypertensive, dyslipidemic patient with radiological findings suggestive of chronic vascular disease. All this added to other hypoperfusion factors (such as the increase in intra-abdominal pressure causing an increase in cerebrospinal fluid pressure and the ulterior compromise of circulation in the Adamkiewicz artery in which – we assume – there were some previous vascular injuries as well as possible phenomena of associated theft) could justify spinal ischemia.

Given the possible complications associated with the beach chair surgical position under general anesthesia, it is recommended, whenever possible, to advocate for a regional anesthetic technique based on interscalenic block and sedation. Although the protective role of general anesthesia is not fully established, its lower systemic hemodynamic impact may be associated with better results.[1,5] Similarly, whenever general anesthesia cannot be performed, invasive monitoring of systemic blood pressure is recommended, especially in patients with cardiovascular risk factors, without forgetting that neurological adverse effects have been described in patients without cardiovascular risk factors. It is difficult to establish a lower limit of mean arterial pressure to maintain cerebral self-regulation, since there is a significant interindividual variability, but it is suggested to aim for mean arterial pressures of at least 70 mmHg, avoiding BP drops greater than 20% of baseline values,[1,5] treating them immediately with the use of ephedrine as the first choice drug or in conjunction with atropine, since it reverses hypotension and induces peripheral vasoconstriction by raising blood pressure.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Dual epidural catheters for labor analgesia in a spinal cord injury patient: a case report

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KEYWORDS
Epidural anesthesia;
Epidural injections;
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Spinal cord injury

Abstract Impediment to local anesthetic solution in the epidural space results in unsatisfactory pain relief during labor epidural. Patients with a history of back trauma and spinal instrumentation have increased rates of epidural failure due to patchy spread of local anesthetic with obliterated epidural space. Dual Epidural Catheters (DEC) can be used in such clinical scenarios with complete labor analgesia and improved patient satisfaction. We present the successful management of a parturient with vertebral fracture at risk for epidural failure and neurologic injury due to bone fragments and inserted cranial and caudal to the fractured vertebra using ultrasound to avoid neurologic sequelae.

Introduction

Spinal Cord Injury (SCI) is a rare but devastating outcome of traumatic injury that involves the spine. The National Spinal Cord Injury Statistical Center (NSCSC) estimates that the annual incidence of SCI is approximately 54 cases per million in the US.[1] The most common causes of SCI are motor vehicle crashes, followed by falls, acts of violence such as gunshot wounds, and sport/recreational activities. As of 2016, 80% of these new cases of SCI were in males and the average age at the time of injury was 42 years old. This makes obstetrical patients with spinal cord injury an uncommon occurrence.

While spinal cord injury is infrequently encountered in the obstetric population, its presence does have some significant impacts on anesthetic management of pregnant patients. One significant concern that can manifest itself unpredictably is the potential for sympathetic hyperreflexia also known as autonomic dysreflexia, which is caused by damage to the thoracic sympathetic chain, most commonly, although not exclusively, with lesions above T6.[2] Although patients may be insensate below the level of the spinal lesion, noxious stimuli such as uterine contractions with labor can cause potentially life-threatening hypertension and bradycardia due to disruption of the sympathetic and parasympathetic balance.

Another consideration in obstetric patients with spinal cord injuries is the potential effects on neuraxial anesthesia because of anatomical barriers in the epidural space to allow free flow of the local anesthetic solution. Scar tissue and other changes resulting from the injury increase the risk of failed epidural due to either mal positioning of the tip of the

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epidural catheter or due to prevention of uniform spread of local anesthetic solution within the epidural space.[3]

During labor, pain progresses along the lower thoracolumbar region depending on the stage of labor. During the first stage of labor, painful uterine contractions are transmitted via the T10 to L1 spinal segments as visceral pain. As labor progresses to the second stage, stretching and pressure on the uterine cervix transitions the pain to the S2—S4 spinal segments combined with the T12 to L1 segments as somatic pain. Pain of second-stage labor is not only more intense but these thick nerve roots are further from the tip of the epidural catheter which may result in sacral sparing with inadequate analgesia during the second stage of labor.[3]

We report a case of a patient with a history of a fractured L3 vertebra for labor analgesia at risk for epidural failure with a single catheter, managed successfully with Dual Epidural Catheters (DEC). A written informed consent was taken from the patient for publication.

Case report

A 19-year-old primigravid female who presented at 39 weeks gestation for induction of labor. The patient was 154.9 cm tall (5'1'') and weighed 79 kg (174 lb). She had a history of paraplegia from a self-inflicted abdominal gunshot wound at the L3 spinal level. At the time, the patient had been submitted to an exploratory laparotomy with splenectomy and bowel resection. The patient had a past medical history of depression and functionally used a wheelchair to move around, but stated that she did have some motor strength in her left lower extremity greater than right lower extremity. Due to her immobility, the patient was on prophylactic enoxaparin for the duration of her pregnancy. The patient also noted that she had urinary incontinence but did not require straight catheterization. The patient was being treated for pyelonephritis during pregnancy with nitrofurantoin.

Upon examination of her outside medical records, the patient's most recent Computer Tomography (CT) scan had showed comminuted fracture of the L3 vertebra and noted a focal mild kyphotic curvature centered at L3. Mild retropulsion of osseous fragments as well as scattered discrete punctate densities, presumably osseous fragments, within the spinal canal were also noted with narrowing of the spinal canal at L3. On physical examination, the patient did have complete numbness at the L3 and L4 level on the right side, had 2/5 strength for dorsiflexion and plantar flexion on the right and 4/5 strength on the left. The patient said that she was not able to regularly ambulate and generally moved in a wheelchair. The patient desired labor analgesia and was counseled extensively regarding the potential increased risk of ineffective analgesia and increased risk of complications. The risk and benefits of alternative analgesic techniques, including dual epidural catheter placement, single or continuous spinal anesthesia, nitrous oxide, intravenous opioid administration, and pudendal block were discussed thoroughly with the patient and her family. To provide effective, safe analgesia throughout all stages of labor as well as to avoid any injured structures or anatomic barriers in the epidural space, a mutual decision was made to place two separate epidural catheters, one above and one below the level of the patient's spinal lesion. In order to accurately visualize and avoid the comminuted fractures present at the patient's L3 level, ultrasound was used to visualize the patient's spine (Fig. 1), and the patient's vertebral levels were marked with a surgical marker on onto the patient's back (Fig. 2).

