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BJAN 75 YEARS

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The BJAN publishes original work in all areas of anesthesia, surgical critical care, perioperative medicine and pain medicine, including basic, translational and clinical research, as well as education and technological innovation. In addition, the Journal publishes review articles, relevant case reports, pictorial essays or contextualized images, special articles, correspondence, and letters to the editor. Special articles such as guidelines and historical manuscripts are published upon invitation only, and authors should seek subject approval by the Editorial Office before submission.

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The Brazilian Journal of Anesthesiology is indexed by **Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS)** since 1989, **Excerpta Médica Database (EMBASE)** since 1994, **Scientific Electronic Library Online (SciELO - Brasil)** since 2002, **MEDLINE** since 2008, **Scopus since** 2010 and **Web of Science (SCIE - Science Citation Index Expanded)** since 2011.

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Brazilian Journal of Anesthesiology 2026;76(3): 844764

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Brazilian Journal of Anesthesiology: 75 years consolidating achievements

"Here we open these welcoming pages hoping that the authors will satisfy our studious curiosity."
Renato Correa Ribeiro, 1951

The Brazilian Society of Anesthesiology (SBA), founded in 1948, published the first issue of its journal in 1951. Seventy-five years later, the Brazilian Journal of Anesthesiology (BJAN) remains one of the most meaningful expressions of Brazilian anesthesiology.

The inaugural editorial written by Ribeiro[1] in 1951 was a mixture of joy, warning, faith, and hope. Actually, the emergence and continued growth of BJAN were only possible because of the philosophy implemented by the founders and absorbed by their followers, allowing its natural, yet methodical, development. Everything in parallel with the very development of Natural Sciences, in which concepts and behaviors, resulting from observation and experimentation, emerge based on empirical, scientific, philosophical, and theological knowledge.

Also in 1951, a copy of the journal was presented to the Editor-in-Chief of the journal Current Researches in Anesthesia and Analgesia, who wrote an editorial entitled "A New Journal is Born".[2] This early international mention, later highlighted by Parsloe in an editorial, where he summarized much of the history of our journal, is particularly meaningful.[3] It shows that, in addition to the internal objectives of the journal's publication, there was a desire to insert it into the international scenario.

The emergence of the journal, and its bimonthly publication schedule over the years, established a strong link between the Institution — the Brazilian Society of Anesthesiology — and its members.[4] Stages were completed with dedication and hard work. Initially, the main objective was to have a journal that could disseminate knowledge and encourage national authors to publish their research, whether scientific or review articles, as well as presentations of clinical cases or anesthetic techniques, with the technical details of international publications. Annually, some selected articles, especially scientific ones, were published only in English in a special issue.

The great progress experienced over the years has been due to the inclusion of topics related to the philosophy of the scientific method in the scientific program of the Brazilian Congresses of Anesthesiology, held annually. The debates have not only consolidated the guidelines emanating from the most frequent and experienced authors, but also have encouraged younger, novice authors. This tradition continues to this day. Thus, our MDs, PhDs, and experts, of which there are many, join youth eager for knowledge, who will certainly become one of them in time. This is part of the SBA's objectives: "to bring together physicians interested in promoting the progress, improvement, and dissemination of anesthesiology, intensive care, pain management, palliative medicine, aerospace medicine, and resuscitation, and to establish standards for training in the specialty". As a result, most of the national articles originate from the 135 Anesthesiology Teaching and Training Centers accredited by the SBA, including those located in universities.

Until 2000, the journal was published in Portuguese, with abstracts in English and Spanish. In 2001, at the initiative of the Editorial Board, approved by the SBA Board of Directors, the journal became bilingual, with texts in Portuguese followed by an English translation. From then on, the number of citations of national papers increased.

In 2012, the publication began to present the articles in both Portuguese and English in full in the same issue. This led to a significant increase in submission from authors from other countries, requiring an expansion of the Editorial Board and the redefinition of goals and guidelines for the acceptance of articles.

In 2019, through the initiative of the Editorial Board and the essential support of the Board of Directors, the SBA decided that BJAN would be published only in English. The decision, implemented in 2020, made it easier to find articles in BJAN. The BJAN has definitively become more accessible to both national and international authors,

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definitively placing it within the international anesthesiology landscape.

Immersed in international literature, BJAN publishes articles from a variety of areas within anesthesiology, showing no preference for specific segments, as long as they adhere to scientific rigor and comply with author guidelines. Although the literature is a tangled web of a large puzzle, the excellent current databases allow for quick searches using well-applied keywords. BJAN, indexed in the institutions that offer such databases, has seen its impact factor gradually increase, reaching 1.9 in June 2025.

Up until the year 2000, the number of article submissions hovered around 250. Over the years, this number has grown, reaching 900 submissions in 2025. To comply with the analysis guidelines, flowchart, and schedule of the editorial process, the Editorial Board has grown significantly, currently comprising 1 Editor-in-Chief, 1 Co-editor, 28 Associate Editors, and 102 members of the Editorial Committee, specialists in the various areas of anesthesiology practice. Associate Editors and members of the Editorial Committee are appointed by the Editor-in-Chief and the Co-editor, subject to approval by SBA. The editorial work is carried out on a voluntary basis by all members of the BJAN Editorial Board. The workload is substantial, but the sense of fulfillment is even greater.

The Editor-in-Chief and Co-editor have always been elected by the SBA Assembly of Representatives for a three-year term, renewable for up to two more terms. However, since 2022, the Editor-in-Chief and Co-editor, with the same term length, are chosen by the SBA Board of Directors from a list of five names compiled by the Editorial Board. Since its launch, BJAN has had 12 Editors-in-Chief.

Brazilian anesthesiologists are very proud of BJAN, treating it with affection and respect. Thus, may future generations appreciate the great effort expended by many, and may they introduce the necessary modifications, with respect for their predecessors, in the constant pursuit of quality, seeking to consolidate achievements with courage and competence.

Therefore, the welcoming pages of BJAN remain wide open to the entire scientific community, hoping that the authors will continue to satisfy the curiosity of scholars.

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Declaration of competing interest

The author declares no conflicts of interest.

Editor

Liana Azi

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

75 years of BJAN: honoring our legacy, sharpening the future of anesthesiology research

Seventy-five years ago, the first pages of what is now known as the Brazilian Journal of Anesthesiology (BJAN) were printed, driven by the visionary spirit of Renato Correa Ribeiro and the founding members of the Brazilian Society of Anesthesiology (SBA). As Prof. Luiz Marciano Cangiani beautifully chronicles in this issue,[1] our journal has evolved from a modest national publication into an internationally recognized scientific platform. He reminds us that BJAN's welcoming pages have always sought to satisfy the "studious curiosity" of our community. Today, as we celebrate this diamond jubilee in issue 76-3, we look back on those years with immense pride and look forward to the future of scientific publishing with renewed enthusiasm.

Over these decades, BJAN has been an important platform for research that has influenced anesthetic practice, accompanying the evolution of our specialty from the era of ether and rudimentary monitoring to the age of precision medicine, ultrasound-guided regional anesthesia, and advanced perioperative monitoring and care. During the past 75 years, our pages have hosted landmark articles that have shaped clinical guidelines and improved patient safety worldwide.[2,3]

Between 1995 and 2003, several goals were achieved, namely: rigorous bimonthly periodicity; encouragement of national authors; inclusion of courses on scientific methodology at Brazilian Congresses of Anesthesiology; approval of the proposal for the elaboration of structured abstracts submitted at the editors' meeting held during the world congress in Sydney (1996); indexing in SciELO (Scientific Electronic Library Online); bilingual publication in Portuguese and English (2001); and gradually preparing the journal, following the guidelines of the USA National Library of Medicine, in order to apply for its indexing in that institution.

A truly important step in the global exposure of BJAN was its indexing in the U.S. National Library of Medicine (MEDLINE/PubMed) platform, which was accomplished in 2008. At that time, BJAN had to adapt to the standards of the system, a process that received strong support from SBA Directors and technical assistance from Elsevier, hired in 2006 for this purpose.

After indexing, the large-scale exposure was reflected in the growth of the bibliometric impact. In the past years, BJAN has experienced a consistent improvement in its Impact Factor. Today, BJAN is the top-ranked anesthesiology journal in Latin America, placed in the second quartile (Q2) of the Anesthesiology and Pain Medicine category, with a SCImago Journal Rank (SJR) of 0.537.[4] This progress reflects the increasing quality of the research published in BJAN since its inception.

The very first article published in BJAN, "Progress in Anesthesia in the Western Hemisphere", by Ralph M. Waters, was visionary. The manuscript framed anesthesia not merely as a technical act, as it was viewed at the time, but as a medical specialty grounded in physiology, pharmacology, research, and ethical responsibility. Waters also emphasized that anesthesiologists must be competent physicians, fully committed to patient safety and to principles that, more than seven decades later, remain extremely relevant: scientific rigor, professional identity, education, multidisciplinary collaboration, and responsible innovation. These principles continue to define the very best of modern anesthesiology.[5]

Collaborative consensus statements, such as the Update on Perioperative Hypersensitivity Reactions,[6] the Brazilian Society of Anesthesiology's Recommendations for Difficult Airway Management in Adults and children,[7,8] and the Consensus on Perioperative Transesophageal Echocardiography developed in partnership with the Brazilian Society of Cardiology,[9] have become highly cited references that actively guide anesthesiologists' daily practice worldwide. These manuscripts clearly illustrate BJAN's historical commitment to publishing not only original research but also practical guidelines that bridge the gap between cutting-edge scientific evidence and real-world clinical care, directly translating robust data into safer, more standardized patient outcomes at the bedside.

As we celebrate our history, we are also looking ahead toward the next chapter. Scientific publishing continues to

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evolve rapidly, demanding greater agility, transparency, and openness. In response, BJAN has launched a targeted Call for Papers to encourage submissions in strategic areas of relevance to our anesthesiology community. Prime examples include our recent Special Issues on Perioperative Care[10] and Patient Blood Management,[11] which brought together leading experts to address important contemporary topics in anesthesiology.

During Prof. Maria Carmona's tenure as Editor-in-Chief, the transition to an English-only format marked a bold and transformative step that firmly established BJAN on the global stage.[12] This strategic decision has been reflected in the substantial growth to more than 900 submissions annually. This journey continues to gain even greater momentum as we fully embrace the principles of Open Science[13] and responsibly explore the potential of Artificial Intelligence to enhance our peer-review processes,[14] all while upholding the rigorous ethical standards that have always defined us.

We are also very proud of our Diamond Open Access model, which is fully funded by SBA. As scientific publishing is becoming increasingly commercialized, BJAN demonstrates that high-quality rigorous research can and should remain freely accessible to readers and authors worldwide, with no financial barriers whatsoever. This model supports broader and equitable access to scientific publishing.

BJAN's success belongs to all of us. Reaching three-quarters of a century of uninterrupted publication is an impressive milestone that reflects the collective dedication of our Editorial Board, the rigorous expertise of our reviewers, and, above all, the sustained trust and outstanding contributions of our authors. As previously mentioned, our pages have always been open.

Happy anniversary, BJAN!

Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Editor

Liana Azi

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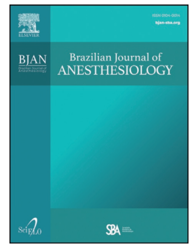

ORIGINAL INVESTIGATION

Developing a concise multivariable predictive model for cesarean delivery following neuraxial analgesia during labor: a prospective observational cohort study

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Cesarean section;
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Obstetric analgesia;
Predictive values of tests

Abstract

Background: Sometimes, planned vaginal deliveries with neuraxial analgesia may result in unplanned cesareans. We aimed to determine the incidence of cesarean among parturients receiving neuraxial analgesia for vaginal delivery, identify associated factors, and develop a predictive model.

Methods: In this prospective observational cohort study, we evaluated parturients receiving neuraxial analgesia for vaginal delivery and analyzed factors associated with progression to cesarean. Multiple logistic regression with a *step-up* procedure was performed. The dataset was split into training (70%) and testing (30%) databases, with the latter used to assess performance metrics. Bootstrap validation with 5,000 repetitions was performed.

Results: We evaluated 331 parturients and 94 (28.4%) underwent cesarean. Variables differing between cesarean and vaginal delivery groups ($p < 0.05$) included patient age, body mass index, gestational age, cervical dilation at analgesia initiation, time under analgesia, labor conducted/monitored by nurses, and oxytocin use after analgesia initiation. Three variables remained predictive [odds ratio (95% Confidence Interval (95% CI))]: patient age: 1.0436 (1.0091 to 1.0835), p = 0.018; time under analgesia: 1.0043 (1.0008 to 1.0081), p = 0.018; and oxytocin use after analgesia initiation: 0.0921 (0.0400 to 0.1945), $p < 0.001$. Predictive area under the curve (95% CI) was 71.8% (60.5%–83.1%). Arrest of descent (35.1%) and fetal distress (34.0%) were the leading indications for cesarean.

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Conclusions: Among parturients receiving neuraxial labor analgesia, older patients, longer analgesia duration, and no oxytocin use after analgesia initiation increase the probability of cesarean, with moderate predictivity. Arrest of descent and fetal distress were the main causes of cesarean.

Introduction

During labor, neuraxial injection of local anesthetics may provide relaxation of the muscles of the pelvic floor and abdominal wall, which are important components in the process of fetal rotation and correct cephalic positioning, prolonging the second stage of labor, increasing the risk of instrumental vaginal delivery, in addition to increasing the use of oxytocin to optimize uterine contractility and avoid dystocia.[1] Although neuraxial analgesia is associated with these outcomes, studies on the increased risk of cesarean delivery have conflicting results.[2,3] Some factors, such as maternal age and the use of oxytocin during labor, have been associated with variations in the incidence of cesarean delivery.[4,5] Other elements, including the time of day when labor occurs and the type of healthcare provider, i.e., nurses, midwives or obstetricians,[6,7] have also been investigated as potential contributors to cesarean rates. A predictive model for cesarean delivery in nulliparous patients during hospital admission revealed a 71% accuracy, and that the factors associated were advanced maternal age, shorter maternal height, greater gestational age, labor lasting more than 24 hours, irregular contractions, less cervical dilation, and higher fetal station.[8] Another predictive model evaluated the risk of cesarean delivery after induction of labor and found that nulliparity and macrosomia were the factors with the highest odds ratios.[9]

However, during labor analgesia, the extent to which some of these factors influence cesarean delivery, particularly when considered in combination, remains to be fully elucidated. We hypothesized that a limited set of clinical variables, easy to collect and observe, selected at the time of neuraxial analgesia, could predict subsequent cesarean delivery. Given the uncertainties about the risk of cesarean during neuraxial labor analgesia for vaginal delivery, this study aimed to determine the incidence of cesarean among parturients who received neuraxial labor analgesia, to identify associated maternal and gestational factors and, thus, construct a predictive model. The causes of cesarean were also evaluated in these patients.

Methods

This is a prospective observational cohort study, approved by the Institutional Ethics Committee, performed with parturients of the Maternity at the Hospital das Clínicas of Botucatu Medical School, Brazil, conducted in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD statement).

During the period between March 2022 and June 2023, all consecutive patients with indication for labor analgesia were invited to participate in the study after signing the informed consent form. Patients of any age who received neuraxial analgesia (spinal, epidural, or combined spinal-epidural) for vaginal delivery were included. In the case of fetal demise, parturients did not participate in the study. The obstetricians requested the analgesic procedure according to their clinical evaluation of pain intensity and cervical dilation, on an individual basis.

The index time for collecting the variables was the onset of analgesia. The variables chosen for the analysis of the possible association with cesarean obtained at the index time were patient age (years); weight (kg); height (cm); body mass index (kg.m^{-2}); gestational age (weeks and days); physical status according to American Society of Anesthesiologists (classification, I to VI); cervical dilation at the time of analgesia administration (cm); previous pregnancies (number of previous pregnancies); previous vaginal deliveries (number and percentage); pain score before analgesia (scale from zero (no pain) to 10 (maximum possible pain)); analgesia performed at night (after 8 pm, number of patients and percentage); analgesia technique (spinal, epidural or combined spinal/epidural, number and percentage); use of oxytocin before analgesia initiation (number of patients and percentage); and labor monitored/accompanied by nursing (number of patients and percentage). The variables chosen for the analysis of the possible association with cesarean obtained after the onset (post-index) of analgesia were time under analgesia (minutes); and use of oxytocin after analgesia initiation (number of patients and percentage).

The choice of the neuraxial technique, whether spinal, epidural, or combined (spinal-epidural), with or without the use of an epidural catheter, as well as the selected drugs and their respective doses, was at the discretion of the attending anesthesiologist.

In cases where cesarean delivery was indicated by the obstetrician, or according to the patient's will, we recorded the reasons for the indication, and the attending anesthesiologist decided on the anesthetic technique for the cesarean.

The primary outcome of the study was to evaluate the percentage of parturients who received neuraxial analgesia and underwent an unplanned cesarean delivery, to identify the possible associated factors, and to construct a predictive model. The secondary outcome was the identification of the causes of cesarean delivery.

Statistical analysis

Based on the number of labor analgesia procedures performed in 2021 (204 cases), according to local records, we made a preliminary convenience analysis with 194 consecutive cases and found that four independent variables were associated with cesarean delivery: body mass index; longer gestational age; longer time under labor analgesia; and no oxytocin use after analgesia. Using the sample size equation for observational studies involving logistic regression as suggested by Bujang et al. (n = 100 +50*i*, where *i* refers to the number of independent variables in the model),[10] the minimum number required for the analysis would be 300 patients. We included approximately 10% more participants than the minimum required sample size, aiming to compensate for potential data loss due to incomplete forms or missing critical information that could compromise the quality and completeness of the dataset, resulting in a total of 331 patients.

To choose the set of variables to compose the predictive model, the difference between groups (vaginal delivery vs. cesarean section) was investigated. Quantitative variables were analyzed via two-tailed Student's *t*-test (stats::t.test) when a Gaussian distribution was verified via the Cramer-Von Mises test (nortest::cvm.test) or the two-tailed Mann-Whitney test (stats::wilcox.test) when the variables did not meet this assumption. A chi-square test (stats::chisq) was used for the qualitative variables.

Following, the dataset was divided into training and testing databases. The training database contained 70% of the randomly selected patients, while the testing database had 30% of the remaining patients using a random stratification sampling by groups without replacements (vaginal delivery and cesarean). The proportion of events (cesareans and vaginal deliveries) was maintained in both databases, according to that observed in the dataset. Then, the variables that were significantly different between the groups were used as predictive variables and the groups were used as predictor variables in a multiple binomial logistic regression model using the training database (stats::glm) (full model). The model was subjected to a *step-up* procedure in which non-significant predictive variables were manually removed from the model. This process was repeated sequentially until all predictive variables were significant (final model). The best model was chosen according to the Root Mean Square Error (RMSE), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and the Area Under the Curve (AUC) (jtools::summ; sjstats::rmse; lmtest::lrtest; pROC::roc; and pROC::ci.auc). The AUC between models was compared via the DeLong test (pROC::roc.test) and we also used a null model for comparisons. The Hosmer-Lemeshow goodness-of-fit test (glmtoolbox:: hltest) was performed to evaluate the final model. Variance Inflation Factor (VIF) was used to assess the multicollinearity among predictive variables (car::vif). A bootstrap resampling with 5,000 repetitions was performed to internally validate the linear and slope coefficients of the final model (car::boot). Least Absolute Shrinkage and Selection Operator (LASSO) with 10-fold cross-validation was applied to the final predictive model obtained after the *step-up* procedure using the training database (glmnet::cv.glmnet and glmnet::glmnet). Events per variable were calculated using the final Bayesian logistic regression model (4 chains, 2,000 iterations, 1,000 warmup) with training database. Expected posterior variance was estimated via posterior predictive simulations: multiple datasets were simulated from the fitted model, refitted, and posterior variances of coefficients averaged to quantify the expected uncertainty of each parameter (brm::brm).

The purpose of the final model was to present a set of variables that could predict the occurrence of cesarean delivery. Finally, the testing database was used to evaluate the quality of the model and to develop the AUC and its 95% Confidence Interval, obtained from the Receiver Operating Characteristics (ROC) curve with 1,001 replicates by bootstrap (pROC::roc; pROC::ci.auc; and pROC::ci.coords). A calibration plot was constructed with the testing database, containing 30% of patients and maintaining the proportion of cesareans observed in the dataset. Decision curve analysis was performed using threshold probabilities ranging from 0.05 to 0.80, in increments of 0.005, and the 95% Confidence Interval was calculated by a bootstrap with 100 repetitions (rmda:: decision_curve and rmda::plot_decision_curve); p-values < 0.05 were considered significant. Statistical analyses were conducted using *R* programming language in the RStudio software (Version 4.1.0; 2021−06−29; RStudio, Inc.). Functions and packages were presented as 'package:: function', corresponding to computational language in *R*.

Results

During the study period, 331 patients received neuraxial analgesia, and 94 (28.4%) progressed to cesarean delivery (Fig. 1). The quantitative and qualitative variables analyzed are presented in Table 1, in relation to the occurrence of vaginal and cesarean deliveries, with their statistical values according to univariate analysis.

Following the split, the training database (70%, 232 out of 331 patients) was composed by 166 (71.5%) cases of vaginal delivery and 66 (28.5%) of cesarean, while the testing database (30%, 99 out of 331 patients) was composed by 71 (71.7%) cases of vaginal delivery and 28 (28.3%) of cesarean.

Table 2 shows the fit parameters of each model, before and after the *step-up* procedure. A null model is also presented for comparison. Unlike the full model, with all variables initially identified as significant, the final model presented all slope coefficients as significant. Their AUC was considered equivalent (p = 0.413).

In the final model, no evidence of lack of fit between predicted probabilities and observed outcomes were supported by the Hosmer-Lemeshow goodness-of-fit test (statistic = 7.4; degrees of freedom = 8; p = 0.487). Collinearity issues were not identified based on the VIFs of patient age (1.02), time under neuraxial analgesia (1.07), and oxytocin use after analgesia (1.07). Table 3 presents outcomes from the bootstrap resampling approach. The older the patients were ($\beta = 0.043$; p = 0.018) the greater the probability of cesarean (1.0436

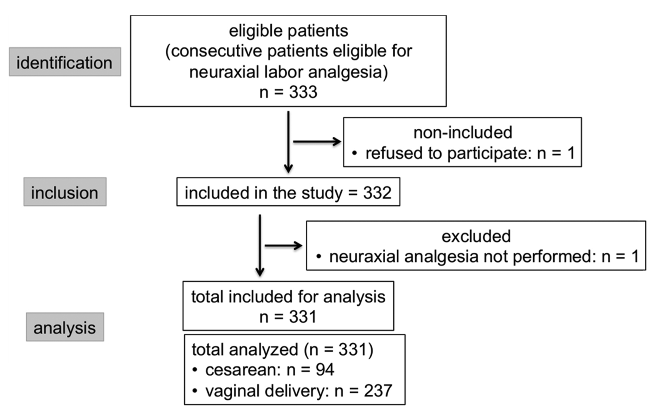

Figure 1 Flowchart.

Table 1 Distribution of quantitative and qualitative variables between parturients who underwent vaginal or cesarean delivery after neuraxial labor analgesia.