Once the patient's anatomy was adequately visualized and marked, the epidural catheters were sequentially placed with standard technique. Upper epidural catheter

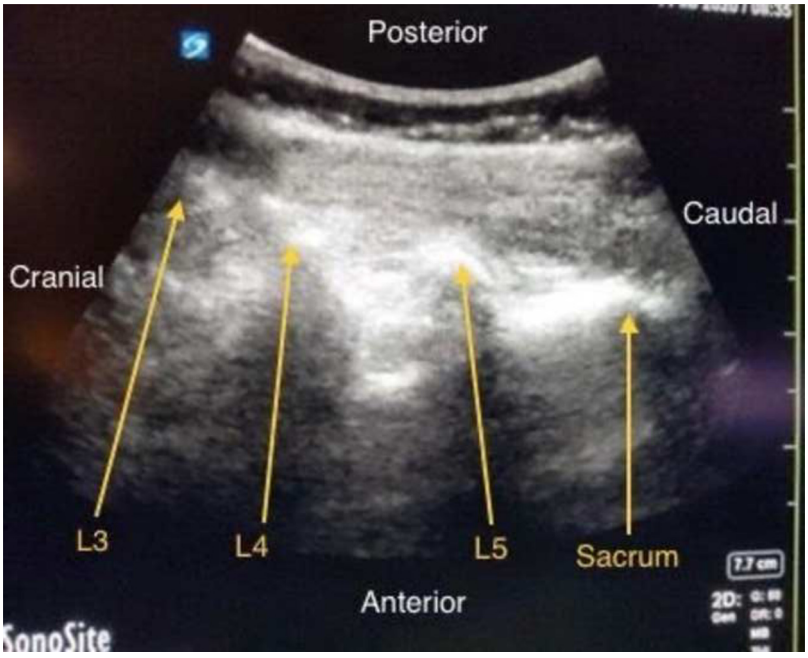

Figure 1 Ultrasound image of patient's vertebral column showing comminuted fracture at L3 spinal vertebra.

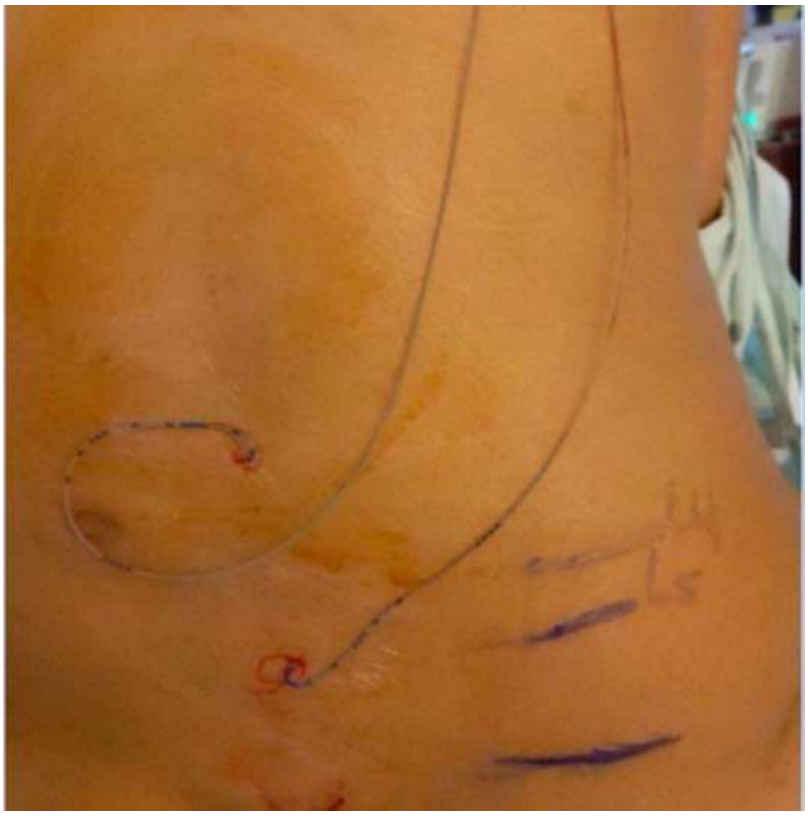

Figure 2 Image of dual epidural catheters in patient's back and relevant spinal levels marked after ultrasound imaging.

started at 6 mL/h infusion of 0.1% bupivacaine with 2 mcg/mL fentanyl to cover the first stage of labor, while the lower epidural catheter was started at 4 mL/h to adequately cover the sacral nerves, with the plan to titrate infusions through both catheters to provide optimal analgesia with labor progression.

The patient had excellent pain relief during the entire course of her labor and had an otherwise uneventful vaginal delivery of her baby. No adjustment of PCEA setting had been made throughout the entire course of labor. The patient's epidural catheters were removed intact in standard fashion.

Discussion

Lumbar epidural catheter placement is the gold standard for labor analgesia and is a common practice worldwide. However, failure of epidural anesthesia and analgesia is a frequent clinical problem which mostly relates to malposition of the epidural catheter or a patient's challenging neuraxial anatomy. Analgesic failure may even occur with a true epidural catheter and 5% to 8% blocks can either be unilateral or may be patchy in an otherwise complete block.[4] The second stage labor analgesia may be inadequate in a prior working epidural due to sacral sparing as perineal nerves are thick and away from the epidural catheter tip which may not bathe these nerves with enough local anesthetic solution. Low epidural catheters inserted at the L4–L5 intervertebral level provide superior perineal analgesia compared to high epidural catheters inserted at the L1–L2 intervertebral level.[5] Patients with a history of chronic low back pain due to back trauma may have increased rate of failures due to scarring and epidural adhesions that either slow the diffusion of local anesthetic past the injured area or block it altogether. Our patient had a history of comminuted fracture at the L3 vertebral level and therefore was at risk for difficult epidural placement, malposition of epidural catheter and epidural failure, either due to sacral sparing or patchy block due to potential fibrosis and adhesions in the epidural space. Epidural placement without imaging would have been difficult and potentially unsafe with a risk of neurologic injury due to osseous fragment dislodgement. A pre-procedural ultrasonographic scan to identify relevant landmarks was done with subsequent needle insertion as increased precision was required due to abnormal spinal anatomy and the presence of unstable bony fragments. Dual Epidural Catheter (DEC) to manage her labor was planned, upper epidural catheter placed at the L1–L2 intervertebral level for first stage analgesia, and lower epidural catheter placed at the L4–L5 intervertebral level for the second stage to avoid sacral sparing. Initial infusions started at 6 mL/h for the upper epidural catheter and 4 mL/h for the lower epidural catheter with the plan to titrate infusions as labor progressed.

The DEC technique to alleviate labor pain was first described in 1949 and later in 1967. Yet, the current literature is sparse in the use of DEC therapy for labor analgesia. Contemporary literature about the use of DEC in scoliosis correction surgery and esophagectomies did not

show an increase in side effects associated with catheter placement as compared to single epidural catheter therapy. In a manuscript published in Chinese with an English abstract, labor analgesia provided by a dual catheter technique was compared to a single catheter. No serious anesthesia related complications were noted in either group with no effects on delivery outcomes.[6]

Despite the relative infrequency of obstetric patients with clinically significant spinal cord injuries, it is important to address their special physiologic and anatomic requirements while still providing them access to effective and safe labor analgesia. The widespread availability of ultrasound provides an excellent means of visualizing patient anatomy and allows for accurate determination of relevant anatomic levels and structures prior to placement of a labor epidural. While there is always concern for anatomic changes to the epidural space after spinal cord trauma, this does not consign the patient to having to endure labor and vaginal delivery without neuraxial analgesia nor does it require cesarean delivery. Here we demonstrate that using an epidural catheter on either side of the spinal cord lesion allows for specific titration of the neuraxial block as well as adjustment as the labor progresses to specifically target the areas responsible for pain during the specific stages of labor.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Awake airway endoscopy in mucopolysaccharidosis: a case report

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KEYWORDS
Mucopolysaccharidosis;
Airway;
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Abstract Mucopolysaccharidosis (MPS) are a group of rare genetic inherited diseases with a progressive course due to the accumulation of glycosaminoglycans resulting in anatomic abnormalities and organ dysfunction, including the respiratory, cardiovascular, skeletal, and neurological systems that can increase the risk of anesthesia complications. Clinical manifestations are variable, multisystemic, and include severe morphological changes. The anesthetic management of these patients is complex, particularly airway management, which can be planned to include a fiberoptic airway investigation prior to surgery. We present two cases of patients with MPS type VI and VII who underwent fiberoptic airway mapping under conscious sedation, with no complications. Since MPS is a rare but challenging disease concerning the airway management, we propose a safe and effective anesthetic technique that could be used for fiberoptic bronchoscopy and allow fiberoptic-assisted tracheal intubation at the time of surgery.

Introduction

Mucopolysaccharidosis (MPS) are inherited lysosomal storage diseases caused by the deficiency of enzymes required for the stepwise breakdown of Glycosaminoglycans (GAGs), being associated with the widespread tissue accumulation of partially degraded GAGs. The characteristic patterns and age of presentation form the basis of MPS classification into seven types.

Typical clinical manifestations include coarse facial features, ear-nose-throat problems, skeletal dysplasia, growth impairment, cervical instability, organomegaly, impaired vision and hearing, joint contractures, hernias, and cardiorespiratory disease.[1] Respiratory complications affect all

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types of MPS and contribute to death and disability. Airway obstruction result from respiratory abnormalities, excessive secretions, skeletal restriction, organomegaly, infections, and neurologic compromise.[2]

Patients with MPS I, II, VI, and VII often develop upper airway obstruction due to an enlarged tongue, thickened gums, and engorged soft tissues of the nasopharynx.[2] Airway problems may be worsened by excessive thick secretions due to recurrent infections.

Most MPS patients require anesthesia for multiple interventions to help manage the disease and complications from anesthesia are commonly related to the airways. Abnormal airway anatomy associated with the above-mentioned risk for airway obstruction can result in extreme difficulty in tracheal intubation.[3] Older patients and sleep apnea are at increased risk of difficult intubation. Anesthesia should be administered at centers experienced in the management of MPS patients. A comprehensive plan should be drawn up before performing general anesthesia.

The exact incidence of MPS VI and VII is unknown, although MPS VI is estimated to occur in 1 of 250,000 to 600,000 newborns,[4] and MPS is estimated to occur in 1 of 250,000 newborns, being one of the rarest types of mucopolysaccharidosis.[5]

In this report, we would like to share two cases of patients with MPS type VI and VII listed to corneal transplant and aortic prosthesis revision surgery, respectively. They underwent preoperative fiberoptic airway mapping. Informed consent for publication was obtained from the patient and his parents.

Case report

A 23-year-old man (40 kg, 116 cm) diagnosed with MPS type VI Maroteaux-Lamy syndrome (Patient 1, Fig. 1a), and a 28-year-old female (37 kg, 134 cm) with MPS type VII Sly syndrome (Patient 2, Fig. 1b) were listed for a corneal transplant and aortic valve prosthesis revision surgery under general anesthesia, respectively.

Patient 1 was diagnosed with MPS at 21 months of age and had a medical history of heart failure (NYHA class III), mitral and aortic valve disease, restrictive lung disease, sleep apnea (CPAP device during the night), and stable cervical spinal stenosis. Physical examination revealed macrocephaly, hearing loss (conduction type), saddle nose, macroglossia, gingival hyperplasia, prominent costal margin, short limbs, and clawed hands. Cognition was not affected. He was submitted to enzyme replacement therapy with galsulfase (once a week) from the age of 9, with improvement of respiratory infection and quality of life. Past surgeries included myringotomy, and tonsillectomy and adenoidectomy, with a difficult airway requiring multiple intubation attempts.

Patient 2 was diagnosed with MPS at 16 years of age and had a medical history of heart failure (NYHA III), and developmental delay and progressive intellectual disability. Physical examination showed macrocephaly, saddle nose, irregular shaped teeth, macroglossia, short neck, and hepatosplenomegaly. Past surgeries included adenoidectomy with myringotomy, glossectomy reduction surgery, aortic valve replacement, unilateral total hip replacement, and cervical decompression surgery, also with a difficult airway requiring multiple intubation attempts, and one postponed surgery.

Given the past difficult airway management, both were proposed for fiberoptic airway mapping, with the aim of predicting further airway complications at the time of surgery, as per our institution's protocol for managing MPS patients.

The patients were premedicated with midazolam intravenous (0.1 $mg.kg^{-1}$), positioned (seated) and monitored with a pulse oximeter, electrocardiogram, noninvasive blood pressure, and Bispectral Index Monitor (BIS). Intranasal phenylephrine (2.5 mg $\times 2$) and topical (1 mL $\times 2$) and nebulized lidocaine 2% (8 mL at 5 $L.min^{-1}$) were applied to the airway (nasopharynx and oropharynx) twenty minutes prior to the procedure. Antisialogogues were not prescribed. Pre-oxygenation was achieved with 100% O_2 via an endoscopy mask (an explorer endoscopy face mask with three one-way valve). A remifentanil Target-Controlled Infusion (TCI) targeting a predicted plasma-site concentration (Minto model) of 1.0 $ng.mL^{-1}$ was started. The fiberscope was nasally introduced, with lidocaine 2% applied according to the spray-as-you-go technique. Remifentanil TCI targeting 3–5 $ng.mL^{-1}$ reduced the airway reactivity, with a BIS objective of 75–80.

The procedures lasted for 15 minutes, and the patients remained awake, calm, and cooperative, with spontaneous ventilation and no sign of breathing difficulty, oxygen saturation of 96–99% with FiO2 100%. There were no airway obstruction or desaturation episodes during both procedures. They remained hemodynamically stable with mean arterial pressure in the range of 80–95 mmHg and a heart rate of 88–110 beats per minute. The airway images of each patient are presented in Figure 1.

After the procedure was finished, remifentanil infusion was stopped, and the patients were transferred to the recovery area fully conscious and with adequate breathing. Both patients were discharged home, with no complication.

Discussion

This report presents the anesthetic management of two adult patients with a rare genetic condition with major structural abnormalities of the upper airway in whom awake fiberoptic airway mapping was performed due to the high risk of difficult intubation and ventilation.

The life expectancy of patients with MPS continues to increase due to improvement in therapy. MPS patients have multiple comorbidities, many of which require surgical interventions. Very little literature is available about anesthesia in adult patients with this condition.[1–3] Besides that, the process of aging can be associated with severe narrowing of the larynx and trachea.