Variables	Vaginal Delivery (n = 237)	Cesarean (n = 94)	p-value
Age (years)	24 (20 – 29)	25 (21 – 29)	0.032
Weight (kg)	75 (68 – 87)	78 (69 – 91)	0.144
Height (cm)	1.63 (1.58 – 1.67)	1.62 (1.57 – 1.67)	0.289
Body mass index ($kg.m^{-2}$)	28.7 (25.8 – 33.2)	30.4 (27.6 – 34.5)	0.018
Gestational age [weeks (w)/days (d)]	39w/1d (38w/1d – 40w/1d)	39w/6d (38w/4d – 40w/3d)	0.006
Physical status			0.308
ASA[a] 2	204 (86.1%)	76 (80.8%)	
ASA 3	33 (13.9%)	18 (19.1%)	
Cervical dilation (cm)[b]	7 (7 – 8)	7 (6 – 8)	0.028
Previous pregnancies	1 (1 – 2)	1 (1 – 2)	0.422
Previous vaginal deliveries	63 (26.6%)	21 (22.3%)	0.424
Time under analgesia (min)	103 (55 – 184)	162 (102 – 233)	< 0.001
Numerical pain scale[c] (before analgesia)	10 (10 – 10)	10 (10 – 10)	0.751
Analgesia performed at night (after 8 pm)	101 (42.7%)	38 (40.4%)	0.787
Analgesia technique			0.397
Spinal[d]	181 (76.3%)	66 (70.2%)	
Spinal + epidural[e]	38 (16.0%)	21 (22.3%)	
Epidural[f]	18 (7.6%)	7 (7.4%)	
Use of oxytocin before analgesia	54 (22.7%)	12 (12.7%)	0.057
Use of oxytocin after analgesia	155 (65.6%)	22 (23.4%)	< 0.001
Labor monitored/accompanied by nursing	23 (9.7%)	22 (23.4%)	0.002

Data are presented as the median (1^{st} – 3^{rd} quartiles) or number of patients (%).

[a] American Society of Anesthesiologists.

[b] Dilation of the uterine cervix at the time of analgesia administration.

[c] Scale from zero (no pain) to 10 (maximum possible pain).

[d] Drugs and doses in groups Vaginal delivery and Cesarean, respectively (mean ± Standard Deviation [SD]): hyperbaric bupivacaine (mg), 2.6 ± 0.6 and 2.8 ± 1.0, and sufentanil (μg), 4.9 ± 0.7 and 5.0 ± 0.8.

[e] Drugs and doses in groups Vaginal delivery and Cesarean, respectively (mean ± SD): hyperbaric bupivacaine (mg), 2.7 ± 0.9 and 2.6 ± 0.3, sufentanil (μg), 5.5 ± 2.3 and 5.0 ± 1.3, and ropivacaine (mg), 18.2 ± 8.6 and 19.8 ± 15.0.

[f] Drugs and doses in groups Vaginal delivery and Cesarean, respectively (mean ± SD): ropivacaine (mg), 27.7 ± 11.4 and 28.3 ± 14.6.

increase for each one-year increase), and the longer the time under analgesia (β = 0.004; p = 0.018) the greater the probability of cesarean (1.0043 increase for each one-minute increase), given the positive slope coefficients (β) and significance (p) of these variables. On the other hand, the use of oxytocin after analgesia (β = -2.386; $p < 0.001$) decreased the probability of cesarean, given the negative slope coefficient (β) and significance (p) of this variable. The odds ratio indicates that the

Table 2 Findings of the fit parameters for each model before and after the *step-up* procedure using the training database. A null model is presented for comparison.

Parameters	Null Model	Full Model (7 identified variables) Before the *step-up*	Final Model (3 selected variables) After *step-up*
χ^2 (df); p-value[a]	0.00 (0); p = not applicable	63.3 (7); $p < 0.001$	55.7 (3); $p < 0.001$
AIC[b]	279.1 (-268.0 to 826.1)	205.1 (-196.8 to 607.1)	204.6 (-196.5 to 605.8)
BIC[c]	282.5 (-271.2 to 836.3)	231.8 (-222.5 to 686.1)	218.0 (-209.2 to 645.3)
RMSE[d]	0.4512 (-0.4331 to 1.3355)	0.3796 (-0.3645 to 1.1236)	0.3912 (-0.3755 to 1.1579)
AUC[e] (95% confidence interval)	50.0 (50.0 to 50.0)[b]	83.0 (76.6 to 89.4)[c]	81.5 (75.5 to 87.5)[d]
Slope coefficients (n)	0	7	3
Significant slope coefficients (n)	0	3	3

[a] χ^2 is the Chi-Square test, and df refers to degrees of freedom.

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; RMSE, Root Mean Square Error; AUC, Area Under the Curve.

[b] $p < 0.0001$, DeLong test comparing the AUC between null and final models.

[c] p = 0.0001, DeLong test comparing the AUC between null and full models.

[d] p = 0.413, DeLong test comparing the AUC between full and final models. The training database contains 70% of the randomly selected patients using a random stratification sampling by groups (232 patients: 166 [71.5%] cases of vaginal delivery and 66 [28.5%]) of cesarean).

Table 3 Findings of the bootstrap resampling approach on the predictive final model using the training database.

Parameters	Original estimated	p-value	Bootstrap		
			Bias	Standard error	95% CI
Linear coefficient (α)	-12.289		-0.995	5.642	-23.802 to -2.6488
Slope coefficients (β)					
Patient age	0.043	0.018	0.003	0.020	0.008 to 0.084
Time under neuraxial analgesia	0.004	0.018	0.001	0.002	0.001 to 0.009
Oxytocin use after analgesia	-2.386	< 0.001	-0.090	0.448	-3.185 to -1.515

The training database contains 70% of the randomly selected patients using a random stratification sampling by groups (232 patients: 166 [71.5%] cases of vaginal delivery and 66 [28.5%] of cesarean).

Table 4 Findings of the predictive final model after the *step-up* procedure using the training database.

Parameters	Estimated value	Standard error	*Z* value	p-value	Odds ratio (95% CI)
Linear coefficient (α)	-12.289	4.978	-2.469	0.014	0.0001 (0.0001 to 0.0463)
Slope coefficients (β)					
Patient age	0.043	0.018	2.359	0.018	1.0436 (1.0091 to 1.0835)
Time under neuraxial analgesia	0.004	0.001	2.367	0.018	1.0043 (1.0008 to 1.0081)
Oxytocin use after analgesia	-2.386	0.401	-5.951	< 0.001	0.0921 (0.0400 to 0.1945)

The training base contains 70% of the randomly selected patients using a random stratification sampling by groups (232 patients: 166 [71.5%] cases of vaginal delivery and 66 [28.5%] of cesarean).

administration of oxytocin after delivery of analgesia is a factor that decreases the probability of occurrence of cesarean, while the greater age of patients and the longer time under analgesia are factors that increase the probability of occurrence of cesarean (Table 4).

Table 5 shows the values of sensitivity, specificity, and AUC of the ROC curve of the *step-up* model using the testing and training databases that include patient age, time under labor analgesia, and use of oxytocin after the administration of labor analgesia. The values of the testing database indicate the performance metrics of the predictive model.

The penalized regression (LASSO) shows the same ranking of importance of the variables included in the final predictive model obtained through the *step-up* procedure using the training database (Supplementary Material Table 1S).

Expected posterior variance for the slope coefficients of all three parameters was very small, suggesting precision of the parameters in estimating their respective effects in the model, while the linear coefficient was relatively large, reflecting a moderate degree of imprecision in its estimation (Supplementary Material Table 2S).

Calibration on the testing database is suboptimal, especially at lower predicted probabilities (Supplementary Material Fig. 1S,), potentially due to the limited sample size and model overfitting. Using the optimal cutoff point determined from the training database, we identified 52 true negative cases, 16 true positives, 13 false positives, and 18 false negatives in the testing database. In the decision curve analysis (Supplementary Material Fig. 2S,), the final predictive model demonstrated a higher net benefit across a wide range of threshold probabilities compared to the strategies of treating all or treating none. This indicates that the model offers potential clinical utility, particularly within threshold probabilities range of approximately 0.15 to 0.45, for identifying parturients who may require cesarean delivery.

The equation for estimating the probability of an unplanned cesarean in patients under labor analgesia for vaginal delivery is described below, using the fixed effects of the model:

Table 5 Outcomes of the Receiver Operating Characteristic (ROC) curve of the training database and of the predictive final model using the testing database.

Parameters	Values (95% CI)	
	Training database	Testing database
Optimal cutoff point (%)	37.9 (16.2 to 54.4)	25.5 (8.5 to 62.9)
Specificity (%)	73.8 (55.5 to 91.5)	65.2 (36.2 to 100.0)
Sensibility (%)	81.8 (60.1 to 95.5)	78.6 (35.7 to 100.0)
Area under the curve (%)	81.5 (75.5 to 87.5)	71.8 (60.5 to 83.1)

The training database contains 70% of the randomly selected patients using a random stratification sampling by groups (232 patients: 166 [71.5%] cases of vaginal delivery and 66 [28.5%] of cesarean), while testing database has 30% of the reminiscent patients (99 patients: 71 [71.7%] cases of vaginal delivery and 28 [28.3%] of cesarean).

$P = \left(\frac{1}{1+e^{-(-12.289+Age*0.043+Analgesia*0.004+Oxytocin*-2.386)}}\right)*100$; p is the probability of cesarean; e is the Euler number $\sim 2.71828182845904523536028 7$; Age is the patient age (years); Analgesia is the time under neuraxial analgesia (minutes); Oxytocin is oxytocin use after analgesia (0 = no, 1 = yes).

The indications for cesarean were arrest of fetal descent (n = 33; 35.1%), fetal distress (n = 32; 34.0%), arrest of cervical dilation (n = 21; 22.3%), and patient's decision to withdraw from vaginal delivery (n = 8; 8.5%).

Discussion

In this study, in a public tertiary hospital, 28.4% of the parturients who received neuraxial analgesia for vaginal delivery progressed to cesarean. In similar studies, in parturients receiving neuraxial analgesia, the conversion rates to cesarean ranged from 21.4% to 28.4%.[11-13] Cultural issues, patients' demographic characteristics, and differences between public and private hospitals may be responsible for the differences between the incidences of cesarean rates in different studies. In the study by Bannister-Tyrrell and collaborators, reporting a 21.4% cesarean rate, epidural analgesia in labor was more common among women aged 35 years and older, primiparous women with labor induction, women at 41 weeks, and in private hospitals.[11] Lawson and collaborators reported an incidence of cesarean rate of 28.4% after labor analgesia. They selected parturients who had not received augmentation of labor by oxytocin and those who received regional analgesia were more commonly nulliparous, obese, admitted to hospital as a private patient and had a higher socioeconomic status.[12] Wang and collaborators recruited patients with cervical dilation larger than 1 cm and willing to have labor analgesia. Their mean age was 27 years, and gestational age ranged from 39 to 40 weeks. Analgesia was standardized as 15-mL epidural analgesic mixture in a single bolus of 0.125% ropivacaine with 0.3 μg.mL^{-1} sufentanil, followed by patient-controlled analgesic pump. The mean rate of cesarean was 23.0% and there was no difference according to initial cervical dilation.[13] In Brazil, unlike in the past few years, currently, in public hospitals, parturients in labor can choose to undergo cesarean at any time, even when they are already under neuraxial analgesia for vaginal delivery. This fact was observed in 8.5% of our patients.

We found that older maternal age and longer duration of labor analgesia were associated with higher odds ratio of cesarean, whereas the administration of oxytocin after analgesia reduced the probability of a change in the type of delivery, in this case, more vaginal deliveries.

An observational study revealed an association between advanced maternal age and cesarean delivery by showing that primiparous women aged between 35 and 39 years had twice the risk of cesarean section, whereas women aged 40 years or older had this risk tripled.[5] Studies have shown that cesarean rates are higher in women aged 35 years or older and that women over 40 years are at greater risk for emergency cesarean.[4,14] This association occurs regardless of the administration of neuraxial analgesia during labor. Possible explanations for the increased chance of cesarean section with increasing maternal age may be the decline in physiological functions, such as those of the genital tract and its muscles, uterine muscle and hormonal system. The contractile function of uterine myometrial cells likely becomes less responsive to oxytocin or prostaglandins with aging, causing differences in the duration of labor.[15]

Regarding the increased risk of cesarean with prolonged time under analgesia, a positive relationship between analgesia and the extension of the first stage of labor has been observed.[16] The interruption of painful stimuli reduces uterine activity due to decreased release of mediators involved in uterine contractility, such as prostaglandin F2α and oxytocin, resulting in a slowed labor progression.[17] However, neuraxial analgesia reduces plasma adrenaline levels, which may favor uterine contractility and potentially shorten the duration of labor.[18]

Neuraxial analgesia may also prolong the second stage of labor.[11,19] There is decreased effectiveness of maternal expulsive efforts due to abdominal muscle relaxation and reduced coordination of efforts during uterine contractions, in addition to pelvic diaphragm relaxation, which impairs fetal head rotation and engagement.[20] Cheng and collaborators observed that patients under neuraxial analgesia had a one-hour longer duration of the second stage of labor than did those undergoing labor without analgesia.[21] Lawson and collaborators reported that the mean duration of the second stage of labor was approximately 30 minutes longer with neuraxial analgesia, in addition to a two-fold-increased risk in cesarean delivery.[12]

Neuraxial analgesia during labor may result in a significant extension of both the dilation and fetal expulsion phases. However, some studies have failed to associate longer analgesia duration with a corresponding increase in cesarean rates,[22,23] which contrasts with the findings of our study.

Oxytocin is used to induce labor, augment uterine contractility, and manage labor progression. However, it can be associated with an elevated risk of instrumental vaginal delivery and cesarean.[24] In patients in prolonged labor, oxytocin can shorten the time of labor by approximately two hours without significantly increasing the risk of cesarean or neonatal morbidity.[25,26] A positive association between labor analgesia and oxytocin administration is observed.[27] This may be attributed to the fact that epidural analgesia prolongs labor, especially the second stage, leading to the use of oxytocin to intensify uterine contractions and promote labor progression. Furthermore, neuraxial analgesia reduces plasma levels of endogenous oxytocin, justifying the more frequent use of exogenous oxytocin for labor induction.

In the present study, not using oxytocin during labor analgesia was the factor with the highest statistical weight in the predictive final model for cesarean. However, our data diverge from previous studies, which did not show any differences in cesarean rates when oxytocin was used for augmentation of spontaneous labor.[28]

The final model constructed with three predictor variables demonstrated a moderate predictive performance for unplanned cesarean delivery in parturients receiving analgesia for vaginal delivery, with an AUC of 71.8%. The construction of the predictive model involved progressive steps to select significant predictive variables (*step-up* procedure), based on the idea that a parsimonious model, i.e., with fewer variables, is preferable to a more complex one. An AUC with values between 70% and 90% is considered moderate with respect to its discriminatory ability, whereas values above 90% would indicate high predictive ability.[29]

The predominant reasons for cesarean are labor dystocia, which includes failure in cervical dilation and fetal descent, followed by changes in fetal heart rate, which may indicate fetal distress.[30] The main causes of cesarean delivery that we observed were arrest of descent and fetal distress. Our findings agree with those in the literature, which identified arrest of descent as the most common indication for cesarean, both for women who received and for those who did not receive epidural analgesia.[2,15,19]

Our model can predict with moderate accuracy the occurrence of an unplanned cesarean in patients expecting to have a vaginal delivery under neuraxial labor analgesia. It is the first predictive model involving parturients receiving labor analgesia and may help doctors on changing treatments, specifically according to the variables of our model, to consider using oxytocin in older parturients in prolonged time under analgesia. Nonetheless, the model still needs external validation in different populations.

This study has some limitations. It is a single-center study conducted in a public hospital, limiting its generalizability to other types of maternity care units. There may also be other unmeasured confounders as we did not investigate aspects related to labor management, such as the frequency of pelvic exams, the analysis of each stage of labor, the dose of oxytocin administered, and the quality of uterine contractions after neuraxial analgesia. These factors could also help clarify some of the discrepancies found when comparing our results with those of other studies. However, we present a parsimonious predictive model contributing to a better understanding of the magnitude of factors associated with unplanned cesarean delivery in parturients under labor analgesia for vaginal delivery. Although the 70%–30% split of the limited-size, single-center dataset may have influenced the final model, it achieved good performance metrics. Although we performed techniques to support the internal validation of the model such as train-test split, Hosmer-Lemeshow goodness-of-fit test, bootstrapping, and LASSO, the *step-up* approach might have led to an overfitting of the model, as suggested by the calibration plot. Nonetheless, as suggested by the decision curve, the model offers potential clinical utility in a fair range of threshold probabilities for identifying parturients who may require cesarean delivery. This study represents only the first of several steps for developing a practical tool to support medical decision-making. Future studies should test and validate the proposed model in multiple medical centers before it becomes available for clinical use.

Conclusion

Among parturients undergoing labor neuraxial analgesia for vaginal delivery, 28.4% had unplanned cesareans. The set of variables, older age, longer time under analgesia, and not using oxytocin during analgesia increased the odds of a cesarean delivery, with moderate predictive value. The most common causes for cesarean delivery in these patients were arrest of descent and fetal distress. This is a preliminary study and, although the model shows moderate discriminative ability, further prospective external validation is needed before clinical application.

Authors' contributions

Paula Daniele Lopes da Costa: Conceptualization, investigation, formal analysis, methodology, visualization, writing - original draft, writing - review & editing; Murilo Henrique da Veiga Ferreira: Investigation, writing - original draft; Joelcio Francisco Abbade: Formal analysis, resources, writing - original draft; Claudia Garcia Magalhães: Formal analysis, resources, writing - original draft; Norma Sueli Pinheiro Módolo: Formal analysis, writing - original draft; Guilherme Antonio Moreira de Barros: Formal analysis, writing - original draft, writing - review & editing; Gabriel Ricardo Correa Turco: Investigation, formal analysis; Pedro Henrique Esteves Trindade: Data curation, formal analysis, methodology - statistics, writing - original draft; Paulo do Nascimento Junior: Conceptualization, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing - original draft, writing - review & editing.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI assistance disclosure

Writing and English review

During the preparation of this work, the authors used Rubriq/American Journal Experts (https://www.aje.com/rubriq) for English language editing. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. No other AI tool was used in the preparation of the manuscript.

Ethics

This study was approved by the Institutional Ethics Committee (Plataforma Brasil, CAAE: 55925621.8.0000.5411; Research Ethics Committee, #5.278.695, issued on March 8, 2022, https://plataformabrasil.saude.gov.br/login.jsf;jsessionid=TSTL-1Zil8DbrAlv0WrlZXP9; https://www.fmb.unesp.br/#!/cep).

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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.2026.844732.

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ORIGINAL INVESTIGATION

The impact of opioid-free labor epidural analgesia maternal and infant outcomes: a retrospective cohort study

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Abstract
Background: Opioid Epidural Labor Analgesia (OLEA) is commonly used during labor. However, opioid use has been associated with adverse effects on maternal and fetal outcomes. Medications administered during epidural analgesia are systemically absorbed; therefore, we performed a retrospective cohort study to investigate whether Opioid-Free Labor Epidural Analgesia (OFLEA) is comparable to OLEA regarding maternal and infant outcomes at delivery.
Methods: Of 1,423 patients initially identified, we excluded those with twin deliveries, duplicate records, or incomplete data. We then matched 1:1 on the mother's age, including 618 patients for final data analysis. Our OLFEA group included an epidural solution of 0.2% ropivacaine, while our OLEA group included an epidural solution of 0.1% ropivacaine + 250 mcg fentanyl. Wilcoxon rank-sum tests were performed to assess our primary outcome of time-weighted pain scores before and after epidural placement. Secondary outcomes included duration (minutes) of maternal hypotension, tachycardia, and bradycardia episodes during labor, and incidence of neonatal fever, C-section, and Apgar scores (1 and 5 mins after delivery).
Results: There was no significant difference between the OLEA and OFLEA groups in the time-weighted pain scores during labor before epidural placement. However, the time-weighted pain score was significantly lower in the OFLEA group (1.05 $\pm$ 1.52) compared to OLEA (1.43 $\pm$ 1.77, $p = 0.006$). Similarly, maximum pain scores after epidural were lower in OFLEA (3.32 $\pm$ 3.23) vs. OLEA (3.87 $\pm$ 3.33, $p = 0.03$). There were no significant differences in maternal hemodynamic events, Apgar scores, neonatal fever, or cesarean delivery rates.

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Conclusions: OFLEA is a safe and feasible alternative to OLEA. Avoidance of opioids may support safer maternal and neonatal care in obstetric anesthesia.

Introduction

Each year, there are approximately 140 million births globally.[1] In the United States, Opioid Epidural Labor Analgesia (OLEA) is used in most births.[2] The burgeoning interest in opioid-free labor epidural analgesia stems from the escalating need to identify non-inferior alternatives to traditional opioid-based methods. This interest is driven by the growing recognition of the potential risks associated with even a single use of opioids during labor, which includes the possibility of Neonatal Opioid Withdrawal Syndrome (NOWS), maternal respiratory depression, and the initiation of long-term opioid dependence.[3-5]

In addition, epidural opioids adversely affect mothers before and after delivery (sedation, hypoxemia, hypotension, prolonged labor, itching, nausea and/or vomiting, infants' health, and prolonged hospital stay).[6-8] Avoiding opioids in epidural solutions is a unique approach because most of it is systemically absorbed and is not necessarily better than giving systemic opioids. Despite this emerging problem, mother and baby are exposed to around 600 mcg of intravenous fentanyl equivalent dose during normal vaginal delivery.[9] It would be clinically impactful if opioid-to-opioid-free epidural analgesia is as effective as continuous opioid epidural labor analgesia.

We, therefore, tested three main aims regarding OFLEA performance. Our primary aim was to determine if OFLEA is as effective as OLEA regarding labor pain management. We hypothesized that OFLEA is non-inferior to OLEA in regards to time weight average and highest pain scores during labor. Our second aim was to determine whether continuous OFLEA reduces the duration of hypotension (Mean Arterial Pressure [MAP] < 65 mmHg) and/or tachycardia (> 90 beats.min^{-1}) and/or desaturation (< 90%) compared to OLEA. We hypothesized that the duration of hypotension, tachycardia, and desaturation would decrease in the OFLEA cohort. Lastly, our third aim was to study the effect of OFLEA on infant outcomes (Apgar scores and if required O_2, intensive care unit admission) and maternal delivery outcomes (fever and incidence of cesarean section). We hypothesized that infant outcomes would improve in the OFLEA cohort. Our primary study hypothesis was that OFLEA is non-inferior to OLEA regarding these three aims.

Methods

Data source

This retrospective cohort study intended to study outcome differences in OFLEA and OLEA in labor pain management, intraoperative events, and infant outcomes. The protocols used were developed by authors at the University of Texas Medical Branch Department of Anesthesiology. The study was reviewed and given approval by the Institutional Review Board (IRB# 22-0149, 21-Jun-2022), and written informed consent was waived by the IRB. All data utilized in this study is from patients enrolled at UTMB between the dates of December 1, 2021, and June 9, 2022. This study adheres to the applicable STROBE guidelines.

Cohort selection and development

The two experimental cohorts received epidural solutions of either continuous 0.1% ropivacaine + 250 mcg fentanyl (OLEA) or solely 0.2% ropivacaine (OFLEA). All parturients in our study received continuous epidural infusion (10–13 mL.hr^{-1}) with Patient-Controlled Epidural Analgesia (PCEA) enabled (4 mL bolus, 15-minute lockout). The only difference between groups was the epidural solution: the OFLEA group received 0.2% ropivacaine, whereas the OLEA group received 0.1% ropivacaine with 250 mcg fentanyl added to the epidural infusion bag. No initial bolus was administered; analgesia was provided solely through continuous infusion. All parturients requesting epidural analgesia for delivery at UTMB Health between December 1, 2021, and June 9, 2022.

Participants were identified using the Epic Electronic Medical Record to stratify for an initial n = 1423 (OFLEA n = 330, OLEA n = 1093). We included pregnant women aged 18–50 years of any parity and race who delivered under epidural spinal anesthesia during hospital admission. Those whose diagnostic criteria had not been clearly documented or established, patients of gestational age before 24 weeks who presented to the labor and delivery unit, and those who did not receive epidural anesthesia during hospital admission were excluded from the study. Patient characteristics including age, mode of delivery, and mode of anesthesia were obtained from chart review. After removing patients having twin deliveries that were duplicated in either group or who had extraneous amounts of missing values, we arrived at a total n = 1346 (OFLEA n = 310, OLEA n = 1036). Matching (1:1) on the mother's age gave a final total of n = 618 (OFLEA/OLEA n = 309) (Fig. 1).

Statistical analysis

For Aim 1, a non-parametric, Wilcoxon rank-sum test (Mann-Whitney *U*), average time-weighted pain scores and max pain scores during labor across OFLEA and OLEA groups were used. For Aim 2, we also utilized a non-parametric Wilcoxon rank-sum test to assess the total duration of episodes of tachycardia (> 90 beats.min^{-1}), hypotension (< 65 mmHg, MAP), and hypoxemia (< 90% O_2 sat) during labor. For Aim 3, the newborn's outcome Apgar score equality was also checked with a non-parametric, Wilcoxon rank-sum test. If specific markers were found statistically significant, a linear regression model was created for the outcome. We found time-weighted pain score during labor after epidural and max pain score were significant and hence followed by multiple linear regression model adjusted for age, ethnicity,

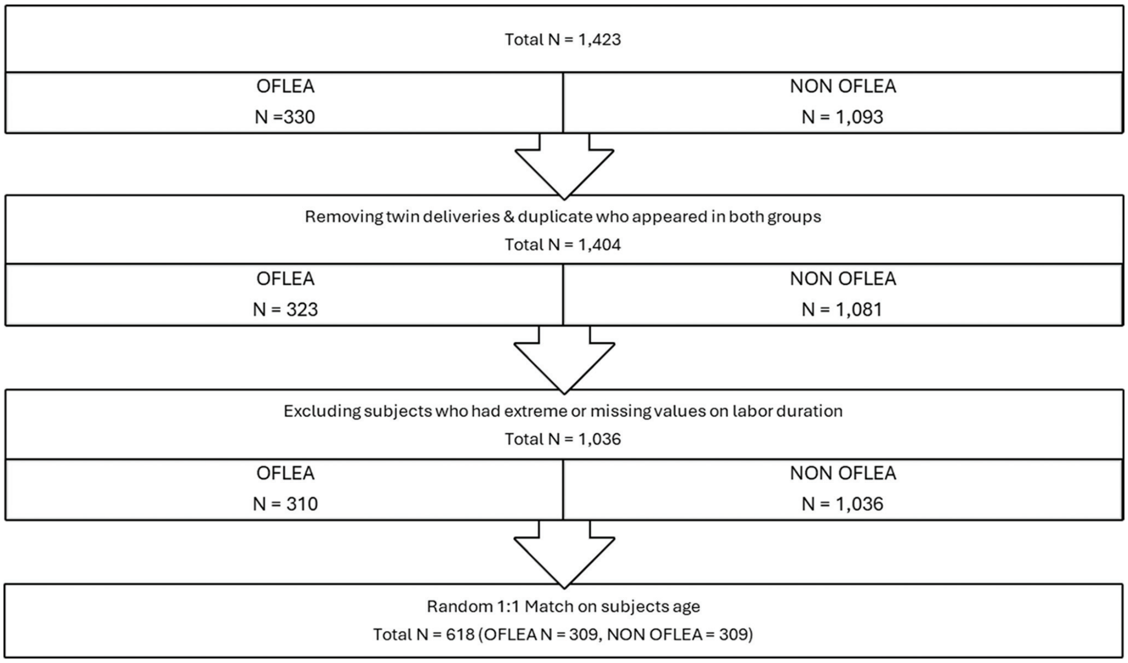

Figure 1 Flow diagram.

and fever, selected based on their potential to confound the relationship between treatment and pain outcomes.

Results

A total of 618 age-matched parturient were included in the final data analysis. The OFLEA and OLEA groups consisted of 309 patients. The mean age in both groups was 26.64 years (SD = 5.59); 59.87% of participants identified as Hispanic (n = 370) and 45.31% of patients experienced fever during labor (n = 280) (Table 1); 80.74% (n = 499) of patients delivered via normal spontaneous vaginal birth, 12.94% (n = 80) had a cesarean delivery, 3.24% (n = 20) had a vaginal, vacuum assisted delivery, as well as 1 breech and 1 forceps assisted deliveries.

Time-weighted and max pain scores after epidural placement

There was no significant difference between the two groups (OLEA and OFLEA) in the time-weighted pain score during labor before epidural placement. The time-weighted pain score (mean ± SD) before epidural for the OLEA group was 2.268 ± 2.217 vs. 2.617 ± 2.063 in the OLFEA group (p = 0.15). The time-weighted pain score during labor after epidural placement in the OFLEA group was statistically significantly lower than the OLEA group. The time-weighted pain score (mean ± SD) after epidural for the OLEA group was 1.430 ± 1.77 vs. 1.054 ± 1.517 in the OLFEA group (p = 0.0057). The parameter estimates for the linear model for the time-weighted pain scored during labor after epidural was -0.413 (95% CI -0.682, -0.144) (p = 0.0035). The max pain score during labor before epidural was not significantly different between groups. The max pain score (mean ± SD) before epidural for the OLEA group was 5.802 ± 2.647 vs. 5.756 ± 2.655 in the OFLEA group (p = 0.9058). The OFLEA group had a significantly lower max pain score during labor after epidural versus the OLEA group. The max pain score during labor after epidural for the OLEA group was 3.866 ± 3.325 vs. 3.318 ± 3.233 for the OFLEA group (p = 0.0345). The parameter estimates for the linear model for the max pain score during labor after epidural was -0.534 (95% CI -1.076, 0.0077) (p = 0.0881) (Table 2).

Table 1 Demographics of study participants.

Demographics	Mean (n)	SD (%)
Age (Mean, SD)	26.64	5.59
Fever		
No	338	54.69%
Yes	280	45.31%
BMI (Mean, SD)	33.44	6.34
Weight (Mean, SD), kg	86.37	18.47
ASA Class		
2	520	84.14%
3	98	15.86%
Gestational Age (Mean, SD), day	268.6	14.73
Gestational Age (Mean, SD), week	38.37	2.1
Ethnicity		
Hispanic	370	59.87%
Not Hispanic	248	40.13%
Delivery Type		
Normal Spontaneous Vaginal Birth	499	80.74%
C-Section, Low Transverse	80	12.94%
Vaginal, Vacuum (Extractor)	20	3.24%
Vaginal Birth after Cesarean Section	15	2.43%
Other (See Comments)	2	0.32%
Vaginal, Breech	1	0.16%
Vaginal, Forceps	1	0.16%

Table 2 Mean time weighted pain scores for OLEA and OFLEA.

Variables/Characteristics	OFLEA				p-value
	No		Yes		
	Mean (SD)	95% CI	Mean (SD)	95% CI	
Time-weighted pain score during labor before epidural	2.87 (2.22)	(2.62, 3.12)	2.62 (2.06)	(2.39, 2.85)	0.15
Time-weighted pain score during labor after epidural	1.43 (1.77)	(1.23, 1.63)	1.05 (1.52)	0.88 (1.23)	0.0057[a]
Max pain score during labor before epidural	5.8 (2.65)	(5.51, 6.1)	5.76 (2.65)	(5.46, 6.05)	0.9058
Max pain score during labor after epidural	3.87 (3.33)	(3.48, 4.25)	3.32 (3.23)	(2.95, 3.69)	0.0345[a]
Outcome Variable	**Intercept**	**R-square**	**OFLEA Estimate**	**95% CI**	**p-value**
Time-weighted pain score during labor after epidural	1.5	0.031	−0.413	(−0.682, −0.144)	0.0035[a]
Max pain score during labor after epidural	3.72	0.017	−0.534	(−1.076, 0.0077)	0.0881
Sensitivity analysis with different margin for non-inferiority					
Margin (Δ)	**Observed Difference**	**Distance from Margin**	**Power**		
1	−0.3763	0.6237	19.70%		
0.75	−0.3763	0.3737	92.30%		
1.5	−0.3763	1.1237	99.10%		

[a] Provides statistical significance at 0.05 level.

Notes: p-values come from nonparametric Wilcoxon rank-sum tests since the data points do not follow normality assumptions. Each linear model was adjusted for age, ethnicity, and fever. Asterisk provides statistical significance at 0.05 level. For the time-weighted pain score during labor after epidural outcome, the p-value is significant. The parameter estimate described as using OFLEA will decrease 0.413 unit time-weighted pain score during labor after epidural.

Hypotension, tachycardia, and bradycardia episodes during labor

The total duration (minutes) of tachycardia episodes during labor before epidural was not significantly different between groups. The total duration of tachycardia episodes during labor before epidural (mean ± SD) for the OLEA group was 200.04 ± 337.56 vs. 154.98 ± 296.64 for the OFLEA group (p = 0.2463). The median (IQR) total duration of tachycardia episodes during labor before epidural for the OLEA group was 54.50 (0 to 222.00) vs. 45 (0 to 167.00) for the OFLEA group (p = 0.2463). The total duration (minutes) of tachycardia episodes during labor after epidural was not significantly different between groups. The total duration of tachycardia episodes during labor after epidural (mean ± SD) for the OLEA group was 132.85 ± 181.40 vs. 128.59 ± 226.10 for the OFLEA group (p = 0.0532). The median (IQR) total duration of tachycardia episodes during labor after epidural for the OLEA group was 61 (3.50 to 197.00) vs. 30 (0 to 150.00) for the OFLEA group (p = 0.0532) (Table 3).

The total duration (minutes) of hypotension episodes during labor before epidural was not significantly different between groups. The total duration of hypotension episodes during labor before epidural (mean ± SD) for the OLEA group was 2.57 ± 7.75 vs. 4.58 ± 10.31 for the OFLEA group (p = 0.6252). The median (IQR) total duration of hypotension episodes during labor before epidural for the OLEA group was 0.0 (0.0 to 0.0) vs. 0.0 (0.0 to 0.0) for the OFLEA group (p = 0.6252). The total duration (minutes) of hypotension episodes during labor after epidural was not significantly different between groups. The total duration of hypotension episodes during labor after epidural (mean ± SD) for the OLEA group was 3.92 ± 10.87 vs. 6.66 ± 21.19 for the OFLEA group (p = 0.6724). The median (IQR) total duration of hypotension episodes during labor after epidural for the OLEA group was 0.0 (0.0 to 2.0) vs. 0.0 (0.0 to 0.0) for the OFLEA group (p = 0.6724) (Table 3).

The total duration (minutes) of bradycardia episodes during labor before epidural was not significantly different between groups. The total duration of bradycardia episodes during labor before epidural (mean ± SD) for the OLEA group was 32.11 ± 68.17 vs. 23.17 ± 48.41 for the OFLEA group (p = 0.3296). The median (IQR) total duration of bradycardia episodes during labor before epidural for the OLEA group was 0.0 (0.0 to 30.0) vs. 0.0 (0.0 to 30.0) for the OFLEA group (p = 0.3296). The total duration (minutes) of bradycardia episodes during labor after epidural was not significantly different between groups. The total duration of bradycardia episodes during labor after epidural (mean ± SD) for the OLEA group was 16.95 ± 40.87 vs. 31.74 ± 59.02 for the OFLEA group (p = 0.2388). The median (IQR) total duration of bradycardia episodes during labor after epidural for the OLEA group was 0.0

Table 3 Mean duration of adverse events during OLEA and OFLEA labor.

Variables/Characteristics	OLEA		OFLEA		p-value
	Mean (SD)	95% CI	Mean (SD)	95% CI	
Total duration (minutes) of episodes of tachycardia during labor before epidural	200.04 (337.56)	(157.99, 242.09)	154.98 (296.64)	(118.39, 191.56)	0.2463
Total duration (minutes) of episodes of tachycardia during labor after epidural	132.85 (181.40)	(109.78, 155.92)	128.59 (226.10)	(100.81, 156.36)	0.0532
Total duration (minutes) of episodes of hypotension during labor before epidural using BP	2.57 (7.75)	(−0.33, 5.46)	4.58 (10.31)	(0.23, 8.94)	0.6252
Total duration (minutes) of episodes of hypotension during labor after epidural using BP	3.92 (10.87)	(1.40, 6.44)	6.66 (21.19)	(1.91, 11.40)	0.6724
Total duration (minutes) of episodes of bradycardia during labor before epidural	32.11 (68.17)	(11.39, 52.84)	23.17 (48.41)	(9.11, 37.22)	0.3296
Total duration (minutes) of episodes of bradycardia during labor after epidural	16.95 (40.87)	(3.7, 30.2)	31.74 (59.02)	(14.41, 49.07)	0.2388

Notes: p-values come from nonparametric Wilcoxon rank-sum tests since the data points do not follow normality assumptions. Since none of the p-values are statistically significant at a 0.05 level, we did not fit regression models. Since the standard deviations are quite high, we also reported the interquartile ranges (Q1 to Q3), and this range shows the middle 50% of values when ordered from lowest to highest. Value of Q1 can be explained as the value under which 25% of data points are found when they are arranged in increasing order. Value of Q3 can be explained as the value under which 75% of data points are found when they are arranged in increasing order.

(0.0 to 15.0) vs. 0.0 (0.0 to 30.0) for the OFLEA group (p = 0.2388) (Table 3).

Incidence of maternal labor side effects

The number of patients who experienced at least 1 episode of tachycardia during labor before epidural for the OLEA group was 250 (80.91%) vs. 255 (82.52%) for the OFLEA group. The incidence, n (%), of patients that experienced at least 1 episode of tachycardia during labor after epidural for the OLEA group was 240 (77.67%) vs. 257 (83.17%) for the OFLEA group (Table 4).

The number of patients that experienced at least 1 episode of hypotension during labor before epidural for the OLEA group was 30 (9.71%) vs. 24 (7.77%) for the OFLEA group. The incidence, n (%), of patients that experienced at least 1 episode of tachycardia during labor after epidural for the OLEA group was 74 (23.95%) vs. 79 (25.57%) for the OFLEA group (Table 4).

The number of patients that experienced at least 1 episode of bradycardia and during labor before epidural for the OLEA group was 44 (14.24%) vs. 24 (15.53%) for the OFLEA group. The incidence, n (%), of patients that experienced at least 1 episode of bradycardia during labor after epidural for the OLEA group was 39 (12.62%) vs. 47 (15.21%) for the OFLEA group (Table 4).

Neonatal outcomes

There was no significant difference in Apgar scores for the infants both 1-minute and 5 minutes from delivery. The Apgar score for the infant 1-min from delivery (mean ± SD)

Table 4 Number of maternal labor side effects OLEA and OFLEA.

Variables/Characteristics	OLEA n (%)	OFLEA n (%)
At least 1-episode of tachycardia during labor before epidural	250 (80.91)	255 (82.52)
At least 1-episode of tachycardia during labor after epidural	240 (77.67)	257 (83.17)
At least 1-episode of hypotension during labor before epidural using BP	30 (9.71)	24 (7.77)
At least 1-episode of hypotension during labor after epidural using BP	74 (23.95)	79 (25.57)
At least 1-episode of bradycardia during labor before epidural	44 (14.24)	48 (15.53)
At least 1-episode of bradycardia during labor after epidural	39 (12.62)	47 (15.21)

Notes: This table shows the number and percentages of subjects who experienced at least one episode for each of the above characteristics during pre and post epidurals. For example, out of 309 'No OFLEA' subjects, 250 (80.91%) subjects experienced at least 1 episode of tachycardia during labor before epidural and 255 (82.52%) 'OFLEA yes' subjects experienced at least one episode of tachycardia before epidural. All other variables/characteristics can be described in a similar way.

Table 5 Mean Apgar scores for OLEA and OFLEA groups.

Variables/Characteristics	OFLEA				p-value
	No		Yes		
	Mean (SD)	95% CI	Mean (SD)	95% CI	
Apgar score for baby 1-min from delivery	7.89 (1.29)	(7.74, 8.05)	7.82 (1.26)	(7.67, 7.97)	0.0892
Apgar score for baby 5 min from delivery	8.76 (1.16)	(8.62, 8.89)	8.74 (1.17)	(8.6, 8.88)	0.5748

Notes: p-values come from nonparametric Wilcoxon rank-sum tests since the data points do not follow normality assumptions. As none of the p-values are statistically significant at the 0.05 level, we did not fit regression models.

for the OLEA group was 7.896 $\pm$ 1.29 vs. 7.819 $\pm$ 1.26 for the OFLEA group (p = 0.0892). The Apgar score for the infant 5 min from delivery (mean $\pm$ SD) for the OLEA group was 8.760 $\pm$ 1.16 vs. 8.743 $\pm$ 1.174 for the OFLEA group (p = 0.5784) (Table 5).

There was also no significant difference in the incidence of fever in neonates between the OFLEA and OLEA groups; 141 (45.63%) neonates in the OLEA group developed fever after delivery compared to 139 (44.98%) in the OFLEA group (p = 0.872). In contrast, 168 neonates in the OLEA group did not develop fever compared to 170 (55.02%) neonates in the OFLEA group (Table 6).

Lastly, no significant difference was identified in the incidence of C-section delivery between the OFLEA and OLEA groups; 47 patients (15.21%) underwent a C-section in both the OFLEA and OLEA groups, while 262 patients (84.79%) did not have a C-section in both the OFLEA and OLEA groups (p = 1.000) (Table 6).

Discussion

Our retrospective cohort study studied the effect of OFLEA on pain reduction after epidural placement in 618 patients compared to OLEA. We found that OFLEA was non-inferior to OLEA after epidural placement in the reduction of pain scores. One meta-analysis identified similar findings of non-inferiority of OFLEA both immediately and 24 hours postpartum.[10] Multimodal analgesia has also been used to achieve similar pain-free responses; one study found a higher dose of propofol alone was needed to achieve loss of response compared to propofol with remifentanil.[11] Our study used a similar approach of administering a higher concentration of ropivacaine in our OFLEA group. Studies further investigating the use of multimodal labor analgesia regimens are necessary to identify avenues to improve pain control.

The OFLEA group in our study used a higher concentration of ropivacaine compared to the OLEA group. A study comparing postoperative pain after epidural analgesia using 0.5% ropivacaine compared to 0.75% ropivacaine and 0.5% bupivacaine found greater pain control with a higher concentration of local analgesia.[12] Although this may not be generalizable to labor, it shows its efficacy as a modality of local analgesia. Another study using 0.0625% bupivacaine/0.0002% fentanyl compared to 0.125% bupivacaine identified no significant difference in pain control during any stage of labor.[13] This dose-dependent effect of local analgesia may partly be explained by a faster onset of sensory and motor loss.[14] In our study, a higher concentration of local analgesia in the OFLEA regimen may explain the noninferiority in pain control. Another benefit of using a higher local analgesic concentration can be attributed to lower side effect profiles in the OFLEA group. Opioid analgesia is associated with adverse effects that may contribute to pain, most notably opioid-induced hyperalgesia.[15,16] This has been shown to contribute to greater levels of pain after labor despite its intended perioperative use.[16] A meta-analysis of opioid anesthesia on postoperative hyperalgesia found that high doses of remifentanil were associated with small yet significant increases in pain levels postoperatively; however, other studies have demonstrated no change in pain levels in surgical patients with opioid anesthesia regimens.[17,18]

Table 6 Fever and C-Section Incidence in OLEA and OFLEA groups.

Variables/Characteristics	Total	n (%)		p-value
		OLEA	OFLEA	
Total	618	309 (50)	309 (50)	
Fever				
No	338	168 (54.37)	170 (55.02)	0.872
Yes	280	141 (45.63)	139 (44.98)	
C-section				
No	524	262 (84.79)	262 (84.79)	1.000
Yes	94	47 (15.21)	47 (15.21)	

Notes: Percentages shown as column percentage. For example, variable 'Fever' percentages can be described as: among 309 No OFLEA subjects, 168 (54.37%) had fever and 141 (45.63%) had no fever. On the other hand, among 309 'OFLEA' subjects, 170 (55.02%) had fever and 139 (44.98%) had no fever. C-Section generated from delivery type information. So, if the delivery type included 'C-Section low transverse' or 'vaginal birth after cesarean section' they were flagged as C-section. The p-values come from the Chi-Square test. As none of the p-values are significant at the 0.05 level, we can conclude that there is no association between fever and OFLEA (yes/no) C-section and OFLEA.

We also studied the effects of OFLEA on the duration of episodes of tachycardia, hypotension, and bradycardia before and after labor. In this study, OLEA was non-inferior compared to OFLEA after epidural placement in duration of these adverse effects. One meta-analysis found that in select surgeries, opioid-free regimens significantly reduced duration of tachycardia, hypotension, and bradycardia without compromising pain control; however, two studies found contrasting evidence, reporting increases in the duration of these episodes when using opioid-free analgesia; one study, in particular, found that a dexmedetomidine dose of 0.4 to 1.4 $\mu g.kg^{-1}.h^{-1}$ is associated with severe episodes of bradycardia compared to an opioid-only regimen. Bradycardia was the most significant adverse effect reported in these two studies, while there were no differences in rates of tachycardia and hypotension between OFLEA and OLEA.[19-21] Possible explanations for this finding are medication-related and dose-dependent effect on adverse outcomes, as a high-dose unimodal opioid-free regimen of dexmedetomidine was used in Beloeil et. al.[20] Our data showed no significant difference in these outcomes when using unimodal ropivacaine. Previous literature has shown that dose reduction can be achieved using multimodal analgesia compared to unimodal analgesia to reduce adverse effects without compromising pain control.[22] Studies using these regimens compared to opioid-inclusive anesthesia are needed to explain further differences in adverse outcomes and potentially identify a dosage that balances adequate pain control with side effect profile optimization.

We lastly studied rates of neonatal Apgar scores, fever incidence, and rates of C-section between OFLEA and OLEA. Our study showed that OFLEA is non-inferior to OLEA in terms of neonatal outcomes after delivery. While literature regarding this data is limited, the existing literature has not found an association between epidural analgesia and neonatal outcomes; the common doses of OLEA show no significant effect on Apgar scores and C-section rates.[23,24] One study did show that epidural analgesia is associated with slightly lower (but above 7) Apgar scores in neonates who were exposed to labor epidural analgesia compared to non-epidural analgesia.[25] Our lack of differences in neonatal outcomes may be due to potential underpowering of the study. Larger, multi-centered randomized controlled trials would be beneficial to further delineate the impact of OFLEA on neonatal outcomes. Neonatal withdrawal syndrome may be associated with maternal opioid usage during pregnancy, but no study has identified this association in the intrapartum setting. Overall, our study findings concurrent with existing literature suggest that OFLEA may be a safer alternative for neonates.