Due to MPS being associated with specific phenotypic facial and airway characteristics which have an impact on ventilation, substantial challenges for perioperative anesthetic management may be expected. There is an increased anesthetic risk due to a difficult airway, cervical spine disease, and a higher prevalence of cardiovascular manifestations.[2] Restrictive or obstructive lung disease,

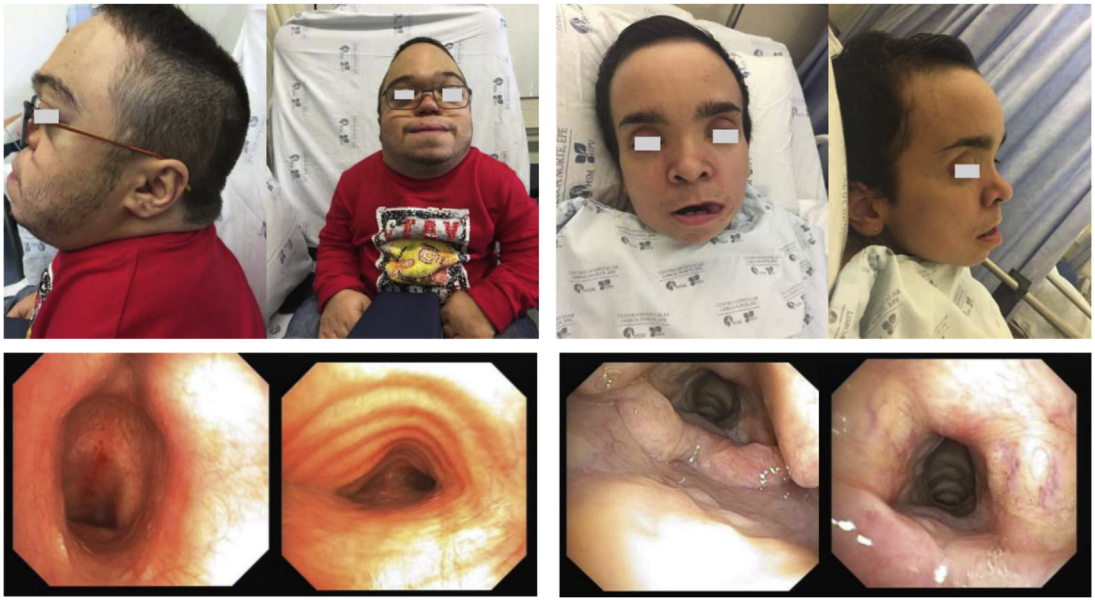

Figure 1 (a) Patient 1 (b) Patient 2. (c) Patient 1: Fiberoptic bronchoscopy demonstrating tracheal rings, carina and subglottic region. (d) Patient 2: Fiberoptic bronchoscopy demonstrating vocal folds and subglottic region.

recurrent lung infections, and obstructive sleep apnea are also common.

It has been reported that 25–50% of MPS patients have problematic airways and 82% of MPS patients receiving anesthesia require urgent airway interventions.[1]

Various airway issues may impact intubation and ventilation of these patients. Supraglottic abnormalities are common due to cranial and spinal deformations and GAG deposition in the mouth, nose, and throat. These include flattened nasal bridge, maxillary hypoplasia, impaired opening of the mouth, high-arched palate, macroglossia, gingival hyperplasia, mucosal oedema, mucoid secretions, narrow hypopharynx, short neck, abnormal cervical vertebrae, and high epiglottis. Excessive tissue at arytenoid cartilages and aryepiglottic can cause stridor and airway compromise in extreme cases. Infraglottic airway abnormalities include tracheobronchomalacia due to GAG deposition in the tracheobronchial cartilage and tracheal collapse due to decreased tracheal traction from decreased lung volume.[6,7]

In the two cases presented in this report, awake fiberoptic airway mapping under local anesthesia plus conscious sedation with low-dose midazolam and plasma-effect TCI remifentanil infusion was undertaken without airway, respiratory or cardiovascular complications in high-risk patients with a known history of difficult airways.

The authors suggest that this technique is safe and effective and could be used for fiberoptic bronchoscopy and allow fiberoptic-assisted tracheal intubation at the time of surgery. No major problems were found and based on this experience, the authors suggest that this technique is safe and effective and could be used for fiberoptic bronchoscopy, allowing fiberoptic-assisted tracheal intubation at the time of surgery. Careful planning and experienced support for difficult airway management are important when anesthetizing such patients.

In MPS patients, the high prevalence of perioperative complications and critical problems related to anesthesia (difficult intubation and airway control) underlies the critical role of a multidisciplinary careful evaluation before the procedure, namely evaluation of the airways. The risk of difficult intubation must always be suspected and requires experienced, expert staff, and the use of advanced airway management.

Implication statement

In mucopolysaccharidosis patients, the most critical problems related to anesthesia are difficult intubation and airway control. Therefore, careful evaluation of anesthetic risk factors should be made before the procedure, namely evaluation of airways.

Conflicts of interest

The authors declare no conflicts of interest.

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SHORT COMMUNICATION

Transcranial Direct Current Stimulation (tDCS) antinociceptive effect is not altered by isoflurane anesthesia in neuropathic pain rats

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KEYWORDS
Neuropathic pain;
Isoflurane;
tDCS;
von Frey Test;
IL-10

Noninvasive neuromodulation techniques are on the rise as adjuvant alternatives for the treatment of chronic pain. In this way, Transcranial Direct Current Stimulation (tDCS) has been demonstrated as a viable non-pharmacological method for the treatment of Neuropathic Pain (NP) in humans. In a recent review, Caumo and colleagues have shown evidence that motor cortex stimulation can bring benefits for the treatment of NP, associated or not with other therapies such as mirror therapy or visual illusion.[1] Additional preclinical research is therefore required to clarify its mechanisms of action, enabling it to become a successful and widely employed therapeutic option. However, tDCS application in awake animals requires animal immobilization, which is considered a stressful procedure[2] related to Stress-Induced Analgesia (SIA), mediated by the activation of the descending inhibitory pain pathway.[3] Furthermore, repeated exposure to stressful events, such as restraint, is related to hyperalgesia and allodynia, as a result of peripheral and central sensitization, which is linked to chronic pain.[4,5] In this way, our research hypothesis is that anesthesia during tDCS application is a reasonable option to improve the quality of rat preclinical neuromodulation assessments. It is important

Abbreviations: An, Anesthesia; BDNF, Brain-Derived Neurotrophic Factor; CCI, Chronic Constriction Injury; IL-10, Interleukin 10; NP, Neuropathic Pain; P, Pain; PFC, Prefrontal Cortex; SIA, Stress-Induced Analgesia; SP, Sham Pain; tDCS, Transcranial Direct Current Stimulation; TNF-a, TNF-alpha.