Limitations

Our study has several limitations. We performed a single-center retrospective cohort study, which limits our power and generalizability. We also did not use the total volume or dose (mL) of local anesthetic administered, which limits our ability to fully evaluate dose-dependent effects on analgesia and motor block. The higher concentration of ropivacaine used in the OFLEA group (0.2% vs. 0.1% in OLEA) may have influenced outcomes and represents a potential confounder. We also did not include maternal side effects such as pruritus, nausea, or vomiting. Further, patient records were not all homogenous which may contribute to the variability seen in some of the data, such as pain scores and duration of maternal adverse outcomes. Our study population is not fully representative of American or global populations. Our average age at delivery was similar to 2021 national statistics (26.64 vs. 27.3). A large portion of our study population was Hispanic (n = 370, 59.87%) compared to 24.2% of mothers in 2021. The majority of our patient population underwent spontaneous vaginal delivery (n = 499, 80.74%) while the 2021 national percentage was 65.7%. Our cesarean delivery rates were lower than national rates (n = 80, 12.94% vs. 32.1%). Our Vaginal Birth After Cesarean Delivery (VBAC) rates were lower than 2021 averages (n = 15, 2.43% vs. 13.5%).[26] These differences reflect institutional practice patterns that may not be generalizable to other centers. Additionally, we matched groups only on maternal age and did not adjust for other important obstetric factors such as parity, body mass index, comorbidities, or labor duration. Residual confounding is therefore likely, and unmeasured differences between groups could have influenced the outcomes. In addition, motor block and ambulation were not assessed in our retrospective data. These outcomes are fundamental when comparing local anesthetic concentrations, as higher doses can impair maternal mobility and affect the course of labor. The inability to evaluate motor block or the ability to walk is therefore an important limitation of our analysis.

Conclusions

Our study findings suggest that OFLEA can be used as a safer alternative to OLEA. OFLEA is non-inferior to OLEA regarding maternal peripartum pain scores, adverse effects, and neonatal outcomes. Future studies identifying differences between OFLEA and OLEA will help tease the differences between these two modalities of analgesia, as the avoidance of opioid analgesia is a potential future alternative to OLEA; prospective trials are warranted to establish safety and efficacy.

AI assistance disclosure

We did not use any AI tools in the preparation of the manuscript or in the analysis.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

Kush Brahmbhatt: This author helped in the protocol development, data extraction, data analysis, and the writing of the manuscript.

Ankith Reddy: This author helped in the protocol development, data extraction, data analysis, and the writing of the manuscript.

Hiram Acevedo Bonilla: This author helped in the protocol development and review of the manuscript.

Ibrahim Tahashilder: This author helped in the data extraction and data analysis in the manuscript.

Mohamed Ibrahim: This author helped in the protocol development, experiment conduction, and review of the manuscript.

Michelle Simon: This author helped in the protocol development, experiment conduction, and review of the manuscript.

Rakesh Vadhera: This author helped in the protocol development, experiment conduction, and review of the manuscript.

Rovnat Babazade: This author helped in the protocol development, experiment conduction, guidance of data extraction and analysis, and review of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Changing patterns of nitrous oxide use and environmental awareness among Brazilian anesthesiologists: a nationwide cross-sectional survey

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Abstract

Background: Nitrous Oxide (N_2O) is a potent greenhouse gas with significant environmental impact and is currently the leading ozone depleting substance in use. Despite its long-standing role in anesthetic practice, data on N_2O use and the environmental awareness of Brazilian anesthesiologists are scarce. This study aimed to describe patterns of N_2O use and assess the level of awareness among anesthesiologists regarding its environmental impact.

Methods: A nationwide cross-sectional survey was conducted among anesthesiologists in a private Brazilian hospital network. The questionnaire addressed the frequency of N_2O use in adult and pediatric anesthesia, knowledge of its environmental effects, and attitudes toward its continued availability.

Results: Of 1,238 eligible anesthesiologists, 941 completed the survey (response rate 76%). Overall, 59.3% (n = 558) reported never using N_2O in adult patients, while 14.5% (n = 136) reported frequent or constant use. In pediatric patients, 27.5% (n = 259) reported never using N_2O, and 38.9% (n = 366) reported frequent or constant use. Eighty percent (n = 753) indicated a reduction in N_2O use since the beginning of their careers, and 34.5% (n = 325) were unaware of its contribution to climate change. Age and years of professional experience were directly proportional to N_2O use in adults ($p < 0.05$), while awareness of its environmental impact was inversely associated with use in pediatric cases ($p < 0.05$).

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Conclusion: The survey demonstrates a shift toward reduced N_2O use, particularly among younger anesthesiologists, although substantial use in adult practice remains. Persistent knowledge gaps highlight the importance of targeted education and policy interventions to mitigate environmental impact.

Introduction

The global average surface temperature has increased ~1.1°C compared to pre-industrial levels. Projections indicate that surpassing a 1.5°C increase by 2050 may significantly hinder global capacity to adapt to the impacts of climate change.[1,2] Within healthcare systems, inhaled anesthetics, particularly Nitrous Oxide (N_2O), are recognized as substantial contributors to greenhouse gas emissions. According to the Intergovernmental Panel on Climate Change (IPCC), N_2O is the third most prevalent anthropogenic greenhouse gas worldwide and has a global warming potential over 100 years (GWP_{100}) of 273, more than double that of sevoflurane (GWP_{100} = 130).[3] This high warming potential, combined with its status as the leading ozone-depleting agent currently in use, raises concerns about its unrestricted use in healthcare. Furthermore, N_2O stands as the leading ozone-depleting agent currently in use.[4]

Despite its environmental implications, the clinical use of N_2O in hospital settings is not comprehensively documented and understood, and its application spans various settings, from pediatric anesthesia to labor analgesia.[5] A longitudinal study conducted in a 1,300-bed tertiary UK hospital revealed a significant decrease in N_2O use over 12 years, yet a quarter of the physicians surveyed did not perceive it as a meaningful contributor to climate change.[6] In the Brazilian context, recent data from a quality improvement initiative conducted in two quaternary hospitals in São Paulo demonstrated that targeted educational and structural measures, such as disconnecting anesthesia workstations from the central N_2O pipeline, reduced anesthesia-related N_2O CO_2-equivalent emissions by 82.5% without adverse clinical effects.[7] This example shows that significant emission reduction is feasible, reinforcing the importance of understanding current clinical practice patterns and practitioners' level of awareness as a baseline for future interventions.

Recognizing anesthesiologists' awareness of the environmental effects of inhalational anesthetics, particularly N_2O, is crucial for guiding sustainable strategies, integrating eco-consciousness into medical training, and promoting routine emissions reporting.[8,9] Furthermore, mapping current patterns of N_2O usage can support targeted interventions aimed at reducing environmental footprint through evidence-based policy development.[10] We hypothesized that awareness among anesthesiologists regarding the environmental impact of N_2O remains limited and that clinicians with more years of clinical practice are more likely to continue its use. This could reflect a generational shift, with newer practitioners opting for alternatives to N_2O. This study aimed to characterize the utilization patterns of N_2O administration among anesthesiologists employed within a private hospital network in Brazil and to evaluate their understanding of its ecological impact.

Materials and methods

This was a nationwide, cross-sectional, observational web-based survey conducted across 72 private hospitals in Brazil between October 2 and November 2, 2024. At the time of data collection, no institutional policies or formal protocols restricting the use of N_2O were in place in the participating hospitals. The study employed a nonprobability census sampling approach that included all anesthesiologists actively employed within the network during the data collection period who had an active institutional registration, a valid institutional email address, and departmental affiliation. Anesthesiologists who did not meet these criteria (including inactive or non-affiliated professionals) were excluded. Heads of departments were contacted directly and asked to forward the survey link, distributed via institutional email, to all eligible anesthesiologists. This process resulted in a total of 1,238 invitations. Participation was entirely voluntary and anonymous, and the survey proceeded only after informed consent was obtained.

The questionnaire was distributed through the leads of anesthesiology teams and department heads at 72 hospitals located across all five Brazilian macro-regions. These institutions represented the full hospital network operated by the private healthcare group involved in the research. While the network has national coverage, it is part of the private sector and therefore the sample does not necessarily reflect the distribution of anesthesiologists in the entire Brazilian healthcare system.

Surveys were completed via Google Forms® (Google, California, USA), enabling respondents to answer at their convenience. No identifying personal data beyond hospital affiliation was collected aside from hospital name; no individual selection or sampling techniques were applied, promoting a comprehensive and inclusive collection of perspectives. Respondents were unable to modify their previous answers, and the survey could not be paused and resumed later. Only fully completed questionnaires were considered for the final analysis. The estimated questionnaire completion time was 3 minutes. To ensure data integrity, responses originated from duplicate IP addresses were evaluated and excluded when confirmed. Additionally, responses completed in under 30 seconds from a single IP address were considered non-engaged and were removed from the dataset.

Questionnaire design

The questionnaire was designed collaboratively by four anesthesiologists affiliated with the network's quality improvement department. Content validity was established through review by a panel of six anesthesiologists with expertise in clinical anesthesia, environmental sustainability, and quality improvement. The survey was then conducted with ten anesthesiologists from the same hospital network who were not included in the final analysis. This pilot test evaluated the clarity of questions, estimated completion time, and technical performance of the online survey tool. Minor adjustments were made before the final distribution. The survey was tested according to previously published guidelines.[11] To maintain objectivity and reduce interpretive bias, the questionnaire employed close-ended, multiple-choice formats.

Based on the American Society of Anesthesiologists' (ASA) guidelines on environmentally sustainable anesthesia[12] and other key publications addressing environmental sustainability in the perioperative setting,[1,13,14] we developed a structured survey aimed to explore the frequency and profile of N_2O utilization, as well as to assess the level of knowledge regarding its environmental impact. The frequency of N_2O use in inhalational anesthesia for both adult and pediatric patients was assessed using a five-point Likert scale with the options "Never", "Rarely", "Sometimes", "Often", and "Always". The final questionnaire comprised 17 items, divided into five sections: 1) Frequency of use in adult and pediatric patients (Questions 6–8); 2) Fresh gas flow determination during inhalational induction (Question 9); 3) Frequency with which respondents had observed gas flow meters left open after the completion of anesthesia and when the anesthesia workstation was no longer in use (e.g., post-transport, during room turnover, or prior to initiating a subsequent anesthesia) (Question 10); 4) Perception of N_2O environmental impact, specifically related to global warming and ozone depletion (Questions 11–14); 5) Patterns in N_2O clinical use and the underlying motivations for its reduction or discontinuation (Questions 15–17). The questionnaire was developed in Portuguese (Supplementary Tables 1–2). The primary endpoint was the self-reported frequency of N_2O use in adult and pediatric anesthesia. Secondary endpoints included awareness of N_2O's environmental impact and attitudes toward its continued availability. Potential harm and/or adverse events were not applicable to this survey-based study.

This study followed the Checklist for Reporting Results of Internet E-Surveys (CHERRIES),[15] the EQUATOR-endorsed guideline for the design and reporting of web-based surveys (see Supplementary Material for the completed checklist). All procedures involving human participants were conducted in compliance with the ethical standards established by the institutional and national research committees, as well as the principles of the Declaration of Helsinki. This study was approved by the Institutional Research Ethics Committee (Protocol n° 7,023,106; CAAE 82170024.0.0000.0087), and the approval can be verified through the public registry at Plataforma Brazil: https://plataformabrasil.saude.gov.br/visao/publico/indexPublico.jsf.

Statistical analysis

To ensure that the number of responses would be sufficient for the planned analyses, we calculated a minimum required sample size of 294 participants using the formula $n = Z^2 \times p \times (1 - p) / E^2$, where n represents the sample size, Z is the Z score corresponding to a 95% confidence level, p is the estimated population proportion, and E is the margin of error set at 5%. Anticipating an overall survey response rate between 40%–60% (based on previous institutional survey experience and published literature on physician survey participation), we invited all eligible professionals (n = 1,238). Only fully completed questionnaires were included in the final analysis. Incomplete or partially completed questionnaires were excluded from all analyses; therefore, no imputation for missing data was performed. Responses completed in less than 30 seconds from the same IP address were considered non-engaged and excluded from the dataset. A total of six questionnaires met these criteria and were removed from the analysis.

Data normality distribution was assessed using the Shapiro-Wilk test. Categorical variables were analyzed using the Chi-Square test to compare proportions. Continuous variables were expressed as means and standard deviations for normally distributed data, or as medians with interquartile ranges otherwise. Non-parametric data were analyzed using the Kruskal-Wallis test for comparisons involving three or more categories, followed by Dunn's post hoc method for multiple comparisons when $p < 0.05$, and the Mann-Whitney U test for comparisons between two categories. Adjusted associations between the self-reported frequency of N_2O administration in adult and pediatric anesthesia ("occasionally", "frequently" or "always") and clinician characteristics were quantified as Odds Ratios (OR) with 95% Confidence Intervals (95% CI). Clinician characteristics included age, years of professional experience, geographic region, and the respondent's belief that N_2O contributes to climate change. Multivariable logistic regression was performed with simultaneous entry of all covariates. A 95% CI and p-value < 0.05 represented statistical significance. All analyses were conducted using R software version 3.4.4 (R Foundation for Statistical Computing, Austria).

Results

All 72 hospitals contacted agreed to participate in the survey, and a total of 941 anesthesiologists answered the questionnaire, yielding a completion rate of 76%. The flow of participants, including invitations, exclusions, and the final analytical sample, is shown in Figure 1. The median age of

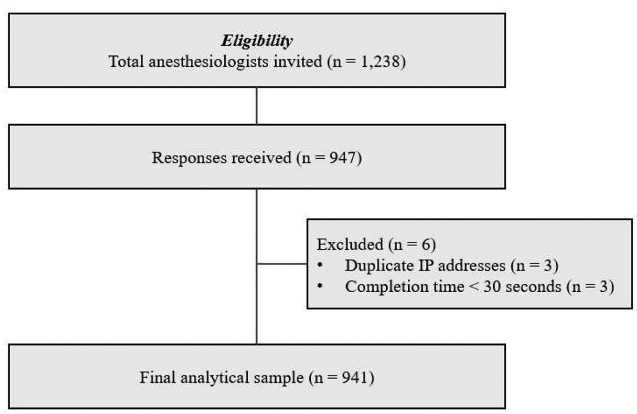

Figure 1 Study flow diagram showing the number of anesthesiologists invited, responses received, exclusions, and the final analytical sample.

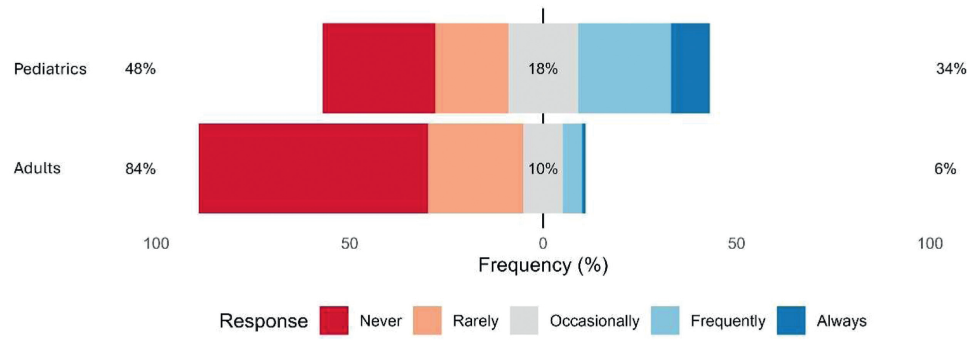

Figure 2 Distribution of respondents' reported frequency of N_2O use in adults and pediatric patients.

the participants was 40 (35–49) years, with a median time of 10 (5–21) years since completing medical residency (Supplementary Figs. 1–2).

A five-point Likert scale was applied to assess the frequency of N_2O use in inhalational anesthesia for both adult and pediatric patients. Regarding adult patients, 59.3% (n = 558) of respondents reported never using N_2O, and 5.8% (n = 55) reported frequent use (Fig. 2). Age and years of experience were directly proportional to the frequency of N_2O use in adult patients ($p < 0.05$; Table 1). There was a significant difference in the proportion of responses indicating the use of N_2O among adult patients by geographic location, with the Southeast (14.2%) and South (14.9%) regions reporting the highest rates of "always", "frequently", and "occasionally" use (p = 0.009) (Fig. 3; Supplementary Table 3). Among those who reported N_2O use in adult patients (n = 383), 15.1% (n = 58) indicated its use for inhalational sedation, and 3.4% (n = 13) for labor analgesia.

The use of N_2O in pediatric anesthesia was reported by 34% (n = 320) of participants (Fig. 2). Unlike in adult practice, neither age nor professional experience were associated with N_2O use in pediatric patients ($p > 0.05$; Table 1). There was no difference in the frequency of N_2O use in pediatric patients across geographic regions (p = 0.38).

Regarding the method for defining Fresh Gas Flow (FGF) during inhalational induction, FGF based on patient weight ($\sim$120 mL/kg/min^{-1}) was reported by 35.9% (n = 338), while 27% (n = 334) indicated using an FGF of 10 L/min or more, regardless of the patient's weight (Table 1). Thirty seven percent (n = 349) based their FGF on clinical assessment at the time of induction. At the conclusion of anesthesia, the practice of verifying whether the gas flow meter has been properly shut off plays a critical role in minimizing wastage, whether oxygen or inhalational agents. Respondents were inquired about how often they observed gas flow meters left open after anesthesia had ended and when the anesthesia workstation was no longer in use (e.g., post-transport, room turnover, or prior to subsequent anesthesia). Twenty-nine percent (n = 273) of anesthesiologists reported frequently or always witnessing gas flow meters left open and unused, whereas only 5.8% (n = 55) stated they had never witnessed this practice.

In response to questions about the environmental consequences of inhalational agents such as N_2O and their contribution to climate change through global warming, 34.5% (n = 325) reported being unaware of any relationship between anesthetic technique and climate change. Seasoned anesthesiologists were more likely to be unaware of this link ($p < 0.05$). Only 35.8% (n = 337) correctly identified that N_2O persists in the environment for over 100 years (Table 2).

When comparing current practices with those at the beginning of their careers, 80% (n = 755) reported a reduction in the use of N_2O over time. Half of the respondents, 50.7% (n = 477), stated that N_2O should not be freely or readily available (Table 2). When asked about future use, 48% (n = 452) of respondents either reported not currently using N_2O or indicated they intended to discontinue its use in the short term. In contrast, 27.8% (n = 262) stated they intended to continue using it. There was no significant association between these responses and either age or years of professional experience ($p > 0.05$).

The main reasons cited for reducing or discontinuing N_2O use were increased incidence of nausea and vomiting (51.9%, n = 489), greater adoption of Total Intravenous Anesthesia (TIVA) (54.2%, n = 510), respiratory adverse effects such as hypoxia and atelectasis (21.1%, n = 199), its contribution to global warming and ozone layer depletion (32.2%, n = 303), pollution and occupational exposure in the operating room (37.0%, n = 349), and the perception that its clinical benefit is negligible (21.3%, n = 201). Most respondents (70%, n = 657) indicated that the withdrawal of N_2O would not impact their anesthetic technique. There was no significant association between this perception and respondents' age or years of professional experience regarding the impact on their anesthetic technique ($p > 0.05$; Table 2).

In the multivariable logistic model constructed to examine determinants of self-reported N_2O use ("occasionally", "frequently", or "always"), age $\geq$ 50 years remained independently associated with N_2O use in adult patients (adjusted OR = 2.99, 95% CI 1.95–4.59) (Table 3). By contrast, the conviction that N_2O aggravates climate change showed an inverse relation with use in adults (adjusted OR = 0.42, 95% CI 0.29–0.61) and constituted the sole significant predictor in pediatric anesthesia (adjusted OR = 0.41, 95% CI 0.31–0.54). Years of professional experience and geographic region did not achieve significance in either model.

Discussion

This study characterized patterns of N_2O use in anesthesia and identified gaps in anesthesiologists' awareness of its environmental impact. Eighty percent of respondents

Table 1 Frequency and profile of nitrous oxide usage, and assessment of anesthesiologists' knowledge regarding the environmental impact of this gas in a network of 72 private hospitals in Brazil: Differences by age (years) and years of professional experience since completion of medical residency in anesthesiology.

Variable	Overall		Age (years)		Years of experience	
	n	%	Median [IQR 25–75]	p-value	Median [IQR 25–75]	p-value
Frequency of N_2O use in adults[a]				< 0.001		< 0.001
Never	558	59.3	39 [34 – 45.75]		9 [4 – 17]	
Rarely	231	24.6	41 [35 – 49.5]		12 [5 – 21.5]	
Occasionally	97	10.3	40 [36 – 52]		10 [6 – 23][c]	
Frequently	46	4.9	52 [42.75 – 58.75]		25 [12.25 – 30]	
Always	9	1.0	55 [51 – 56][c]		30 [22 – 30][c]	
Frequency of N_2O use in pediatrics[a]				0.09		0.07
Never	274	29.1	42 [36 – 52]		12 [5 – 24]	
Rarely	177	18.8	39 [35 – 46]		9 [4 – 17]	
Occasionally	170	18.1	39 [33.25 – 45.75]		10 [4 – 18.75]	
Frequently	226	24.0	40 [35 – 47]		10 [5 – 19]	
Always	94	10.0	41 [35 – 52]		10 [5 – 26.25]	
FGF induction method[a]				< 0.001		< 0.001
Patient weight (≈120 mL/kg/min)	338	35.9	42 [36 – 51]		12 [5 – 24.75]	
FGF of 10 L/min or more	254	27.0	38 [33.25 – 45][c]		8 [4 – 16][c]	
Clinical assessment	349	37.1	40 [35 – 49]		10 [5 – 21]	
Gas flow shutdown frequency[a,d]				0.02		0.08
Never	55	5.8	44 [40 – 54]		14 [8 – 26.5]	
Rarely	286	30.4	41 [35 – 50.75]		11 [5 – 21.75]	
Occasionally	327	34.7	40 [35 – 47]		9 [4 – 20]	
Frequently	262	27.8	40 [35 – 46.75]		10 [5 – 20]	
Always	11	1.2	42 [33 – 52]		15 [4.5 – 19]	
N_2O climate change Belief[b]				0.01		0.01
No	325	34.5	41 [36 – 51]		12 [5 – 23]	
Yes	616	65.5	40 [34 – 48]		10 [4 – 20]	
Respondents N_2O elimination time[a]				<0.001		< 0.001
1 year	228	24.2	45 [38 – 53.25]		16 [6.75 – 27]	
5 years	149	15.8	40 [35 – 48]		9 [4 – 18]	
15 years	134	14.2	38 [34.25 – 42][c]		8 [4 – 14][c]	
50 years	93	9.9	37 [32 – 42][c]		8 [3 – 15][c]	
Above 100 years	337	35.8	40 [35 – 48]		10 [5 – 21]	

[a] Kruskal-Wallis test.
[b] Mann-Whitney U test.
[c] Post hoc multiple comparisons using Dunn's method FGF: Fresh Gas Flow.
[d] Respondents were inquired about the frequency with which they had observed gas flow meters left open after the completion of anesthesia and when the anesthesia workstation was no longer in use (for instance, following patient transport, during room preparation, or prior to initiating preparations for subsequent anesthesia).

reported a reduction in use since the beginning of their careers, and nearly half expressed reservations about its unrestricted availability. In contrast, 34.5% of anesthesiologists were unaware of its role in climate change. These patterns may be related to differences in training exposure, evolving clinical preferences, or increasing awareness of sustainability issues in more recent generations of practitioners. Given the cross-sectional nature of this study, these factors should be interpreted as possible contributors rather than causal determinants.

Understanding these usage patterns is essential for informing strategies aimed at sustainable environmental impact. Our results support the development of targeted practice protocols aimed at curtailing N_2O use, particularly in cases where its clinical benefits are outweighed by alternative anesthetic agents/techniques. Additionally, reports of frequent gas flow meter misuse after procedures (29%) suggest inefficiencies that warrant attention, as they may result in unnecessary emissions and resource waste.[16] If N_2O consumption is minimal and not critical for clinical practice, healthcare leaders should reassess the need to maintain N_2O supply infrastructure and focus on interventions aimed at optimizing consumption patterns.[17,18]

In a Brazilian quality improvement initiative for adult patients, baseline data over the 16-week pre-intervention period indicated an average N_2O usage rate of 11%, decreasing to 2% post-intervention.[7] Considering these results, the use of N_2O in adult patients remains a prevalent practice, and a cultural shift is necessary to reduce its usage in more restricted contexts, such as the inhalational induction of pediatric patients.[6,8] In pediatric anesthesia, targeted quality improvement interventions have shown substantial

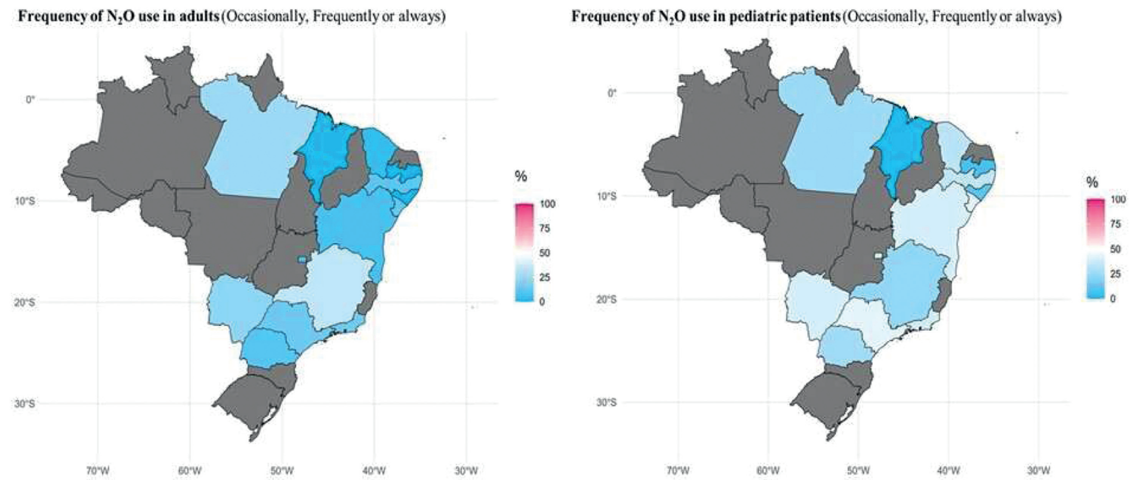

Figure. 3 Heatmap of geographical distribution of respondents by frequency of N_2O use in adults and pediatric patients (occasionally, frequently, or always).

Table 2 Longitudinal changes in nitrous oxide usage, access to N_2O in operating rooms and trends in N_2O use, in a network of 72 private hospitals in Brazil: differences by age and years of professional experience since completion of anesthesia residency.

Variable	Overall		Age (Years)		Years of experience	
	n	%	Median [IQR 25–75]	p-value	Median [IQR 25–75]	p-value
Longitudinal N_2O usage change[a,c]				< 0.001		< 0.001
Maintaining	186	19.8	37 [32 – 43]		6 [3 – 13]	
Reduction	755	80.2	41 [36 – 50]		12 [5.5 – 22]	
N_2O free access in operating room[a]				0.93		0.45
No	477	50.7	41 [35 – 47]		10 [5 – 20]	
Yes	464	49.3	40 [34.75 – 50.25]		10 [4 – 23]	
Trend in the use of N_2O[b]				0.05		0.14
Do not use at all	249	26.5	41 [35 – 50]		11 [5 – 22]	
Consider eliminating	203	21.6	42 [36 – 50]		11 [5 – 22]	
Consider reducing	227	24.1	39 [34 – 46.5]		10 [4 – 18]	
Consider maintaining	262	27.8	40 [35 – 49]		10 [4 – 21]	
Anesthetic technique impact from N_2O removal[a]				0.37		0.33
No	657	70.0	41 [35 – 49]		10 [5 – 21]	
Yes	284	30.0	40 [35 – 48.25]		10 [4 – 20]	

[a] Mann-Whitney U test.
[b] Kruskal-Wallis test.
[c] Comparing the current period with the period since the beginning of their training as anesthesiologists.

environmental benefits. In a 20-month project involving over 33,000 inhalational inductions, reducing N_2O use from 80% to less than 20% and lowering FGF by 28% was achieved through education, expert engagement, and visual reminders, without affecting induction times or patient behavior.[8] This suggests that even minor regulatory or logistical barriers could substantially reduce N_2O use.[5,19]

The practice of using high FGF during inhalational induction was also analyzed. High FGF is often employed to hasten induction or to compensate for mask leaks during facemask ventilation. However, this practice results in the consumption of large quantities of volatile agents, almost all of which are wasted directly into the environment.[20] Strikingly, less than 40% of anesthesiologists regulate FGF based on the patient's weight, even though exceeding the minute-ventilation does not meaningfully accelerate induction and leads to significant volatile agent consumption.[21] Since minute-ventilation is correlated with the patient's weight, the Society for Pediatric Anesthesia (SPA) recommends using a weight-based minimum safe and effective FGF of 0.15 L/min/kg during inhalational induction.[22] This recommendation includes a safety margin to ensure no rebreathing and accounts for differences between anesthesia delivery systems and individual patient variation.[8] However, our data demonstrated that pediatric anesthesiologists often used fixed high FGF (e.g., 10 L/min of oxygen and N_2O, with or without sevoflurane), regardless of patient's size, contradicting best practices and exacerbating environmental impact. Coupled with prior studies indicating that elevated FGF during induction is correlated with increased sevoflurane consumption and higher FGF levels throughout cases, these results underscore the importance of adopting an

Table 3 Adjusted odds ratios (95% CI) from multivariable logistic regression of clinician characteristics associated with self-reported nitrous oxide administration ("occasionally", "frequently" or "always") in adult and pediatric anesthesia.

Characteristics	Self-reported nitrous oxide use ("occasionally" "frequently" or "always")						
	Overall n (%)	No n (%)	Yes n (%)	Crude OR (CI 95%)	p-value	Adjusted OR (CI 95%)	p-value
Adult patients							
Age							
Up to 40 years	468 (50.1)	409 (52.2)	59 (38.8)	1		1	
41 to 49	240 (25.7)	213 (27.2)	27 (17.8)	0.88 (0.53 – 1.41)	0.60	0.97 (0.57 – 1.60)	0.90
≥ 50 years	227 (24.3)	161 (20.6)	66 (43.4)	2.84 (1.91 – 4.23)	< 0.001	2.99 (1.95 – 4.59)	< 0.001
Years of experience							
Less than 10 years	58 (6.2)	49 (6.3)	9 (5.9)	1		1	
10 years or more	877 (93.8)	734 (93.7)	143 (94.1)	1.06 (0.53 – 2.35)	0.87	0.75 (0.36 – 1.74)	0.47
Geographic Region							
North	4 (0.3)	3 (0.3)	1 (0.7)	1		1	
Northeast	334 (25.7)	309 (26.9)	25 (16.5)	0.24 (0.03 – 5.00)	0.22	0.19 (0.02 – 4.38)	0.19
Central-West	169 (13)	156 (13.6)	13 (8.6)	0.25 (0.03 – 5.25)	0.24	0.31 (0.03 – 7.29)	0.37
Southeast	767 (59)	658 (57.3)	109 (71.7)	0.50 (0.06 – 10.10)	0.54	0.50 (0.04 – 11.09)	0.57
South	27 (2.1)	23 (2)	4 (2.6)	0.52 (0.05 – 12.00)	0.60	0.56 (0.04 – 14.44)	0.67
N_2O Climate Change Belief							
No	324 (34.7)	244 (31.2)	80 (52.6)	1		1	
Yes	611 (65.4)	539 (68.8)	72 (47.4)	0.41 (0.29 – 0.58)	< 0.001	0.42 (0.29 – 0.61)	< 0.001
Pediatric patients							
Age							
Up to 40 years	468 (50.1)	210 (46.9)	258 (53)	1		1	
41 to 49	240 (25.7)	124 (27.7)	116 (23.8)	0.76 (0.56 – 1.04)	0.08	0.78 (0.56 – 1.08)	0.13
≥ 50 years	227 (24.3)	114 (25.5)	113 (23.2)	0.81 (0.59 – 1.11)	0.18	0.76 (0.54 – 1.07)	0.11
Years of experience							
Less than 10 years	58 (6.2)	25 (5.6)	33 (6.8)	1		1	
10 years or more	877 (93.8)	423 (94.4)	454 (93.2)	0.81 (0.47 – 1.39)	0.44	0.93 (0.52 – 1.63)	0.80
Geographic Region							
North	4 (0.3)	3 (0.4)	1 (0.2)	1		1	
Northeast	334 (25.7)	218 (26.8)	116 (23.8)	1.60 (0.20 – 32.47)	0.68	1.66 (0.15 – 37.61)	0.68
Central-West	169 (13)	113 (13.9)	56 (11.5)	1.49 (0.19 – 30.43)	0.73	2.05 (0.18 – 46.89)	0.57
Southeast	767 (59)	464 (57)	303 (62.2)	1.96 (0.25 – 39.70)	0.56	2.85 (0.25 – 64.23)	0.40
South	27 (2.1)	16 (2)	11 (2.3)	2.06 (0.23 – 44.77)	0.55	2.78 (0.21 – 69.59)	0.44
N_2O Climate Change Belief							
No	324 (34.7)	110 (24.6)	214 (43.9)	1		1	
Yes	611 (65.4)	338 (75.5)	273 (56.1)	0.42 (0.31 – 0.55)	< 0.001	0.41 (0.31 – 0.54)	< 0.001

CI, Confidence intervals; OR, odds ratio.

optimized and environmentally sustainable approach to anesthetic management.[14,23]

Data from Italy align with our observations, showing a gradual reduction in the use of inhalational agents and a persistent lack of awareness of environmental issues among anesthesiologists.[24] Indeed, the majority of anesthesiologists stated that TIVA could replace anesthetic gases in more than 40% of cases, while only 5% believed this could happen in less than 20% of cases.[24] Similarly, 65% of anesthesiologists were partially or completely unaware of the environmental impact of anesthetic gases, and the use of high FGF remains a common practice in inhalational anesthesia.[24] Similar to the reduction observed in our study, a longitudinal evaluation in a 1,300-bed tertiary hospital in the United Kingdom demonstrated a marked decline in N_2O use over 12 years, indicating that the decrease in N_2O utilization is not limited to Brazil; however, in that UK cohort, one quarter of physicians did not recognize it as a significant contributor to climate change.[6]

Senior anesthesiologists were more likely to report frequent N_2O use in adult patients, although no significant generational difference was observed in pediatric use. There were no differences in age or professional experience regarding the perception of its impact on anesthetic technique or the tendency to reduce its use. This suggests that, despite the historical use of N_2O among more senior anesthesiologists, they may be open to reducing its utilization, with unwanted clinical effects being the main driver for limiting its use. This contrasts with results from the UK, where environmental impact was the primary reason for reducing N_2O use.[6] Such differences imply that "green anesthesia" remains in early stages in Brazil, despite global acknowledgement of climate change as "the biggest threat to global health in the 21st century".

Our results delineate a marked generational gradient in practice patterns: anesthesiologists aged ≥ 50-years were nearly three times more likely to administer N_2O to adult patients, whereas acknowledging its climate impact was inversely associated with use and remained the sole significant determinant in pediatric anesthesia. One plausible explanation is that sustainable practice is still insufficiently embedded in medical training: the environmental knowledge gap among senior educators hampers the transmission of sustainability principles to trainees, creating a persistent barrier to behavior change. Accordingly, environmental stewardship should be formally integrated into residency curricula and continuing professional development for practicing anesthesiologists, as multiple studies across different countries have already advocated.[24,25]

Several factors may influence the discontinuation of N_2O use in Brazil, operating as either barriers or drivers of change. Cultural barriers include the long-standing tradition of using N_2O for pediatric inhalational induction and the absence of environmental sustainability as a structured component of anesthesiology training. Institutional barriers involve the persistence of central pipeline supply systems (which are often faulty/leaky) and the lack of infrastructure modifications needed to reduce systemic losses. Educational barriers stem from limited exposure to concepts of sustainable anesthesia and occupational safety related to anesthetic gases during both residency and continuing professional development. On the other hand, important drivers for reducing N_2O use include the growing global and national emphasis on climate change mitigation, the increasing availability and familiarity with TIVA, and awareness of the occupational hazards associated with waste anesthetic gases. Evidence from successful Brazilian initiatives, such as the 82.5% reduction in N_2O emissions achieved in two quaternary hospitals through targeted education and pipeline disconnection, reinforces the feasibility of large-scale change.[7] These national experiences, in line with the global trend toward N_2O phase-out, highlight that meaningful reductions are possible when clinical engagement is combined with infrastructure and policy interventions.[7,9,26,27]

Despite consistent evidence that occupational exposure to inhalational anesthetics, particularly in operating rooms without active scavenging systems, exceeds international safety limits and poses health risks,[28,29] only 37% of respondents in our study cited pollution or occupational exposure as a reason to reduce N_2O use. This underestimation is particularly concerning since longitudinal evidence shows that such exposures are not merely theoretical risks.[30] A prospective study evaluating young physicians before, during, and at the end of their medical residency demonstrated that working in unavenged operating rooms leads to substantial exposure to inhalational anesthetics, resulting in lipid and protein oxidation, oxidative DNA damage, impairment of antioxidant systems, modulation of gene expression involved in DNA repair, and measurable genotoxic effects.[31] Our results suggest a significant gap in awareness or a tendency among anesthesiologists to underestimate the occupational hazards associated with waste anesthetic gases in the operating room and/or global environment.

The results of this study have relevant implications for policy, education, and clinical practice in Brazil. In the educational sphere, environmental stewardship and occupational safety related to anesthetic gases should be incorporated into undergraduate, residency, and continuing medical education curricula to build awareness from the earliest stages of training. In clinical practice, dissemination of best practices for optimizing FGF, greater adoption of TIVA when clinically appropriate, and institution-led quality improvement programs can collectively contribute to reducing N_2O emissions. Aligning these strategies with international sustainability goals offers a pathway for Brazilian anesthesiology to achieve measurable environmental impact reduction without compromising patient care.[12,24,25]

Contemporary guidance from professional societies and health systems increasingly supports the reduction of nitrous oxide use and the decommissioning of centralized piped N_2O systems, primarily due to their disproportionate contribution to emissions through chronic leakage. The World Federation of Societies of Anaesthesiologists and partner organizations have endorsed principles of environmentally sustainable anesthesia that include minimizing or eliminating routine N_2O use, optimizing fresh gas flows, and addressing avoidable infrastructural losses.[1] More recent consensus from the United Kingdom and Ireland recommend the removal of piped N_2O manifolds and transition to point-of-use cylinders, driven by data indicating that a substantial proportion of N_2O supplied via pipelines may be lost to leakage before reaching patients, thereby generating emissions with minimal clinical benefit.[6,18] Similar action plans and toolkits from NHS systems and other jurisdictions highlight N_2O mitigation as a priority, emphasizing leak detection, decommissioning of underused manifolds, and alignment with net-zero strategies.[17,32] These positions are consistent with analyses showing that N_2O is a long-lived greenhouse gas and a leading ozone-depleting substance, and that infrastructural waste rather than conscious clinical use can account for a large share of its footprint.[4] In this context, the reduction in self-reported N_2O use observed among Brazilian anesthesiologists – particularly the limited perceived dependence on N_2O for routine practice – supports the feasibility of targeted institutional policies and infrastructure reviews aimed at rationalizing or discontinuing N_2O supply where clinically appropriate, while maintaining patient safety.

Our results should also be interpreted in light of the evolving Brazilian regulatory framework for medical gases. ANVISA RDC n° 870/2024 and Normative Instruction n° 301/2024, n° 301/2024 classify medicinal gases, including N_2O, as regulated medicinal products and establish contemporary requirements for notification, registration, and quality assurance, with defined implementation timelines.[33,34] Within this framework, hospitals are expected to ensure that centralized medical gas systems and gas mixers comply with technical standards such as ABNT NBR 12188 (centralized medical gas pipeline systems) and ABNT NBR 15882 (oxygen-nitrous oxide gas mixers). Decisions to maintain, rationalize, or decommission centralized N_2O infrastructure should follow these standards, be guided by documented low clinical demand, robust safety assessments, and leak prevention, and be integrated into broader environmental sustainability and patient safety strategies.[35,36] While our survey did not directly audit regulatory compliance or engineering practices, the observed trend toward reduced N_2O use among Brazilian anesthesiologists is consistent with and supportive of this regulatory direction.

This study has limitations. First, the web-based design and voluntary participation introduce potential selection bias, as the sample was drawn from a convenience census of eligible anesthesiologists and relied on self-reporting, which may not reflect actual clinical behavior. Second, although the sample size calculation was appropriately performed and largely exceeded, with 941 completed questionnaires and a high response rate of 76%, the study employed a nonprobability sampling approach restricted to anesthesiologists from a private hospital network in Brazil. This may limit the generalizability of the results to other healthcare systems, including public hospitals and rural settings. Third, the questionnaire was not formally validated through psychometric testing, which may affect the reliability and reproducibility of the results, although content review by experts was performed before distribution. Fourth, social desirability bias may have influenced responses, particularly for items related to environmentally responsible behaviors. Fifth, the absence of objective data or verification regarding the actual use of N_2O limits the ability to validate self-reported information. Sixth, the study did not collect information on the surgical case mix of each participating hospital, which could influence N_2O usage patterns, as hospitals with surgical profiles less likely to require N_2O, such as those without pediatric, obstetric, or specific inhalational sedation cases, might have contributed disproportionately to lower reported usage rates. Lastly, the cross-sectional design and absence of longitudinal follow-up prevent the assessment of temporal trends and causality, and other potentially relevant variables, such as institutional policies, availability of TIVA, or local anesthetic protocols, were not examined.

Conclusion

This national survey identified reduced N_2O use among younger anesthesiologists, suggesting evolving practice patterns potentially driven by changes in training, increased familiarity with alternative anesthetic techniques, and heightened awareness of occupational and environmental considerations. However, a substantial proportion of practitioners, particularly older anesthesiologists, remain unaware of N_2O's long atmospheric lifetime and its role in global warming. Addressing this knowledge gap through targeted educational strategies, coupled with evidence based institutional and national policies, could support the optimization of N_2O use while reducing its environmental footprint. The fact that half of the respondents questioned its continued unrestricted availability underscores the opportunity for policy makers to act. Future research using validated instruments and nationally representative samples will be essential to confirm these results and inform sustainable anesthesia practices in Brazil and beyond.

Conflicts of interest

The authors declare no conflicts of interest and confirm that no artificial intelligence tools were used in the conception, analysis, or preparation of this manuscript.

Data availability statement

The anonymized dataset analyzed during the current study is available from the corresponding author upon reasonable request.

Disclosure statement

This study did not receive or require any funding sources. The authors have no commercial or non-commercial affiliations representing potential conflicts of interest, nor do they have any associations with consultants of any type.

Ethics statement

This investigation was approved by the São Luiz & Rede D'Or Hospitals Research Ethics Committee (Protocol number 7,023,106; CAAE 82170024.0.0000.0087). The approval can be verified through the official public registry at Plataforma Brazil: https://plataformabrasil.saude.gov.br/visao/publico/indexPublico.jsf.

Previous presentation in conferences

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Declaration of generative AI in scientific writing

The authors did not use generative artificial intelligence in the preparation of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844739.

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ORIGINAL INVESTIGATION

Airway management and outcomes in surgical drainage of severe odontogenic infections: a retrospective cohort study

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Abstract
Background: Severe odontogenic infections requiring surgical drainage pose significant airway management challenges. This study aimed to compare perioperative characteristics and clinical outcomes between patients managed with conventional laryngoscopy versus awake fiberoptic intubation, to identify factors associated with the selection of airway management technique, and to determine predictors of hospital length of stay.
Methods: This single-center retrospective study included 85 adult patients who underwent surgical drainage of severe odontogenic infections under general anesthesia between 2015 and 2024. The primary objective was to identify factors associated with awake fiberoptic intubation selection. Secondary objectives included comparison of perioperative outcomes and identification of predictors of hospital discharge. Multivariable logistic regression and Cox proportional hazards modeling were used.
Results: Of 85 patients, 60% were managed with AFOI. Multivariable analysis identified trismus (OR = 6.67, 95% CI 1.53, 39.53, p = 0.010) and higher BMI (OR = 1.15, 95% CI 1.03, 1.33, p = 0.013) as

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independent predictors of AFOI selection. AFOI patients experienced more complex postoperative courses, with intraoperative tracheostomy, ICU admission, and septic shock occurring exclusively in this group. Spontaneous ventilation postoperatively was associated with earlier discharge (HR = 2.14, 95% CI 1.23, 3.73, p = 0.007), while septic shock (HR = 0.26, 95% CI 0.07, 0.91, p = 0.036) and lower BMI (HR = 0.95, 95% CI 0.90, 1.00, p = 0.040) were associated with delayed discharge.

Conclusion: AFOI was preferentially selected for anatomically complex odontogenic infections based on objective criteria, particularly trismus and elevated BMI. The ability to achieve spontaneous ventilation postoperatively serves as a key prognostic indicator, while septic shock is strongly associated with prolonged recovery. These findings support evidence-based airway management protocols and early identification of high-risk patients to optimize outcomes in this challenging population.

Introduction

Deep neck space infections of odontogenic origin, a severe manifestation of dental pathology, can rapidly disseminate through fascial planes, potentially resulting in life-threatening complications, including airway compromise, sepsis, and even death.[1-3] Surgical drainage of these abscesses under general anesthesia introduces significant anesthetic challenges. Common presentations include trismus, floor-of-mouth edema, pharyngeal swelling, and distorted airway anatomy, all of which significantly complicate airway management.[4,5]

Several airway management strategies have been described for this patient population, ranging from conventional direct laryngoscopy to video laryngoscopy, Awake Fiberoptic Intubation (AFOI), and tracheostomy under local anesthesia.[6,7] However, the optimal approach remains unresolved, with each technique carrying unique benefits and risks in the setting of distorted anatomy and potentially compromised airways.

Current international guidelines distinguish between approaches for anticipated and unanticipated difficult airways, providing structured algorithms to guide decision-making.[8,9] For patients with severe odontogenic infections, where a difficult airway is often anticipated, these guidelines suggest considering awake techniques or securing the airway before induction when appropriate. However, the final approach must be tailored to each patient's clinical presentation.