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to highlight that no previous study has evaluated the impact of anesthetics during the application of tDCS in rodents. Among the most commonly used compounds for non- and minimally invasive procedures in preclinical studies, isoflurane is an ideal inhalation anesthetic that produces mild induction, excellent muscle relaxation, and rapid recovery, which can be an alternative to alleviate the effects of stress during containment;[6] however, how it interferes with the expected results during brain stimulation has to be investigated. Additionally, it has been demonstrated that tDCS modulates central inflammatory levels, which could account for its antinociceptive effects.[7] Considering the absence of studies on this theme, this investigation aimed to evaluate the effects of isoflurane anesthesia during tDCS application on the nociceptive response and the Prefrontal Cortex (PFC) IL-10 levels in rats submitted to a neuropathic pain model.

Forty-eight male Wistar rats (50—60 days), from the Laboratory Animal Breeding and Experimentation Center (CREAL/Universidade Federal do Rio Grande do Sul — UFRGS), were kept under strictly controlled environmental conditions (3 animals/polypropylene cage, 12 h light/dark cycle, 22 ± 2°C, water, and rodent chow *ad libitum*). The animals (n = 48, a number based on the sample size used in previous studies[4,7] and calculated using G*Power software to obtain a minimum effect size of 15%, with an alpha error of 0.05 and power of 80%) were housed in groups of three in Microisolator cages (49 × 34 × 16 cm) with sawdust-covered floors. Cages were environmentally enriched using pieces of wood, ropes, cardboard rolls, and shredded paper, increasing the animals' well-being, motivating them to perform new behaviors, and reducing stress, anxiety, and frustration. All experiments and procedures were approved by the Institutional Committee for Animal Care and Use (GPPG-HCPA protocol #20200689) and conformed to the Guide for the Care and Use of Laboratory Animals (8th ed. 2011) and law #11.794, which establishes procedures for the scientific use of animals in Brazil. All experimental procedures were approved by the Institutional Committee for Animal Care and Use (GPPG/HCPA protocol #2018–0025). The experimental protocol complied with the ethical and methodological standards of the ARRIVE guidelines. All efforts were made to minimize animal suffering.

The current study had as primary outcome the nociceptive response, and as secondary outcome, the prefrontal cortex (PFC) IL-10 levels in rats submitted to a neuropathic pain model. The animals were habituated to the environment for fourteen days and afterward randomly (baseline von Frey data) allocated to one of the following groups: Sham pain (Sp, n = 24) and Pain (P, n = 24). On the following day, the animals were submitted to surgery for Chronic Constriction Injury (CCI) of the left sciatic nerve and NP model induction, as described by Bennett and Xie[8] with minor modifications. Animals from the Sp group were submitted to surgery without sciatic nerve constriction. Fourteen days after surgery, the establishment of NP was confirmed by the von Frey test. Then, rats were allocated to one of the eight following subgroups: Sham pain (Sp, n = 6); Sham pain + Sham tDCS (SpSt, n = 6), Sham pain + tDCS (Spt, n = 6), Sham pain + tDCS + Anesthesia (SptAn, n = 6); Pain (P); Pain + Sham tDCS (PSt, n = 6); Pain + tDCS (Pt, n = 6); and Pain + tDCS + Anesthesia (PtAn, n = 6). Afterward, the bicephalic tDCS treatment was initiated. tDCS was applied once a day for eight consecutive days for 20 minutes. The animals in the anesthesia groups were anesthetized with isoflurane (5% for induction and 2.5% for maintenance). Twenty-four hours after the end of treatment, the animals were again submitted to the behavioral test (von Frey) and were killed by decapitation the following day, having the PFC removed and stored at -80°C for later analysis. Biochemical assays were performed using Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) for quantification of the levels of the anti-inflammatory Interleukin 10 (IL-10), using specific monoclonal antibodies (R&D Systems, USA). Data were expressed in $pg.mg^{-1}$ of protein. The timeline of the experimental protocol is demonstrated in Supplementary Figure 1.

The Shapiro-Wilk test revealed that the variables did not have a normal distribution ($p \leq 0.05$), which was confirmed by histograms. Thus, for repeated measures, the Generalized Estimating Equation (GEE) test was adopted, adjusting the comparisons for the following factors: Time (baseline vs. D14 vs. D22), CCI (exposed vs. not exposed to the model), tDCS (tDCS vs. shamtDCS vs. no intervention), and interactions between factors (Time vs. CCI vs. tDCS). In case of significant interaction, experimental groups were independently evaluated using the Bonferroni test. For IL-10 levels, all groups were compared using the Kruskal-Wallis test. Data were expressed as a median and interquartile range, considering significant differences with $p \leq 0.05$, and were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL).

All animals completed the experiment, and none were excluded from the analysis. According to the GEE, there was no difference between groups at baseline (Fig. 1, Panels 1A and 1B, n = 24/group); Time ($\chi^2(2) = 311.618$, $p < 0.001$) and CCI ($\chi^2(1) = 78.718$, $p < 0.001$) affected the animal's nociceptive threshold (Fig. 1, Panels 1A and 1C). Besides, an interaction was observed between Time and CCI ($\chi^2(2) = 159.783$, $p < 0.001$); animals exposed to CCI (P) displayed reduced nociceptive threshold, 14 (Bonferroni: -24.5g, $p < 0.001$, Fig. 1, Panel 1A, n = 24/group, Panel 1C, n = 24/group) and 22 (Bonferroni: -8.42g, $p < 0.001$, Fig. 1, Panels 1A and 1D, n = 6/group) days after surgery, compared to Sham pain (Sp) animals. An interaction was also observed between Time and tDCS ($\chi^2(4) = 20.025$, $p < 0.001$); in the intervention period, tDCS increased the nociceptive threshold in 5.51 g when compared to shamtDCS (Bonferroni: $p < 0.033$), and in 10.1 g when compared to no intervention (Bonferroni: $p < 0.001$) groups (Sp and P groups).

The Kruskal-Wallis test revealed significant differences between groups regarding PFC IL-10 levels ($\chi^2(7$, n = 48) = 38.687, $p < 0.001$, Fig. 2). The pairwise comparison showed that Sp was different from P ($\chi^2(1$, n = 12) = 33.500, $p < 0.001$), PSt ($\chi^2(1$, n = 12) = 34.500, $p < 0.001$), and PtAn ($\chi^2(1$, n=12) = 26.500, $p < 0.05$). SpSt was different from P ($\chi^2(1$, n = 12) = 29.000, $p < 0.01$), and from PSt ($\chi^2(1$, n = 12) = 30.000, $p < 0.01$). Spt was different from P ($\chi^2(1$, n = 12) = 27.000, $p < 0.05$), and PSt ($\chi^2(1$, n = 12) = 28.000, $p < 0.05$). Thus, untreated pain animals showed a significant increase in IL-10 levels,which was reversed by tDCS treatment. On the other hand, the association of tDCS and anesthesia led to a partial reversal of these effects, since it is not equivalent to the Sham pain group.