The incidence of severe odontogenic infections requiring hospital admission has been increasing in developed countries,[10] with these infections remaining clinically challenging despite modern treatment.[11] The multifaceted nature of these infections demands a comprehensive understanding of how patient characteristics, anatomical spread patterns, and airway management decisions interact to influence clinical outcomes.[12,13]

While existing literature provides insights into surgical management of these infections, critical knowledge gaps persist regarding the factors that guide airway management decisions and their downstream effects on patient outcomes and hospital resource utilization. In this descriptive, exploratory study, we present a single-center experience aimed at describing the perioperative characteristics and outcomes of patients managed with different airway techniques, identifying factors influencing the choice of airway management, and determining predictors of hospital length of stay, rather than evaluating the causal impact of airway management strategy on clinical outcomes.

Methods

Ethics, design, and settings

This retrospective cohort study was conducted at Rabin Medical Center, Beilinson Hospital, Israel. Ethical approval (0202-22-RMC) was provided by the Institutional Review Board (Chairperson Prof. Ran Tur-Kaspa). This manuscript adheres to the STROBE statement (Supplementary Table S3).[14]

Study population

All adult patients (≥ 18 years) who underwent surgical drainage of severe odontogenic infections under general anesthesia between January 2015 and December 2024 were consecutively included. Exclusion criteria included arrival at the operating room already intubated and mechanically ventilated, awake tracheostomy before anesthesia induction, and substantially incomplete anesthesia or surgical documentation.

Anesthetic and surgical care

All patients underwent comprehensive preoperative anesthesia evaluation, with particular emphasis on airway assessment, given the presence of severe odontogenic infection. Preoperative airway evaluation included assessment for trismus, floor-of-mouth involvement, pharyngeal edema, and overall infection spread pattern. Standard monitoring, according to the American Society of Anesthesiologists (ASA) guidelines, was implemented for all patients, including electrocardiography, non-invasive blood pressure, pulse oximetry, capnography, and temperature monitoring. Additional monitoring modalities were applied based on individual patient comorbidities and clinical presentation.

Patients were managed with one of two airway approaches: laryngoscopy after induction (laryngoscopy group) or AFOI before induction (AFOI group). The airway management strategy was determined by the attending anesthesiologist based on preoperative assessment and clinical judgment rather than a formal institutional protocol, with special consideration given to the extent and location of infection, presence of trismus, and anticipated surgical approach.

For patients in the laryngoscopy group, anesthesia was induced with intravenous agents, and neuromuscular blocking agents were administered to facilitate endotracheal intubation. The choice between direct laryngoscopy and video laryngoscopy was based on anesthesiologist preference and anticipated difficulty.

For patients in the AFOI group, topical anesthesia of the airway was achieved using lidocaine spray and/or nebulization. Conscious sedation was provided with various combinations of midazolam, fentanyl, ketamine, and/or propofol, carefully titrated to maintain spontaneous ventilation and patient cooperation while ensuring comfort. Nasotracheal intubation was preferred for most AFOI cases to optimize surgical access.

Following successful airway securing in both groups, anesthesia was maintained with inhalational agents (typically isoflurane or sevoflurane) with or without nitrous oxide, supplemented with opioid analgesics as needed. Fluid management, antibiotic administration, and additional medications were provided according to standard institutional protocols.

Maxillofacial surgeons performed surgical drainage following standard procedures for abscess treatment. Intraoperative tracheostomy was performed when deemed necessary based on the extent of infection and anticipated postoperative airway compromise. Decisions regarding postoperative airway management, including extubation versus continued mechanical ventilation, were made collaboratively by the anesthesia and surgical teams based on the extent of infection, degree of airway edema, and overall patient condition.

Postoperatively, patients were transferred to the Post-Anesthesia Care Unit (PACU) and monitored according to institutional protocols. Patients requiring continued airway support or hemodynamic monitoring were admitted to the Intensive Care Unit (ICU). All patients received appropriate antibiotic therapy, analgesics, and supportive care throughout their hospital stay.

Study outcomes

The primary objective was to identify factors associated with the selection of AFOI versus conventional laryngoscopy. Secondary objectives were to compare perioperative characteristics and clinical outcomes between groups, and to determine predictors of hospital length of stay.

Measurements and data collection

Data were extracted from electronic medical record systems by trained investigators with domain expertise: anesthesia and operative data were extracted from Metavision (iMDsoft, Israel) by two anesthesiologists, and clinical and surgical data from Chameleon™ (Elad Health, Israel) by two oral and maxillofacial surgeons. Data accuracy was verified through cross-checking between investigators within each domain. Demographic data included age, gender, Body Mass Index (BMI), ASA physical status, active smoking status, and relevant comorbidities (chronic obstructive pulmonary disease, diabetes mellitus, hypertension, ischemic heart disease, and psychological disorders).

Infection characteristics were documented, including etiology (peri-implant disease, pericoronitis, post-extraction infection, or pulp necrosis) and anatomical spaces involved (anterior, masticator, peri-mandibular, and pharyngeal spaces). The presence of trismus, defined as limited mouth opening (interincisal distance < 20 lt; 20 mm), was also recorded.

Preoperative data included vital signs (heart rate, mean arterial pressure, and oxygen saturation) prior to anesthesia induction. Airway management details were recorded, including the technique used (direct laryngoscopy, video laryngoscopy, or AFOI), medications administered for induction or sedation (propofol, midazolam, ketamine, fentanyl), neuromuscular blocking agents (succinylcholine, rocuronium), endotracheal tube characteristics (size, route), and time required to secure the airway (defined as the time from patient entry into the operating room until confirmation of successful endotracheal intubation).

Postoperative data included ventilation status at the conclusion of surgery (spontaneous versus mechanical ventilation), duration of mechanical ventilation if applicable, PACU length of stay, occurrence of septic shock, ICU admission and length of stay, and total hospital length of stay.

Statistical methods

Descriptive statistics were used to summarize the data. The distribution of continuous variables was assessed visually using histograms and Q-Q plots. Continuous variables were presented as median (25^{th}, 75^{th} percentiles). Hodges-Lehmann estimators with 95% Confidence Intervals (95% CI) were calculated to quantify median differences between groups for continuous variables. Risk differences with 95% CI were calculated for categorical variables. Comparisons between groups were performed using the Mann-Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. Categorical variables were presented as counts and percentages (%). Given the limited Events Per Variable (EPV < 10), firth penalized logistic regression was used for all logistic analyses to address potential sparse data bias. Univariate logistic and Cox regression analyses were performed to screen potential predictors. Variables with $p < 0.20$ in univariate analysis were included in the multivariable models. Multivariable logistic regression was performed to identify factors associated with AFOI selection. Hospital length of stay was analyzed using Kaplan-Meier survival analysis and Cox proportional hazards regression; the proportional hazards assumption was assessed using Schoenfeld residuals. Multicollinearity was assessed using Variance Inflation Factors (VIF). Results were presented as Odds Ratios (OR) with 95% CI for logistic regression and Hazard Ratios (HR) with 95% CI for Cox regression, representing the probability of hospital discharge at any time point. Patients with missing data were excluded from the respective analyses (complete case analysis). All statistical tests were two-sided; $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using R statistical software (version 4.4.1).

Results

A total of 90 consecutive patients who underwent surgical drainage of severe odontogenic infections under general anesthesia were identified between 2015 and 2024. After

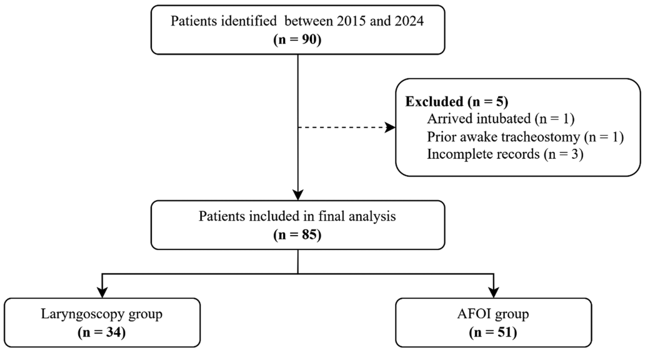

Figure 1 Patient inclusion flow chart. AFOI, awake fiberoptic intubation.

exclusions, 85 patients were included in the final analysis. The patient inclusion flow chart is presented in Figure 1. Patients were divided into two groups based on airway management technique: laryngoscopy (n = 34, 40.0%) and AFOI (n = 51, 60.0%).

The median age of the cohort was 39.0 years (26.0, 48.0), with similar distribution between groups. Males comprised 48.2% of the overall cohort. Most patients were classified as ASA I or II (93.0%) and nearly half were active smokers (47.1%). Pulp necrosis was the predominant etiology of infection (55.3%), followed by post-extraction infection (32.9%). Peri-mandibular spaces were most involved (77.6%), followed by pharyngeal spaces (47.1%). Patients with pharyngeal space involvement (58.8% vs. 29.4%, p = 0.009) and trismus (92.2% vs. 61.8%, p < 0.001) were more frequently managed with AFOI. Median BMI was significantly higher in the AFOI group (24.9 vs. 22.3 $kg.m^{-2}$, p = 0.024). Detailed patient characteristics are presented in Table 1.

Preinduction vital signs showed a median heart rate of 90.0 bpm (80.0, 100.0), median mean arterial pressure of 100.0 mmHg (92.0, 108.0), and median oxygen saturation of 99.0% (98.0, 100.0).

Table 1 Baseline characteristics and clinical variables stratified by airway management technique.

	Overall (n = 85)	Laryngoscopy (n = 34)	AFOI (n = 51)	Effect size (95% CI)	p-value
Age, y	39.0 (26.0, 48.0)	32.5 (26.0, 52.5)	40.0 (27.5, 46.5)	-0.0 (-6.0, 7.0)	0.971
Male sex	41 (48.2%)	13 (38.2%)	28 (54.9%)	16.7 (-4.6, 38.0)	0.184
BMI, $kg.m^{-2}$	23.3 (21.1, 28.6)	22.3 (20.3, 26.1)	24.9 (22.0, 29.4)	2.4 (0.3, 4.5)	**0.024**
ASA physical status					0.196
Class I	27 (31.8%)	7 (20.6%)	20 (39.2%)	18.6 (-0.5, 37.7)	
Class II	52 (61.2%)	25 (73.5%)	27 (52.9%)	-20.6 (-40.8, -0.4)	
Class III	5 (5.9%)	2 (5.9%)	3 (5.9%)	0.0 (-10.2, 10.2)	
Class IV	1 (1.2%)	0 (0.0%)	1 (2.0%)	2.0 (-1.8, 5.8)	
Active smoking	40 (47.1%)	18 (52.9%)	22 (43.1%)	-9.8 (-31.4, 11.8)	0.387
Background disease					
COPD	4 (4.7%)	2 (5.9%)	2 (3.9%)	-2.0 (-11.5, 7.6)	1.000
Diabetes mellitus	10 (11.8%)	7 (20.6%)	3 (5.9%)	-14.7 (-29.8, 0.3)	0.081
Hypertension	8 (9.4%)	4 (11.8%)	4 (7.8%)	-3.9 (-17.0, 9.2)	0.708
Ischemic heart disease	2 (2.4%)	2 (5.9%)	0 (0.0%)	-5.9 (-13.8, 2.0)	0.157
Psychological disorder	6 (7.1%)	3 (8.8%)	3 (5.9%)	-2.9 (-14.5, 8.6)	0.679
Infection etiology					
Peri-implant disease	5 (5.9%)	3 (8.8%)	2 (3.9%)	-4.9 (-15.8, 6.0)	0.385
Pericoronitis	5 (5.9%)	2 (5.9%)	3 (5.9%)	0.0 (-10.2, 10.2)	1.000
Postextraction infection	28 (32.9%)	10 (29.4%)	18 (35.3%)	5.9 (-14.3, 26.0)	0.642
Pulp necrosis	47 (55.3%)	19 (55.9%)	28 (54.9%)	-1.0 (-22.5, 20.6)	1.000
Anatomical spaces involved					
Anterior	18 (21.2%)	10 (29.4%)	8 (15.7%)	-13.7 (-32.0, 4.6)	0.176
Masticator	17 (20.0%)	6 (17.6%)	11 (21.6%)	3.9 (-13.2, 21.0)	0.785
Peri-mandibular	66 (77.6%)	25 (73.5%)	41 (80.4%)	6.9 (-11.5, 25.3)	0.596
Pharyngeal	40 (47.1%)	10 (29.4%)	30 (58.8%)	29.4 (9.0, 49.8)	**0.009**
Trismus	68 (80.0%)	21 (61.8%)	47 (92.2%)	30.4 (12.5, 48.3)	< **0.001**

Categorical variables are presented as counts (%). Continuous variables are presented as a median (25^{th}, 75^{th} percentiles). Effect sizes presented as median difference (95% CI) for continuous variables and risk difference in percentage points (95% CI) for categorical variables; positive values indicate higher values in the AFOI group. The Mann-Whitney *U*-test for comparing medians, and Fisher's exact test is used for comparing proportions. p-values compare the laryngoscopy group with the AFOI group. AFOI, Awake Fiberoptic Intubation; ASA, American Society of Anesthesiologists; BMI, Body Mass Index; CI, Confidence Intervals; COPD, Chronic Obstructive Pulmonary Disease.

Among laryngoscopy patients, direct laryngoscopy was used in 58.8% and video laryngoscopy in 41.2%. Anesthesia was induced with propofol (97.1%, median dose 150.0 mg [120.0, 200.0]), midazolam (50%, median dose 2.0 mg [1.0, 2.0]), ketamine (5.9%, median dose 22.5 mg [21.2, 23.8]), and fentanyl (88.2%, median dose 125.0 μg [100.0, 200.0]). Neuromuscular blockade was achieved with succinylcholine (41.2%, median dose 100.0 mg [81.2, 100.0]) or rocuronium (55.9%, median dose 50.0 mg [40.0, 50.0]).

For AFOI patients, sedation was provided with midazolam (80.4%, median dose 2.0 mg [1.0, 2.0]), ketamine (31.4%, median dose 32.5 mg [20.0, 50.0]), fentanyl (56.9%, median dose 100 μg [50.0, 100.0]), and propofol (29.4%, median dose 50.0 mg [40.0, 100.0]). Nasotracheal intubation was preferred for AFOI cases (94.1% vs. 41.2%, $p < 0.001$). Time to secure the airway was significantly longer with AFOI (21.0 [13.0, 28.0] vs. 12.0 [8.0, 21.5] minutes, p = 0.002).

In univariate analysis, factors associated with AFOI selection included male sex, higher BMI, diabetes mellitus, trismus, pharyngeal space involvement, and anterior space involvement (Supplementary Table 1). Multivariable logistic regression identified trismus (OR = 6.67, 95% CI 1.53, 39.53, p = 0.010) and higher BMI (OR = 1.15, 95% CI 1.03, 1.33, p = 0.013) as independent factors associated with AFOI selection (Table 2).

Mechanical ventilation at surgery conclusion was more common in AFOI patients (52.9% vs. 29.4%, p = 0.045), as was prolonged PACU stay (median 6.0 [1.9, 32.1] vs. 2.3 [1.5, 4.5] hours, p = 0.037). Intraoperative tracheostomy was performed exclusively in the AFOI group (27.5% vs. 0.0%, $p < 0.001$). ICU admission occurred only among AFOI patients (17.6% vs. 0.0%, p = 0.010). Septic shock developed in 7.8% of AFOI patients. Detailed postoperative outcomes are presented in Table 3.

The overall median hospital length of stay was 5.0 days (3.0, 8.0). Univariate Cox regression analysis identified BMI, ASA class, AFOI technique, pharyngeal space involvement, peri-mandibular space involvement, spontaneous ventilation postoperatively, and septic shock as factors potentially associated with time to discharge (Supplementary Table 2). In the multivariable Cox proportional hazards model (Table 4), spontaneous ventilation postoperatively (HR = 2.14, 95% CI 1.23, 3.73, p = 0.007) was associated with earlier discharge, while septic shock (HR = 0.26, 95% CI 0.07, 0.91, p = 0.036) and lower BMI (HR = 0.95 per $kg.m^{-2}$, 95% CI 0.90, 1.00, p = 0.040) were associated with delayed discharge. The relationship between pharyngeal space involvement and hospital length of stay is visualized in the Kaplan-Meier curve (Fig. 2, log-rank p = 0.054).

Table 2 Multivariable logistic regression analysis of factors associated with AFOI selection.

Variable	Adjusted OR (95% CI)	p-value
Male sex	1.30 (0.47, 3.59)	0.607
BMI, per $kg.m^{-2}$	1.15 (1.03, 1.33)	**0.013**
Diabetes mellitus	0.76 (0.12, 4.71)	0.762
Trismus	6.67 (1.53, 39.53)	**0.010**
Pharyngeal space involvement	1.61 (0.51, 5.12)	0.413
Anterior space involvement	0.71 (0.21, 2.49)	0.586

Firth penalized logistic regression was used to address sparse data bias. The dependent variable is airway management technique (AFOI vs. laryngoscopy). Independent variables with $p < 0.20$ in univariate analysis were included in the model. Multicollinearity was assessed using VIF (all VIF $\leq$ 1.51). OR represents the increased likelihood of AFOI selection associated with each factor. AFOI, Awake Fiberoptic Intubation; BMI, Body Mass Index; CI, Confidence Interval; OR, Odds Ratio; VIF, Variance Inflation Factors.

Discussion

This retrospective cohort study of patients undergoing surgical drainage of severe odontogenic infections revealed several notable insights into airway management strategies and clinical outcomes. Our findings demonstrate that AFOI was selected for anatomically challenging cases, with selection primarily associated with trismus and elevated BMI. These patients experienced significantly different perioperative trajectories, likely reflecting underlying disease complexity rather than airway technique-related effects.

The striking association between trismus and AFOI selection aligns with emerging evidence establishing mouth opening as the most reliable predictor of airway difficulty in maxillofacial infections. Riekert et al. identified that trismus significantly predicted difficult airways and ICU admission.[15] Our finding that 92.2% of AFOI patients presented with trismus, compared to 61.8% in the laryngoscopy group, reflects appropriate clinical decision-making based on this anatomical limitation. This is supported by difficult airway guidelines, which specifically recommend awake techniques when mouth opening is severely restricted.[8,9] The longer time required to secure the airway with AFOI (21.0 vs. 12.0 minutes) reflects the technical demands of this approach rather than complications, as all patients were successfully intubated without reported adverse events.

BMI emerged as a unique bidirectional predictor: higher BMI was associated with AFOI selection (OR = 1.15 per $kg.m^{-2}$, p = 0.013), while lower BMI was associated with delayed hospital discharge (HR = 0.95, p = 0.040). This dual association reflects the complex interplay between body habitus and infection severity. The association with AFOI selection aligns with established literature documenting increased airway management challenges in obese patients.[16] However, the relationship between lower BMI and prolonged hospitalization may reflect underlying nutritional compromise or systemic illness affecting recovery capacity. Malnutrition has been independently associated with nosocomial infections and prolonged hospital stay.[17-19]

Pharyngeal space involvement emerged as a notable anatomical consideration, occurring in 58.8% of AFOI patients compared to 29.4% in the laryngoscopy group (p = 0.009). While not reaching statistical significance in multivariable analysis for AFOI selection, the trend toward prolonged hospitalization (HR = 0.63, p = 0.073) represents a hypothesis-generating finding that warrants further investigation in larger cohorts. This finding is consistent with existing literature identifying parapharyngeal and retropharyngeal space involvement as independent predictors of airway

Table 3 Intraoperative details and postoperative outcomes.

	Overall (n = 85)	Laryngoscopy (n = 34)	AFOI (n = 51)	Effect size (95% CI)	p-value
Intraoperative data					
Endotracheal tube size, mm	7.0 (6.5, 7.0)	7.0 (6.6, 7.4)	6.5 (6.5, 7.0)	-0.5 (-0.5, -0.0)	**0.002**
Endotracheal tube route					
Nasal	62 (72.9%)	14 (41.2%)	48 (94.1%)	52.9 (35.2, 70.7)	< **0.001**
Oral	23 (27.1%)	20 (58.8%)	3 (5.9%)	-52.9 (-70.7, -35.2)	< **0.001**
Time to secure AW, min	17.0 (12.0, 25.0)	12.0 (8.0, 21.5)	21.0 (13.0, 28.0)	7.0 (2.0, 11.0)	**0.002**
Surgery time	33.0 (19.0, 42.0)	30.0 (19.0, 41.2)	33.0 (22.0, 43.5)	3.0 (-4.0, 10.0)	0.490
Intraoperative tracheostomy	14 (16.5%)	0 (0.0%)	14 (27.5%)	27.5 (15.2, 39.7)	< **0.001**
Postoperative data					
Ventilation status at surgery conclusion					**0.045**
Spontaneous ventilation	48 (56.5%)	24 (70.6%)	24 (47.1%)	-23.5 (-44.1, -3.0)	
Mechanical ventilation	37 (43.5%)	10 (29.4%)	27 (52.9%)	23.5 (3.0, 44.1)	
Duration of mechanical ventilation (h)	28.0 (12.3, 45.6)	20.3 (8.9, 47.9)	30.1 (13.7, 42.1)	5.5 (-21.3, 32.9)	0.580
PACU length of stay	2.6 (1.7, 17.0)	2.3 (1.5, 4.5)	6.0 (1.9, 32.1)	1.2 (0.0, 9.9)	**0.037**
Septic shock	4 (4.7%)	0 (0.0%)	4 (7.8%)	7.8 (0.5, 15.2)	0.146
ICU admission	9 (10.6%)	0 (0.0%)	9 (17.6%)	17.6 (7.2, 28.1)	**0.010**
ICU length of stay, days	12.0 (9.8, 18.0)	-	12.0 (9.8, 18.0)		
Hospital length of stay	5.0 (3.0, 8.0)	4.0 (3.0, 6.8)	6.0 (3.0, 10.5)	1.0 (-0.0, 3.0)	0.059

Categorical variables are presented as counts (%). Continuous variables are presented as a median (25^{th}, 75^{th} percentiles). Effect sizes presented as median difference (95% CI) for continuous variables and risk difference in percentage points (95% CI) for categorical variables; positive values indicate higher values in the AFOI group. The Mann-Whitney *U*-test for comparing medians, and Fisher's exact test is used for comparing proportions. The p-values compare the laryngoscopy group with the AFOI group. AFOI, Awake Fiberoptic Intubation; AW, Airway; ICU, Intensive Care Unit; PACU, Post-Anesthesia Care Unit.

Table 4 Multivariable Cox regression analysis of factors associated with time to hospital discharge.

Variable	Adjusted HR (95% CI)	p-value
BMI, per kg.m^{-2}	0.95 (0.90, 1.00)	**0.040**
ASA, per class	0.83 (0.55, 1.27)	0.396
AFOI (vs. laryngoscopy)	1.60 (0.91, 2.82)	0.102
Pharyngeal space involvement	0.63 (0.38, 1.04)	0.073
Peri-mandibular space involvement	0.75 (0.42, 1.34)	0.331
Spontaneous ventilation postoperatively	2.14 (1.23, 3.73)	**0.007**
Septic shock	0.26 (0.07, 0.91)	**0.036**

Analysis based on 79 patients with complete data. HRs represent the relative probability of hospital discharge at any time point. HR > 1 indicates faster discharge (shorter hospital stay). Variables with $p < 0.20$ in univariate analysis were included in the model. Multicollinearity was assessed using VIF (all VIF ≤ 1.51). The proportional hazards assumption was assessed using Schoenfeld residuals (global test p = 0.126). AFOI, Awake Fiberoptic Intubation; ASA, American Society of Anesthesiologists physical status; BMI, Body Mass Index; CI, Confidence Interval; HRs, Hazard Ratios; VIF, Variance Inflation Factors.

compromise and severe complications.[20,21] The exclusive need for intraoperative tracheostomy in the AFOI group underscores the anatomical challenges and severity of infection involving critical airway structures, often necessitating temporary airway bypass.[22,23]

The ability to achieve spontaneous ventilation at surgery conclusion emerged as the strongest predictor of favorable outcomes (HR = 2.14 for earlier discharge, p = 0.007). This marker likely represents a composite indicator of infection severity, successful source control, and preserved physiologic reserve. The higher rate of postoperative mechanical ventilation in AFOI patients (52.9% vs. 29.4%, p = 0.045) reflects the underlying complexity of these cases rather than a consequence of the airway technique itself.

The exclusive occurrence of septic shock in the AFOI group, while based on only four cases, aligns with Weise et al.'s findings that 3.3% of hospitalized odontogenic infection patients develop septic complications requiring intensive support.[11] All septic patients in their series required tracheostomy and prolonged ICU care, with 18.8% developing multiorgan dysfunction. Our finding that septic shock was strongly associated with delayed discharge (HR = 0.26, p = 0.036) emphasizes the need for early recognition and aggressive management of systemic complications. These observations are particularly relevant given recent epidemiological trends indicating rising ICU admission rates and hospital lengths of stay for odontogenic infections.[24,25] In our

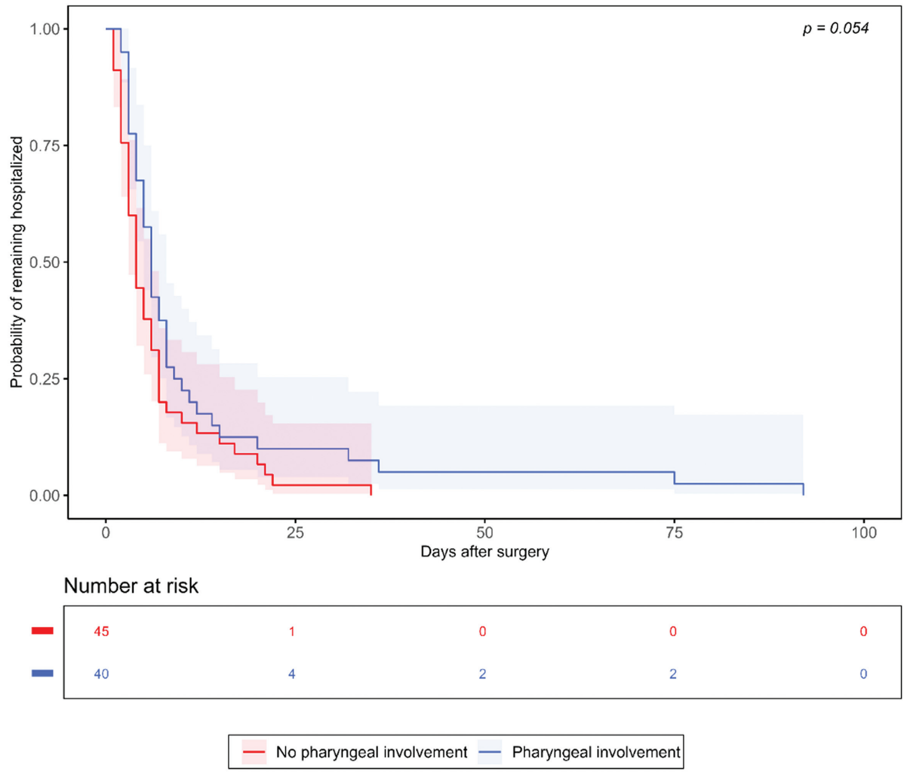

Figure 2 Kaplan-Meier analysis of hospital length of stay by pharyngeal space involvement. Kaplan-Meier curves showing time to hospital discharge stratified by pharyngeal space involvement. Patients without pharyngeal space involvement (red line) demonstrated shorter hospital stays compared to those with pharyngeal involvement (blue line). Log-rank test p = 0.054. Shaded areas represent 95% CI. Numbers at risk are shown below the plot. CI, Confidence Interval.

study, 10.6% of patients required ICU admission, exclusively in the AFOI group, highlighting both the increasing severity of disease and the appropriate selection of advanced airway techniques for higher-risk patients.

Dexmedetomidine has emerged as a promising sedation agent for AFOI due to its ability to provide cooperative sedation with preserved spontaneous ventilation.[26,27] However, its associated bradycardia and hypotension[28] warrant caution in patients with sepsis or hemodynamic instability, as observed in our cohort.

Our findings support an individualized approach to airway management in severe odontogenic infections, with particular attention to trismus and elevated BMI. The prognostic significance of postoperative ventilation status and septic shock development aids patient counseling, resource allocation, and early identification of cases requiring intensive care. The observed pattern of AFOI selection for more complex cases, followed by appropriate postoperative management, reflects sound clinical judgment in perioperative care. From a practical standpoint, these findings support the use of trismus and elevated BMI as objective criteria for AFOI selection, and highlight the importance of postoperative ventilation planning and early sepsis recognition in institutional protocols for managing severe odontogenic infections.

Limitations and future directions

This study has several limitations that warrant consideration. First, the retrospective single-center nature may introduce selection bias and limit generalizability to other institutions or healthcare settings, particularly as the extended study period (2015 to 2024) may encompass changes in clinical protocols or practice patterns, and availability of resources such as video laryngoscopy and dedicated maxillofacial surgical coverage. Second, the non-randomized selection of airway techniques creates potential confounding, as patients with more severe presentations are typically more likely to undergo AFOI. This selection bias, while clinically appropriate, prevents definitive conclusions about the superiority of either technique. Third, our modest sample size limits statistical power and the ability to perform detailed subgroup analyses. As severe odontogenic infections requiring surgical drainage under general anesthesia are relatively uncommon, we conducted a complete enumeration of all eligible cases during the study period rather than employing sample size calculations. This approach, while ensuring capture of all available data, limits statistical power for some comparisons. Fourth, reliance on medical records for clinical features, such as trismus, rather than standardized measurements, may introduce variability in assessment. Fifth, we lack long-term follow-up data beyond hospital discharge, which prevents an assessment of delayed complications or readmission rates.

Future research should include prospective studies with standardized assessment protocols and larger cohorts to better elucidate relationships between patient characteristics, infection patterns, airway management, and outcomes. The observed bidirectional association between BMI and outcomes warrants prospective validation with standardized nutritional assessments. Developing risk stratification tools incorporating predictors of prolonged hospitalization and ICU admission could optimize resource allocation. Investigating targeted interventions for high-risk patients, particularly those with pharyngeal space involvement or risk factors for septic shock, may improve outcomes in this vulnerable population.

Conclusion

This retrospective analysis demonstrates that AFOI was preferentially selected for anatomically challenging cases of severe odontogenic infections, particularly those with trismus and elevated BMI. While these patients experience more complex perioperative courses, including higher rates of postoperative mechanical ventilation and ICU admission, these outcomes reflect underlying disease severity rather than technique-related complications. The ability to achieve spontaneous ventilation postoperatively emerges as a key prognostic indicator, while septic shock, though rare, is strongly associated with prolonged recovery. These findings support individualized airway management strategies based on objective clinical criteria and highlight the need for institutional preparedness to manage these increasingly complex infections.

Data availability statement

Data may be obtained from the authors upon reasonable request, with the requisite permission from the Institutional Review Board of Rabin Medical Centre – Beilinson Hospital.

Funding

None.

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.2026.844756.

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ORIGINAL INVESTIGATION

Preoperative gastric ultrasound in children with cerebral palsy: a cross-sectional observational study

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Abstract
Background: Pulmonary aspiration during anesthesia, though rare, can be catastrophic. Gastric ultrasound provides an objective assessment of gastric contents and may be particularly relevant for children with Cerebral Palsy (CP), who are at risk of delayed gastric emptying.
Methods: We conducted a cross-sectional study in a pediatric hospital including children scheduled for elective surgery per ASA fasting guidelines. Preoperative gastric ultrasound measured antral CSA in right lateral decubitus, and gastric volume was estimated using the Perlas formula. Fasting time, medication use, and clinical data were recorded. Group comparisons used Wilcoxon, Fisher's exact, or Chi-Square tests; multiple linear regression adjusted for confounders.
Results: Sixty-two children were studied: 30 with Cerebral Palsy (CP) and 32 controls. No patient exceeded the high-risk gastric volume threshold (1.5 $mL.kg^{-1}$) and no surgeries were cancelled. CP patients had shorter fasting times (6.5 vs. 8.0 h; $p < 0.001$) and higher medication use (47% vs. 6.3%; $p < 0.001$). Gastric CSA (4.0 vs. 3.0 cm^2; $p < 0.001$) and estimated gastric volume per kg (0.7 vs. 0.4 $mL.kg^{-1}$; $p < 0.001$) were greater in CP. Multivariable models showed attenuation, but quantile regression confirmed higher lower CSA (+1.25 cm^2; $p = 0.007$). Excluding medication users, CP remained associated with greater gastric volume.
Conclusions: Children with cerebral palsy exhibit larger CSA and higher gastric volumes despite adequate fasting. Although clinically safe, these findings support the role of gastric ultrasound in preoperative risk assessment for this vulnerable group.

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Introduction

Pulmonary aspiration during anesthesia is a rare but catastrophic event, which can lead to a mortality rate of 9%.[1] Preoperative fasting is essential to prevent complications of this nature. Over the years, fasting protocols have been updated and there has been a trend towards flexibility, especially in relation to ingested liquids.[2-5]

Current guidelines encourage the ingestion of liquids without residues up to two hours before surgery, to reduce patient discomfort, catecholamine release and hemodynamic complications related to dehydration.[6]

The growth of portable ultrasound in surgical centers has sparked interest in its use as a diagnostic method to evaluate gastric contents. Measuring the Cross-Sectional Area (CSA) of the gastric antrum has proven useful for scenarios in which fasting is doubtful or there is some risk factor for pulmonary aspiration.[7]

The gastric residual volume that increases the risk of aspiration is considered to be above 1.5 $mL.kg^{-1}$.[8] Therefore, patients taking continuous medications could take them together with a glass of water up to two hours before surgery without compromising fasting. However, there is significant interindividual variation in gastric emptying, regardless of the duration of fasting, with some patients still presenting residual gastric content even after prolonged fasting.[9]

Despite the current trend towards reducing fasting time for clear liquids recommended by several international pediatric societies;[2] other societies continue to recommend traditional fasting times.[6] This conflict in the literature has raised questions and many studies are underway to try to clarify the ideal fasting time for different populations.

Patients with cerebral palsy represent a group of individuals who may benefit from advances in this specific research area. They are considered a challenge in anesthetic induction, as they may have delayed gastric emptying and are frequently consuming anticonvulsants and muscle relaxants that should not be discontinued.[10]

This study was designed to estimate gastric content and volume by ultrasonography in children with and without cerebral palsy undergoing elective surgical procedures and who followed the traditional preoperative fasting strategy recommended by the American Society of Anesthesiology (ASA).[6]

Also, we wanted to verify whether patients with cerebral palsy require a preoperative fasting period longer than recommended, in order to increase safety of anesthetic induction in this group of individuals.

Methods

The study was performed in an exclusive pediatric hospital, and was submitted to and approved by the research Ethics Committee and registered under number CAAE 52573121.0.0000.0097. Patients were selected on the day of surgery in the admission room of the surgical theater and after the application of the informed consent form. Data collection was performed at a single time before anesthetic induction by the same trained operator, according to the standard scanning protocol,[11] no premedication was used. The period of recruitment was 12 months. This article followed EQUATOR Reporting Guidelines.

Children under 18 years of age, with or without cerebral palsy scheduled for elective surgical procedures were selected. All patients without cerebral palsy were ASA I class (without comorbidities or healthy). We excluded patients with previous gastrointestinal surgery, gastric tubes or stomas, anatomical abnormalities of the gastrointestinal tract and pregnancy.

All patients followed the preoperative fasting guideline recommended by the ASA.[3]

A convenience sample of 30 patients with cerebral palsy and 32 healthy patients was recruited representing the two groups of study.

The use of medications was not an exclusion criterion due to the difficulty of sampling without their use. No formal a priori sample size calculation was performed. The chosen sample size was based on feasibility within the study period.

Ultrasound assessment

All ultrasound scans were performed in the morning to avoid prolonged fasting, with the same ultrasound device (M-turbo Sonosite) and a low-frequency curved transducer (2 to 6 MHz) by a single operator. Patients were first scanned in the Supine Position (SP) and then in the Right Lateral Decubitus (RLD). The transducer was placed in the sagittal plane at the epigastric region to visualize the gastric antrum between the left hepatic lobe and the pancreas at the level of the aorta. The cross-sectional area of the gastric antrum (CSA) was calculated using the RLD ultrasound image, based on the two-diameter Craniocaudal (CC) and Anteroposterior (AP) method formula as previously described by Perlas et al.:[8] $CSA = (AP \times CC \times \pi) / 4$.

Qualitative assessment of the gastric content was initially performed, resulting in three possibilities: 1) Empty-anterior and posterior walls juxtaposed; 2) Hypoechoic liquid content or 3) Solid content, distended lumen with a "ground glass" appearance. Then, the total Volume (V) of gastric fluid was estimated in milliliters using the mathematical model validated and suggested by Perlas et al., through the following formula:[8] $V = 27.0 + 14.6 \times CSA\ in\ RLD - 1.28 \times age$; where: Volume in milliliters (mL); CSA in right lateral decubitus in cm^2; Age in full number of years.

Parameter data were recorded on an electronic spreadsheet where individual data regarding age, sex, weight, type of surgery, fasting time and continuous medications were also recorded.

For each patient, fasting intervals for solids and clear liquids were recorded separately, in accordance with ASA guidelines. These variables were analyzed both as continuous values (hours) and categorical thresholds (< 8 h vs. ≥ 8 h), for solids and liquids independently.

Statistical analysis

Continuous variables were summarized as medians with Interquartile Ranges (IQR) and compared between groups using the Wilcoxon rank-sum test. Categorical variables were compared using Fisher's exact test or the Chi-Squared test, as appropriate. The primary outcome was the gastric antral Cross-Sectional Area (CSA). Between-group differences in CSA were estimated using the Hodges-Lehmann method for the median difference, with 95% Confidence

Intervals (95% CI). To adjust for potential confounding, a multivariable linear regression model was fitted including age, weight, fasting time (in hours, as a continuous variable), and continuous medication use. Model assumptions were verified through residual diagnostics, and robust (HC3) standard errors were applied when heteroscedasticity or non-normality was identified. Sensitivity analyses were performed using quantile regression to explore the effect of group status across the distribution of CSA, rather than focusing solely on the mean. In addition, estimated gastric volume (mL) and weight-adjusted volume ($mL.kg^{-1}$), derived from established ultrasound-based equations, were evaluated as secondary complementary outcomes to provide clinically interpretable measures. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

The study included 62 patients, 30 with cerebral palsy and 32 without cerebral palsy. No patient presented solid or liquid content above 1.5 $mL.kg^{-1}$; therefore no one had an "at-risk stomach". No surgical procedures were postponed or canceled. The most common interventions were application of botulinum toxin in the cerebral palsy patients and circumcision in the healthy ones.

Half of the patients in the cerebral palsy group were users of anticonvulsant medications and muscle relaxants such as Baclofen, carbamazepine, phenobarbital, cannabidiol, valproic acid, quetiapine, risperidone, lamotrigine (summarized in Supplementary Table).

Baseline characteristics are summarized in Table 1. Median age and weight were comparable between groups. However, fasting duration was significantly shorter in children with cerebral palsy (6.5 vs. 8.0 h, $p < 0.001$), and continuous medication use was more frequent (47% vs. 6.3%, $p < 0.001$). The gastric antral Cross-Sectional Area (CSA) was significantly larger in the cerebral palsy group (median 4.0 vs. 3.0 cm^2, $p < 0.001$), as was the estimated gastric volume per kilogram (0.7 vs. 0.4 $mL.kg^{-1}$, $p < 0.001$). Visible residual fluid in the right lateral decubitus position was observed only in the cerebral palsy group (13%, p = 0.049).

In the multivariable linear regression model for CSA (Table 2), cerebral palsy was associated with a mean CSA increase of +0.92 cm^2 after adjustment for age, weight, fasting time, and medication use. This effect did not reach statistical significance (95% CI -0.27 to 2.10, p = 0.13). None of the covariates showed significant independent associations with CSA.

Quantile regression results are presented in Table 3. The effect of cerebral palsy on CSA was most pronounced at the lower quartile (τ = 0.24), with an estimated difference of +1.25 cm^2 (95% CI 0.36 to 2.16, p = 0.007). At the median (τ = 0.50) and upper quartile (τ = 0.75), the differences were smaller and not statistically significant. These findings suggest that children with cerebral palsy consistently avoided the very low CSA values observed in controls.

For estimated gastric volume (Table 4), the unadjusted comparison showed significantly higher values in the cerebral palsy group (median 23 vs. 10.5 mL, $p < 0.001$). However, in the adjusted model, the group effect was attenuated (+1.9 mL, 95% CI -4.0 to 7.8, p = 0.50). Age was strongly associated with increased gastric volume (+2.9 $mL.year^{-1}$, 95% CI 1.8 to 4.0, $p < 0.001$), whereas fasting time and medication use did not reach significance.

Table 3 Quantile regression for gastric CSA.

Quantile (τ)	Estimate (cm^2)	95% CI	p-value
0.25	+1.26	0.36 to 2.16	0.007
0.50	+0.68	−0.28 to 1.64	0.16
0.75	+1.00	−0.66 to 2.66	0.23

CSA, Cross-Sectional Area; CI, Confidence Interval.

Table 1 Clinical and demographic characteristics of the study population.

Variable	Healthy controls (n = 32)	Cerebral palsy (n = 30)	p-value
Age, years, median (IQR)	6.5 (3.0–12.0)	9.0 (6.0–12.0)	0.10
Weight, kg, median (IQR)	31.0 (18.0–42.5)	29.0 (18.0–40.0)	0.90
Fasting time, h, median (IQR)	8.0 (8.0–9.5)	6.5 (2.0–8.0)	< 0.001
Gastric CSA, cm^2, median (IQR)	3.0 (2.0–4.0)	4.0 (4.0–5.0)	< 0.001
Volume, $mL.kg^{-1}$, median (IQR)	0.4 (0.3–0.6)	0.7 (0.6–0.9)	< 0.001
Visible fluid (right lateral)	0 (0%)	4 (13%)	0.049
Continuous medication use, n (%)	2 (6.3%)	14 (47%)	< 0.001

CSA, Cross-Sectional Area; IQR, Interquartile Range.

Table 2 Multivariable linear regression for gastric CSA.

Characteristic	Beta (cm^2)	95% CI	p-value
Group (cerebral palsy vs. control)	+0.92	−0.27 to 2.10	0.13
Age (years)	−0.02	−0.24 to 0.19	0.80
Weight (kg)	+0.02	−0.05 to 0.10	0.60
Fasting time (h)	−0.07	−0.28 to 0.13	0.50
Continuous medication (yes vs. no)	+0.96	−0.54 to 2.50	0.20

CSA, Cross-Sectional Area; CI, Confidence Interval.

Table 4 Multivariable linear regression for estimated gastric volume.

Characteristic	Beta (mL)	95% CI	p-value
Group (cerebral palsy vs. control)	+1.9	−4.0 to 7.8	0.50
Age (years)	+2.9	1.8 to 4.0	< 0.001
Weight (kg)	−0.25	−0.63 to 0.12	0.20
Fasting time (h)	−0.88	−1.9 to 0.13	0.087
Continuous medication (yes vs. no)	+3.5	−4.0 to 11	0.40

CI, Confidence Interval.

Table 5 Descriptive characteristics of the study population (three-group comparison).

Variable	Healthy controls (n = 32)	Cerebral palsy – With medication (n = 14)	Cerebral palsy – Without medication (n = 16)	p-value[a]
Age (years)	6.5 (3.0 – 12.0)	9.0 (6.0 – 11.0)	10.0 (5.5 – 12.0)	0.20
Weight (kg)	31.0 (18.0 – 42.5)	28.0 (20.0 – 38.0)	31.5 (18.0 – 42.0)	0.90
Fasting time (hours)	8.0 (8.0 – 9.5)	2.0 (2.0 – 2.0)	8.0 (7.5 – 8.0)	< 0.001
Type of last intake				< 0.001
Breast milk or formula	0 (0 %)	1 (7.1 %)	3 (19 %)	
Clear liquid	0 (0 %)	11 (79 %)	1 (6.3 %)	
Solid food	32 (100 %)	2 (14 %)	12 (75 %)	
Gastric CSA (cm^2)	3.0 (2.0 – 4.0)	4.5 (4.0 – 7.0)	4.0 (3.5 – 4.5)	< 0.001
Estimated gastric volume ($mL.kg^{-1}$)	0.4 (0.3 – 0.6)	0.7 (0.6 – 1.4)	0.6 (0.5 – 0.8)	< 0.001
No visible fluid (supine)	32 (100 %)	14 (100 %)	16 (100 %)	–
No visible fluid (right lateral)	32 (100 %)	10 (71 %)	16 (100 %)	0.002

[a] Kruskal-Wallis rank-sum test for continuous variables; Fisher's exact test for categorical variables.
Data are median (Q1, Q3) or number (%).
CSA, Cross-Sectional Area.

A subgroup analysis excluding children on continuous medication (16 cerebral palsy vs. 30 controls) showed that, with comparable fasting times and no gastroparesis-inducing drugs, cerebral palsy was associated with an 8–10 mL higher gastric volume (p = 0.03) (Supplementary Table).

Descriptive statistics and group comparisons are shown in Table 4. Median fasting time and type of intake differed significantly across groups ($p < 0.001$). Children with CP using medications presented markedly shorter fasting times and larger gastric antral Cross-Sectional Areas (CSA) and estimated gastric volumes per kilogram. Significant group differences were confirmed for both CSA and gastric volume.kg^{-1} ($p < 0.001$). Visible fluid in the right lateral decubitus position was observed only in the medicated CP group (p = 0.002).

Table 5 Descriptive characteristics of the study population by group. An additional comparative analysis including three distinct groups: 1) Healthy controls, 2) Children with Cerebral Palsy (CP) using medications known to affect gastric emptying, and 3) Children with CP not using such medications.

Discussion

It is well known that prolonged fasting (over 24 hours) can delay gastric emptying.[12] According to the most current protocols, early refeeding in the postoperative period, as well as a minimum period of preoperative fasting, is ideal.[2,4,13]

In addition to fasting, the use of ultrasound has improved the safety and quality of anesthesia by guiding the adoption of more appropriate strategies to reduce aspiration and by assessing the nature and volume of gastric contents.[7,14,15] With adequate training, the success rate in the evaluation and correct measurement of the gastric antrum can reach 95%.[15,16]

Cerebral palsy is a permanent condition of delayed neuropsychomotor development attributed to non-progressive fetal or early childhood disorders.[17,18] Furthermore, delayed gastric emptying in patients with cerebral palsy has been reported even with adequate fasting.[19]

In this series, cerebral palsy patients presented a higher antrum CSA than healthy patients and consequently a larger estimated gastric volume.