This study demonstrates that the association of isoflurane anesthesia does not alter the complete reversion of the mechanical allodynia induced by repeated tDCS in rats

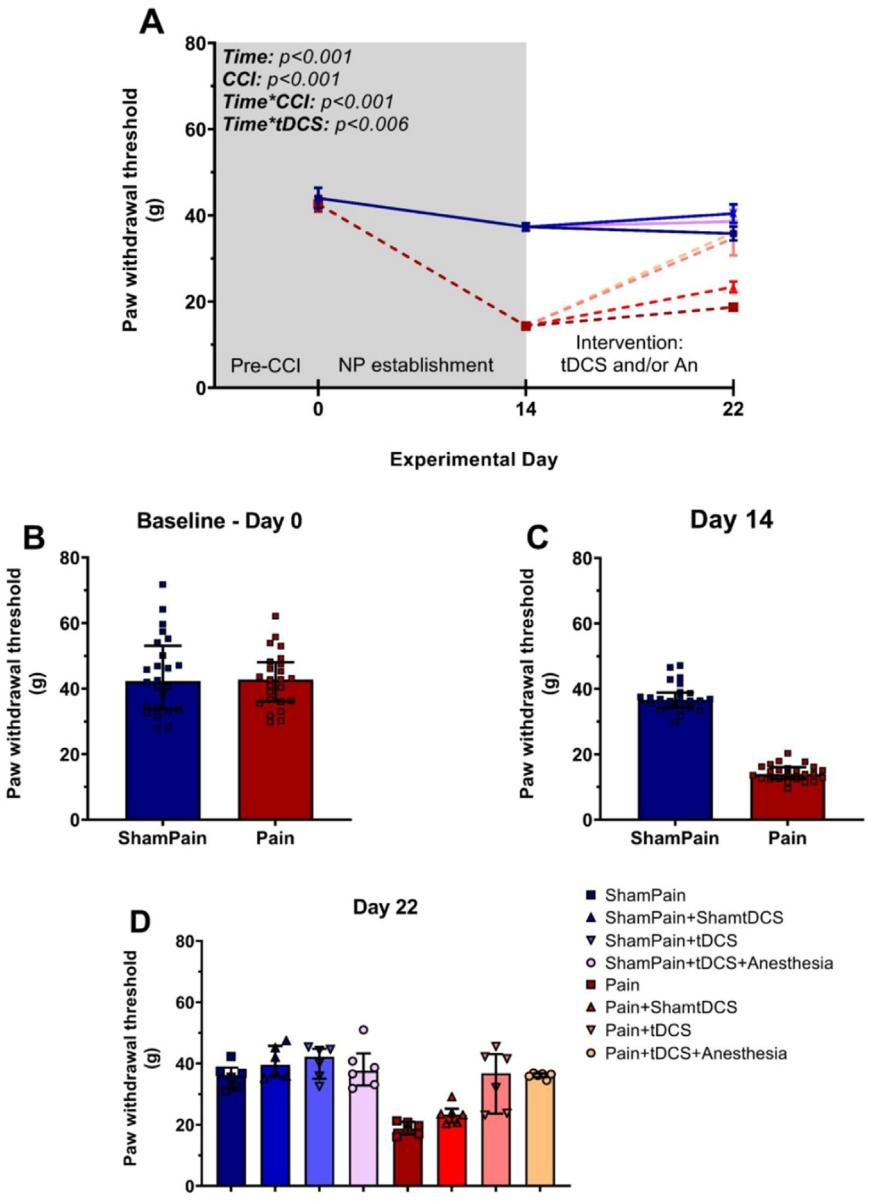

Figure 1 Data from the von Frey test. Panel A: von Frey test at baseline, 14 days after surgery and 24 hours after the end of treatment; Panel B: at baseline (D0), animals were allocated into two groups (Sham pain and Pain) with similar nociceptive thresholds; Panel C: fourteen days after surgery, animals allocated to the Pain group presented lower paw withdrawal threshold when compared to Sham operated rats; Panel D: on day twenty two, animals from the Pain group that received tDCS, showed restored nociceptive thresholds, regardless of having been anesthetized during treatment. An, Anesthesia; CCI, Chronic Constriction Injury; NP, Neuropathic Pain; Tdcs, Transcranial Direct Current Stimulation. Data are presented as mean ± SEM (n = 6/group).

submitted to the CCI model,[7] being pioneering in this field. A previous study from our group, using the same chronic pain model in restrained and awake animals during tDCS application showed partial or total reversal of mechanical allodynia.[7] Thus, this result is in agreement with our hypothesis that anesthesia during tDCS application is an option to improve the quality of rat preclinical neuromodulation assessments. In this way, isoflurane anesthesia provides more reliable preclinical studies in the search for the tDCS action mechanisms as an effective and widely used therapeutic technique.

Volatile anesthetic isoflurane appears to act on the lipid matrix of the neuronal cell membrane, increasing membrane fluidity and inhibiting signal transduction. In addition, it has been suggested that isoflurane suppresses pain activating a distinct population of GABAergic neurons in the central amygdala, which produces profound analgesia, including in a model of neuropathic pain.[6] Considering that tactile allodynia can be reduced, in part, by the descending modulation from higher areas, it is feasible to suggest that isoflurane potentiates the tDCS analgesic effect from neuromodulation of these areas, including the central

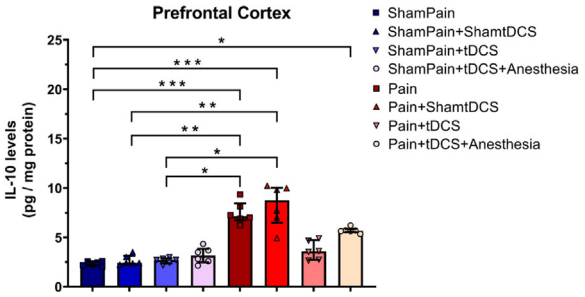

Figure 2 Data from the IL-10 levels in the PFC. Significant differences were observed between groups (Kruskal-Wallis test, $p < 0.001$). *$p < 0.05$; **$p < 0.01$; ***$p = 0.001$ (pairwise comparison). Data are expressed as a median and interquartile range of pg.mg^{-1} of protein (n = 6/group).

amygdala.[6] In addition, isoflurane promotes the release of GABA, increases glutamate reuptake, and alters cytokine levels, such as IL-6 and IL-10.[6]

Corroborating the isoflurane action altering the levels of cytokines, the present study showed that isoflurane associated with tDCS partially reverses the increase in the IL-10 levels induced by NP, attenuating the tDCS effect, which reversed this increase. In this way, it is possible to suggest that the analgesic effect of tDCS occurs through IL-10 level modulation in the PFC, since NP is also involved in chronic inflammatory processes.[9]

A previous study using a similar NP model (partial peripheral nerve ligation) showed a reduction in IL-10 levels in the dorsal root ganglion and an increase in the PFC, corroborating the involvement of the central nervous system in neuropathies.[9] The NP mechanism involves inflammation at the affected nerve, which initiates a cascade of events increasing and activating innate immune cells at the tissue injury site.[6] The release of immunoreactive markers such as cytokines promotes local actions resulting in a generalized immune response.[6] Previous studies have shown that the anti-inflammatory cytokine IL-10 plays a role in promoting the relief of the painful condition established by NP, by reducing the bioavailability of pro-inflammatory cytokines.[5] On the other hand, besides the classic anti-inflammatory role, IL-10 seems to be involved with the development of NP. Increased IL-10 expression and levels[10] were found after peripheral nerve injury for at least 6 weeks after NP model induction, corroborating the data of the current study. In addition, we showed that bicephalic tDCS decreases the nociceptive response and modulates PFC IL-10 levels, returning them to the levels of the sham groups. This effect was attenuated by isoflurane anesthesia.

Some limitations are important to consider in the present study: (i) Considering that in humans both electrodes are placed on the head during tDCS application, we set them in similar positions in animal models. However, the small head size of the rat contributes to bicephalic stimulation; (ii) The levels of IL-10 can be influenced by the time of brain collection. Animals were killed 48 hours after the last session of tDCS because the behavioral test at 24-hours was performed after the last session of treatment.

In summary, this study demonstrates that, even when animals are subjected to inhaled anesthetic during a brain stimulation procedure, they still benefit from its analgesic effects, even though isoflurane reduces the effects of tDCS in lowering IL-10 levels. Therefore, in the current study, we demonstrated that using an inhalation anesthetic could be a good option to avoid bias during repeated tDCS application in pain preclinical studies.

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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.2023.03.002.

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CLINICAL IMAGES

Tracheal bronchus: implications for lung isolation

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A tracheal bronchus is an anomalous or accessory bronchus that arises directly from the supracarinal tracheal wall. When the tracheal bronchus supplies the entire right-upper-lobe, it is referred to as *bronchus-suis* (pig-bronchus). This tracheobronchial arrangement, commonly found in pigs, is rare in humans with a reported incidence of 0.2%.[1] The accompanying images demonstrate this anatomical variation of the tracheobronchial tree (Fig. 1: Panel A and B) and are from a patient who needed right lung isolation during an esophagectomy.

Achieving satisfactory right lung isolation in patients with bronchus-suis morphology may be challenging. As the right-upper-lobe does not arise from the right-mainstem-bronchus, a right-sided double-lumen-tube would only facilitate isolation of the right-middle and lower-lobes. Consequently, bronchoscopy guided placement of left-sided double-lumen-tube is preferred. With the bronchial-cuff positioned just below the carina, right lung isolation is achievable when the tracheal-bronchus's opening remains distal to the tube's tracheal-cuff. If the tracheal-bronchus is situated proximal to or at the level

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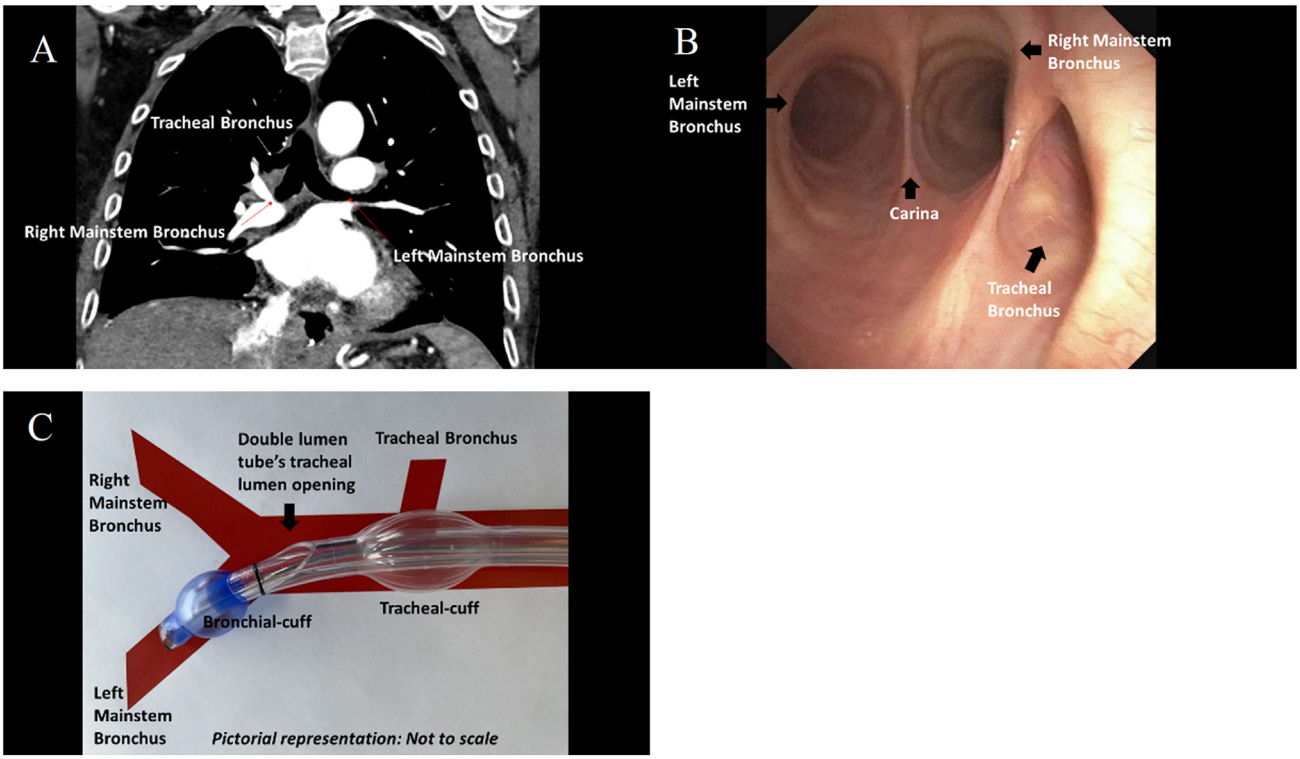

Figure 1 Radiographic imaging (Panel A) and bronchoscopy (Panel B) demonstrate carinal bifurcation into left mainstem bronchus and right mainstem bronchus and presence of a supracarinal tracheal bronchus originating from the right tracheal wall. When establishing right lung isolation with a left-sided double-lumen-tube, the aberrant tracheal bronchus is at risk of being obstructed by the left-double-lumen-tube's tracheal cuff, especially if its opening lies proximal to or at the level of the tube's tracheal lumen opening, as seen in the pictorial representation (Panel C).

of the tube's tracheal-cuff, obstruction of it's opening by the inflated tracheal-cuff, may hinder right-upper-lobe collapse (Fig. 1: Panel C). In such circumstances, it may be necessary to place a single-lumen-tube and guide individual bronchial blockers into the right-mainstem-bronchus and tracheal-bronchus to achieve right lung isolation.[2,3]

Declaration of Competing Interest

The author declares no conflicts of interest.

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LETTER TO THE EDITOR

In response to the letter to the editor regarding "Comparison of the intubation success rate between the intubating catheter and videolaryngoscope in difficult airways: a prospective randomized trial"

Dear Editor,

We thank Dr. Muller for his interest in our study and the Editor-in-Chief, Dr. Schmidt, for allowing us to reply to the letter written about our article.[1]

The author stated that due to the lack of quality publications, unanticipated difficult airway management varies depending on personal preferences. However, it would be wrong to attribute personal preference only to the lack of quality publications. Difficult airway management guidelines, which provide the basic clinical framework for the strategy that clinicians should follow when faced with a difficult airway, offer recommendations based not only on publications but also on clinician experience supported by synthesis and analysis of ideas and open forum comments. These guidelines are subject to revision commensurate with experience, skills, knowledge, and technology evolution. The selection of appropriate drugs and techniques for anesthesia care and airway management depends on the clinician's experience, training, and preference, the needs or limitations of the patient's relevant medical problems, the type of procedure, and the environment in which airway management is performed. Therefore, difficult airway management guidelines may be modified or even rejected depending on clinical needs and limitations. In addition, these guidelines are not designed as standard or absolute requirements, and their compliance will not guarantee a special result. Also, their non-compliance does not result in a legal responsibility.[2]

As the author mentioned, laryngoscopy and intubation are separate procedures. However, unlike the authors, we do not think different troubleshooting techniques should always be used in case of difficulties in performing these two procedures because both procedures are intertwined, and the ultimate goal is successful endotracheal intubation. On the other hand, when trying to intubate pediatric patients, it may be necessary to use two different techniques for these two separate procedures. Given pediatric patients' different upper airway anatomy, visualization of vocal cords during laryngoscopy does not guarantee successful endotracheal intubation. Even experienced clinicians have difficulty in directing the endotracheal tube to the vocal cords and performing successful intubation, even in the case of easy laryngoscopy in pediatric patients.[3] Considering the Cormack-Lehane (CL) results of our study, the author claimed that the Frova Intubation Catheter (IC) is indicated in cases where the laryngoscopy view is unsatisfactory. Video laryngoscope used in adult patients with difficult intubation improves the CL score. However, it does not guarantee that every patient can be intubated using a video laryngoscope. Of course, in our study, some patients were easier to intubate using the video laryngoscope and Frova IC, but this is not the case in all scenarios. As the tip of the Frova IC is soft to avoid damage, this makes it difficult to direct it to the vocal cords in some patients on whom a video laryngoscope is used for intubation. In such a scenario, using classical laryngoscopy instead of video laryngoscope and performing assistive maneuvers makes directing the Frova IC to the vocal cords easier.

On the other hand, the authors asked some questions about the method section of our study. Most of the patients included in our study underwent elective otolaryngological surgery. This is the main reason why we prefer an endotracheal tube with a large inner diameter. Although we mentioned the range of endotracheal tube diameters in the article, it does not mean that the largest tube in this range was used on every patient, most of our patients undergoing elective otolaryngological surgery were heavy smokers and exposed to airway intervention. We prefer to use an endotracheal tube with a larger inner diameter than that applied to non-smoker patients to manage the ventilation of these patients easily. Assist maneuvers were used when necessary, during the endotracheal intubation procedure, and the related data were given in Table 4.

In our hospital, general anesthesia is provided by the consultant clinician (OO) to approximately 1750 patients per year in the Ear Nose Throat operating theatre. Experienced anesthesia residents AO, IGO, and EA were present in the operating theatre for randomization, data collection, and supply of the necessary device when an anticipated or unanticipated difficult intubation situation was encountered during the study. Patients were ventilated until successful

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intubation was achieved. Written consent was obtained from all patients included in the study. Randomization and allocation concealment were performed with a randomly numbered envelope of patients with previously known difficult intubation, while a random number and letter generating application was used in unanticipated difficult intubation cases.

Although the authors state that the retrospective registration of the data of our study in the New Zealand Clinical Trials registry is a cause for concern, our study was the specialty thesis of the first author (AO), and the entire 100-page thesis was uploaded to the same site in 2018.

We agree with the authors that the potential impact of our study is vast and influential. Based on our clinical experience and studies on this subject, all anesthesia clinics and emergency departments should have the Frova IC for successful intubation of difficult intubation cases.[4] At the same time, the easy learning of applying the Frova IC will make it easier for anesthesia and emergency service residents to learn to manage the airway of patients with difficult intubation. In our clinical practice, we experience that practicing with Frova IC during intubation of patients with easy airways is beneficial for inexperienced clinicians in the airway management of difficult intubation cases. Against this, we must state that our inexperienced residents do not have the same positive experience by using video laryngoscope in patients with an easy airway. In clinicians unfamiliar with the conventional laryngoscope, video laryngoscopes can cause a false sense of security that cannot be guaranteed before attempting intubation. In addition, video laryngoscopes delay and hinder the development of inexperienced clinicians' skills from intubating with direct laryngoscopy. Even experienced anesthesiologists may forget the importance of difficult intubation estimation and intubation planning with careful airway examination, which they should perform for each patient after they start using a video laryngoscope instead of a conventional laryngoscope, and may even partially lose their intubation skills with conventional laryngoscopes.[5]

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Comment on "Comment on: Effect of magnesium sulfate with ketamine infusions on intraoperative and postoperative analgesia in cancer breast surgeries: a randomized double-blind trial"

Dear Editor,

Thanks for the valuable comments.[1]

First, the index study relies on the hemodynamic parameters as surrogates for intraoperative nociception and hence, fentanyl administration. Alongside the debatable sensitivity and specificity of the former in nociception monitoring, the matter is compounded by the lack of comparative account of hypertensives in the two study groups (albeit, the authors describe uncontrolled hypertension as an exclusion criterion).

This method was used after exclusion of other causes (e.g., tachycardia and hypotension due to blood loss) that may affect the increase in mean arterial blood pressure (MAP) and heart rate (HR).

This method has been used in many trials such as the study of Abdelraheem et al.[2]

The equipment for monitoring of depth of anesthesia (such as bispectral index) is not available in our institute.

Second, the authors fail to present any details on whether/or not any form of depth of anesthesia monitoring was employed.

The equipment for monitoring of depth of anesthesia (such as bispectral index) is not available in our institute.

Third, the comparable postoperative pain and sedation scores between the two groups are difficult to explain, in background of a substantially lower postoperative morphine requirement and/or consumption in the magnesium sulfate + ketamine group as opposed to the ketamine alone group.[1]

In our study,[3] PCA on demand was used for postoperative analgesia. NRS pain score was comparable between both groups as we didn't wait to administer analgesia at times of recording only. Therefore, postoperative morphine requirement and/or consumption was lower in the magnesium sulfate + ketamine group as opposed to the ketamine alone group with the same level of NRS.

Lastly, while the ability of the study to detect any statistically meaningful differences in chronic pain could have been precluded by a small sample size, the incorporation of patient satisfaction and/or postoperative recovery would have added incremental value.

Patient satisfaction is a subjective method and affected by other factors.

Postoperative recovery was out of our scope (not primary nor secondary outcomes). Further studies are needed to focus on this item.

Conflicts of interest

The authors declare no conflicts of interest.

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