However, when we inferred about gastric emptying by correcting the variables for fasting time, age and medication use, this difference was not statistically significant, probably due to the limited sample size. Adjusted analysis indicates that part of the higher CSA observed in children with cerebral palsy is associated with confounding factors (especially fasting time and medication use), as controlling for these factors reduced the significance of the difference between the groups. However, robust statistical methods indicate that the difference in CSA still persists, suggesting that the neurological condition itself possibly contributes to greater gastric filling independently of these factors.

Although children with cerebral palsy presented more fluid in the lateral decubitus position, this was associated with the use of continuous medications and shorter fasting time. Children with cerebral palsy and their parents were advised not to discontinue anticonvulsants and muscle relaxants before procedures resulting in shorter fasting time, which was a confounding factor in half of the children of this group.

No child had a full stomach (solid or liquid content above 1.5 $mL.kg^{-1}$). This may be attributable to the rigorous preoperative fasting and it aligns with results of similar studies in the recent literature.[20]

One limitation of dealing with this disease is that there are several degrees of impairment in cerebral palsy; some patients are completely dependent on mechanical ventilation, and other patients are able to walk and feed themselves without the help of tubes or stomas.[21] This variability in the degrees of impairment of cerebral palsy may have led to no difference being initially found in the groups, since the most severe cases were excluded for being users of gastrostomy.

In a recent study, it was not possible to correlate the severity of the disease and the increase in gastric volume,[20] possibly due to the same limitation of number and homogeneity present in the sample of our study.

Furthermore, the mathematical formula used to estimate gastric volume has not yet been validated in children, especially in those with cerebral palsy, who may have distortions in their results since, compared to healthy children of the same age, they are smaller.[21]

There was difficulty in increasing the sample of patients with cerebral palsy because it is an uncommon condition, and the most severe patients with gastrostomies and gastric tubes were excluded from the study. In addition, during the data collection period, although some patients had returned to the hospital to undergo a new procedure, they were not included again in the sample.

The use of gastric ultrasound in this specific area of clinical investigation still requires some standardization, including, for example, the definition of minimum training requirements for anesthesiologists to ensure accurate assessments.[15] The gold standard for more accurate assessment continues to be scintigraphy,[22] however, its use in a preoperative scenario is unfeasible. In addition, most of the data currently published refer to healthy adults. The volume assessment models, in particular, have only been validated for adult and non-pregnant populations, and more data are needed from pediatric populations.[23]

A subgroup analysis excluding children on continuous medication suggests that medication use and shorter fasting partially masked the effect of the neurological condition. When controlled, cerebral palsy itself impacted residual gastric volume, likely due to reduced gastrointestinal motility. Despite reduced sample size and potential selection bias, the evidence supports a genuine effect of cerebral palsy on increasing gastric volume.

The three-group comparative analysis confirmed that the use of medications known to delay gastric emptying is associated with shorter fasting times and higher gastric volume. However, even among non-medicated children with cerebral palsy, gastric volume remained higher than in healthy controls, suggesting that the neurological condition itself contributes to altered gastric motility independently of pharmacologic effects.

Possibly a larger and more homogeneous sample, excluding the use of medications that can affect gastric emptying, could show a more reliable result regarding the neurological disease and its impact on the digestive tract.

The major difficulty in carrying out this type of work was obtaining a relatively large, homogeneous sample, free of confounding factors such as the use of medications, surgeries or malformations of the gastrointestinal tract.

Our results reinforce the use of tools such as ultrasound in special cases, such as pregnant women, diabetics, and those with neurological and digestive tract diseases, since there is no harm to the patient in applying this method.[7]

3D and 4D ultrasound are newer imaging modalities that may play a future role in gastric ultrasound evaluation and bring greater safety to clinical practice.[24]

Conclusion

Pediatric patients with cerebral palsy demonstrated significantly larger gastric antral CSA and higher estimated gastric volumes than healthy controls, despite adherence to preoperative fasting guidelines. Although none exceeded the threshold for aspiration risk, these findings suggest that neurological impairment itself may contribute to increased residual gastric content, and these patients may require individualized preoperative fasting strategies, incorporating adjunctive tools such as gastric ultrasound. Larger studies, including patients across the full spectrum of cerebral palsy severity, are warranted to confirm these results and refine clinical recommendations.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI assistance disclosure

The authors declare that no Artificial Intelligence (AI) tools were used in the preparation, writing, language editing, or analysis of this manuscript. The authors take full responsibility for the integrity and accuracy of its content.

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Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

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ORIGINAL INVESTIGATION

Erector spinae plane block versus thoracic paravertebral block in pediatric patients undergoing percutaneous nephrolithotomy: a prospective randomized clinical trial

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Postoperative pain

Abstract
Background: Percutaneous Nephrolithotomy (PCNL) is a well-established surgical procedure for removal of large, multiple, and complex renal calculi in children. Combining loco-regional techniques with general anesthesia has gained increasing popularity in pediatric anesthesia. The objective of this trial was to evaluate the efficacy of Erector Spinae Plane Block (ESPB) versus thoracic Paravertebral Block (PVB) in pediatric patients undergoing PCNL procedure.
Methods: Fifty-six children, aged 2–7 years, who underwent PCNL procedure under general anesthesia were randomly assigned to receive either ESPB (n = 28) or thoracic PVB (n = 28) with the same anesthetic mixture of 0.3 $mL.kg^{-1}$ bupivacaine 0.25% in epinephrine 1:100000. The primary outcome was time to first rescue analgesia (nalbuphine).
Results: The time to first rescue analgesia was 15.98 ± 10.17 hours (95% CI: 12.14–19.82) in the ESPB group versus 18.18 ± 9.18 hours (95% CI: 14.7–21.58) in the thoracic PVB group with no significant difference (p = 0.464, log-rank test). Moreover, the total dose and frequency of administration of nalbuphine during the first 24 postoperative hours were comparable between the two studied groups (p = 0.488 and 0.479 respectively). However, the time to conduct the block was significantly shorter in the ESPB group versus the thoracic PVB group (4.37 ± 1.08 minutes vs. 5.05 ± 1.17 minutes respectively, p = 0.028).
Conclusion: ESPB was not found to be more effective than thoracic PVB for postoperative pain management in children undergoing PCNL procedure. Moreover, intraoperative hemodynamics

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and maximum sevoflurane concentration were comparable. The time to conduct ESPB was significantly shorter; hence, it could be considered as an easy alternative to thoracic PVB for this procedure.

Introduction

Over the past decades, Percutaneous Nephrolithotomy (PCNL) has become a well-established procedure for extraction of large, multiple, and complex renal stones in pediatric patients.[1] Despite being a minimally invasive procedure, patients still experience postoperative pain that is attributed to renal capsule & parenchymal tract dilation, the creation of access tract via the tissues, and the nephrostomy tube inserted by the end of the procedure.[2]

Nowadays, regional blocks are frequently used as adjuvants to general anesthesia in pediatric patients to achieve better operating conditions and less opioid consumption, and to provide better postoperative analgesia.[3]

Paravertebral Block (PVB) has been used effectively for pain relief in pediatric patients after renal surgeries including PCNL procedure.[4,5] Nevertheless, it requires high experience to minimize probable complications such as pneumothorax, pleural puncture, epidural or intrathecal spread, or vascular injury.

Erector Spinae Plane Block (ESPB) is a recently introduced interfascial plane block that was first conducted for neuropathic pain management.[6] Thereafter, ESPB was reported for management of postoperative pain in numerous surgical procedures in pediatric patients.[7-9]

The objective of this trial was to test whether ESPB is more effective than thoracic PVB block for management of postoperative pain in pediatric patients undergoing PCNL procedure considering the time to first rescue analgesia as the primary outcome.

Materials methods

Trial design, setting, and ethics

This prospective, randomized, assessor-blind, superiority clinical study was performed at Assiut University Urology Hospital after approval of its protocol by the Institutional Review Board (IRB) of the Faculty of Medicine, Assiut University, Egypt, on July 21, 2022 (IRB number: 17300787). It was also registered in clinicaltrials.gov (NCT05589649) before recruitment. The study protocol was discussed with the parents/legal guardians of the participants prior to obtaining written informed consents. This study was carried out in accordance with the Helsinki declaration (2013) and considering the Consolidated Standards of Reporting Trials (CONSORT) guidelines, including the flow diagram.[10]

Participants, randomization, and masking

The inclusion criteria were children aged 2 to 7 years with American Society of Anesthesiologists (ASA) physical status class I or II who were scheduled for PCNL procedure. Exclusion criteria were refusal of the parent or legal guardian, coagulation disorders, local site infection, known allergy to the used drugs, spinal cord abnormalities, or neurological deficits.

Based on a computer-generated random list conducted by a biostatistician, the children who fulfilled the inclusion criteria were allocated either to the ESPB group (n = 28) or thoracic PVB group (n = 28). Opaque, sealed envelopes were used to conceal the allocation and were unsealed in the morning of the procedure by a nurse who had no further roles. For all patients, the regional blocks were conducted by the same anesthesiologist who is well-experienced in ultrasound-guided regional blocks in pediatric patients. This anesthesiologist had no further participation in the perioperative management. Another anesthesiologist, who was unaware of the regional block performed, was responsible for intraoperative monitoring and management according to the study protocol. Furthermore, assessment and management of postoperative pain were achieved by a pediatrician and trained nurses who were unaware of the group allocation.

General anesthesia and regional blocks

Thirty minutes before shifting to the Operative Theatre (OT), all children were sedated orally with midazolam (0.5 $mg.kg^{-1}$, maximumly 15 mg). Inhalational induction of anesthesia was performed with sevoflurane (2%–8%). Thereafter, propofol (1 $mg.kg^{-1}$), cis-atracurium (0.15 $mg.kg^{-1}$), and fentanyl (1 $\mu g.kg^{-1}$) were administered to facilitate intubation then ventilation with parameters adjusted to keep $EtCO_2$ as 35–40 mmHg. Anesthesia was continued with sevoflurane (1–2 MAC) and incremental doses of cis-atracurium.

After ensuring stable hemodynamic parameters, the patient was turned into prone position then under fully aseptic conditions, either ESPB or thoracic PVB was performed according to the patient's group allocation. For all patients, blocks were given under ultrasonographic guidance using a linear transducer (Vivid S6, GE, 4–13 MHz). For both blocks, the same volume was given as 0.3 $mL.kg^{-1}$ of the anesthetic mixture (bupivacaine 0.25% in epinephrine 1:100000) in the ipsilateral side of the surgical procedure.

In the ESPB group: T11 spinous process was identified by counting from C7 spinous process downwards. The ultrasound transducer was then applied at this level in transverse position to locate the tip of the T11 transverse process. The transducer was then rotated to a longitudinal position to visualize the Erector Spinae Muscle (ESM). Thereafter, a 22-G echogenic needle (50—80 mm) was inserted using the in-plane technique in a caudal-to-cranial direction aiming to contact T11 transverse process. After negative aspiration, the accurate needle tip position was verified by injecting 1–

2 mL saline to elevate the ESM. Finally, the anesthetic mixture was injected.

In the thoracic PVB group, T10 and T11 spinous processes were identified by counting from C7 spinous process downwards. The ultrasound transducer was then applied in a parasagittal position slightly lateral to T10 and T11 spinous processes to visualize the superior costotransverse ligament, pleura, and paravertebral space. Thereafter, the needle was inserted using the in-plane technique in a caudal-to-cranial direction to penetrate the ligament targeting the T10–T11 paravertebral space. After negative aspiration, hydrolocalization was done by injecting 1–2 mL saline to confirm the correct position of the needle tip by displacing the ipsilateral pleura anteriorly. Finally, the same anesthetic mixture was injected.

Surgery was authorized to begin 15 minutes after the regional blockade. Rise of the Heart Rate (HR) > 20% in response to the surgical procedure was controlled first by increasing the inspired concentration of sevoflurane to 4% and then with a single bolus dose of fentanyl (1 $\mu g.kg^{-1}$). Prior to the end of surgery, IV dexamethasone (0.2 $mg.kg^{-1}$), ondansetron (0.1 $mg.kg^{-1}$), and paracetamol (15 $mg.kg^{-1}$) were administered to the patient. After returning the patient to the supine position; sevoflurane was turned off, and the neuromuscular agent was reversed. After extubation, the child was transferred to the Post-Anesthesia Care Unit (PACU) for two hours and then to a surgical intermediate care unit.

Surgery

The surgical technique was standardized for all patients as follows: while the patient in lithotomy position, the urethra was anesthetized with lidocaine gel then, a 5-French ureteric catheter was inserted. The patient was then put into prone position with careful padding of the knees and feet. A 16-gauge needle was used to access the pelvicalyceal system through the targeted calyx under fluoroscopic guidance with injection of contrast material through the ureteric catheter. After introduction of a guidewire through the needle, the percutaneous tract was dilated by serial dilators and established by placing an 18-French access sheath. Nephroscopy was done using a 12-French rigid nephroscope. After stone disintegration using a ballistic lithotripter, the maneuver was concluded by the placement of a 14-French nephrostomy tube that remained in place at least 24 hours postoperatively.

Postoperative pain management

Starting from admission to the PACU, patients were allowed to be accompanied by one of their parents/care givers. Postoperative pain was scored from 0–10 based on the Face, Legs, Activity, Cry and Consolability (FLACC) scale.[11] Pain assessment was done in the PACU at 0.5-, 1-, and 2 hours of arrival; then in the surgical intermediate care unit at 4, 6, 12, and 24 hours. IV paracetamol was prescribed regularly every six hours. If the pain score was ≥ 4 during routine assessment or in between upon patient or relative request, nalbuphine (0.1 $mg.kg^{-1}$) was administered. If the pain score remained ≥ 4, another dose of nalbuphine was administered. Block failure was considered if the patient received two doses of nalbuphine in the PACU.

Study outcomes

The primary outcome was time to first rescue analgesia (nalbuphine) based on FLACC ≥ 4. The secondary outcomes included the total dose and frequency of nalbuphine in the first 24 hours postoperatively, the time needed to conduct the block, the intraoperative HR and Mean Arterial Pressure (MAP), the maximum inspired sevoflurane concentration, and the incidences of complications.

Sample size calculation and statistical analysis

Based on a former trial,[5] in which the time to first rescue analgesia after PVB was 664.4 ± 223.4 minutes, G*Power 3 was used to compute the minimum sample size as 26 patients in each arm to detect an absolute difference of 0.8 in the meantime to first rescue analgesia assuming 40% change and a power of 80%. A two-tailed p-value was considered statistically significant if < 0.05. To compensate for probable dropouts, the sample was increased to 28 patients in each arm.

SPSS-IBM (23.0) was utilized for data analysis. Variables are presented as mean ± standard deviation, number (%), or median (Q1, Q3). Survival analysis with log Rank test and Kaplan-Meier plot was done for time to first rescue analgesia. Numerical variables were compared with independent-samples *t*-test/Mann-Whitney *U* test as appropriate. Chi-Square/Fisher's exact test was used as appropriate to compare the categorical variables.

Results

From October 2022 to September 2023, we screened 73 patients. Out of them, 56 patients fulfilled the inclusion criteria of this trial and were randomly enrolled into two equal groups to receive ESPB or thoracic PVB. The surgical procedure was changed for one patient intraoperatively. So, the final analysis included 27 patients in the ESPB group and 28 patients in the thoracic PVB group (Fig. 1).

Patients' characteristics are presented in Table 1. The time to conduct the block was significantly shorter in the ESPB group compared to the thoracic PVB group (p = 0.028). The side and duration of surgery was not significantly different between both groups (Table 1).

The survival analysis and the Kaplan-Meier plot showed no significant difference between both groups in the time to first rescue analgesia postoperatively (15.98 ± 10.17 h [95% CI: 12.14–19.82] in the ESPB group versus 18.18 ± 9.18 h [95% CI: 14.7–21.58] in the thoracic PVB group, [p = 0.464, log-rank test]) (Fig. 2).

The percentages of patients who had FLACC scores < 4 without any rescue analgesia were comparable between both groups during the first 2, 6, 12, and 24 hours postoperatively. Furthermore, during the first 24 hours postoperatively, the total dose and frequency of rescue analgesia showed no significant differences between both groups (Table 2). Only one patient in each group received two doses of nalbuphine in the PACU to achieve a pain score < 4.

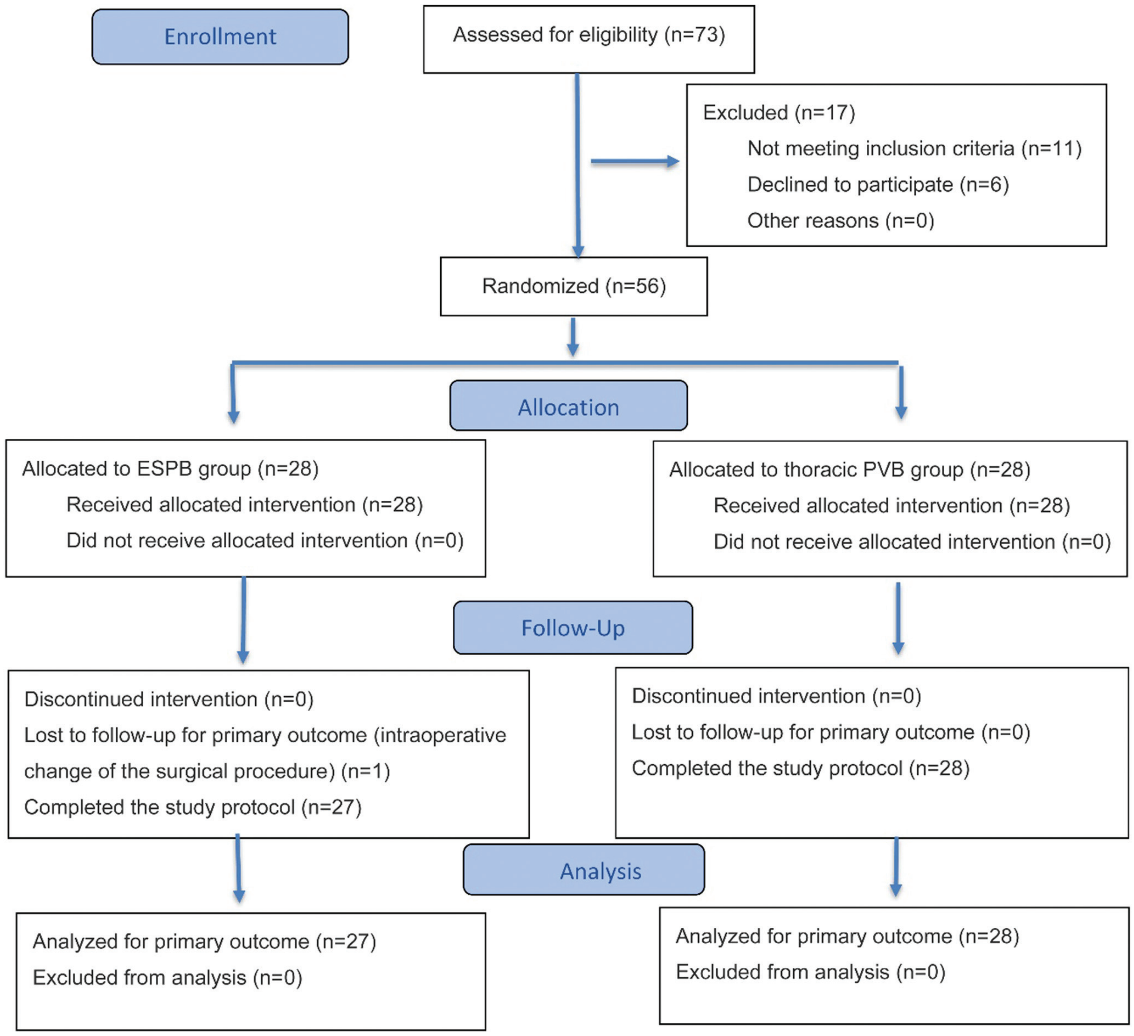

Figure 1 Consolidated standards of reporting trials (CONSORT) flow diagram of the participants. ESPB, Erector Spinae Plane Block; PVB, Paravertebral Block.

Baseline HR and MAP were comparable between both groups, and so were the next intraoperative measurements. Moreover, the percentage of children who had ≥ 20% increase in the HR after nephroscopy did not significantly differ between both groups. There was also no significant difference in the maximum inspired sevoflurane concentration (Table 3). No cases of pneumothorax, Local Anesthetic (LA) toxicity, repeated vomiting, or significant hemodynamic changes were reported.

Table 1 Patients' characteristics and anesthetic and surgical data.

Parameters	ESPB group (n = 27)	Thoracic PVB group (n = 28)	p-value
Age (years)	4.49 ± 1.66	4.91 ± 1.44	
Gender (male/female)	12/15	11/17	
Weight (kg)	16.0 (13.0–19.0)	17.0 (15.0–20.0)	
Height (cm)	106.0 (90.0–110.0)	107.0 (101–115)	
ASA PS (I/II)	18/9	15/13	0.322[a]
Time to conduct the block (min)	4.37 ± 1.08	5.05 ± 1.17	0.028[b]
Side of surgery (right/left)	16/11	13/15	0.341[a]
Duration of surgery (min)	86.41 ± 21.89	84.75 ± 31.73	0.823[b]

Data are presented as mean ± SD, median (Q1, Q3), or number.
ESPB, Erector Spinae Plane Block; PVB, Paravertebral Block; ASA PS, American Society of Anesthesiologist Physical Status.
[a] Chi-Square test.
[b] Independent sample *t*-test
Statistically significant difference is considered as p-value < 0.05.

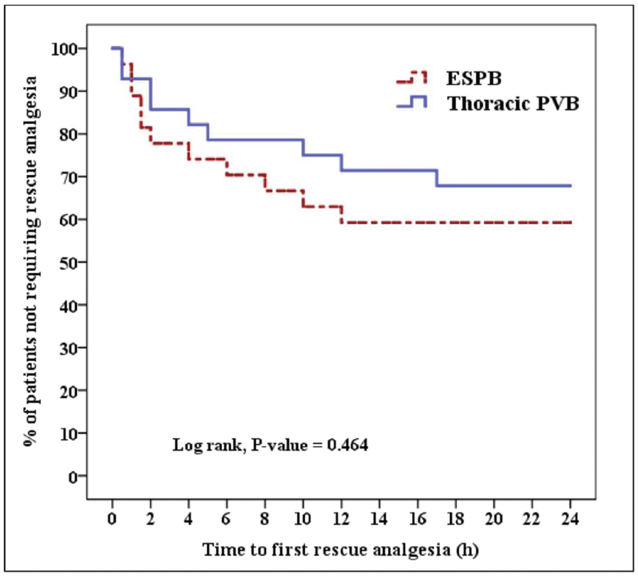

Figure 2 Kaplan-Meier survival plot illustrating the time to first rescue analgesia in both groups. ESPB, Erector Spinae Plane Block; PVB, Paravertebral Block.

Discussion

In this trial, the analgesic efficacy of ESPB was compared to that of thoracic PVB in children undergoing PCNL procedure. The main findings of this trial were that the time to first rescue analgesia and the total dose and frequency of nalbuphine administration in the first 24 hours postoperatively were comparable in both arms.

Over several decades, caudal block was the most common regional block to be conducted with general anesthesia for pediatric patients undergoing infraumbilical surgeries.[12] However, with the advances in ultrasound technology, new regional techniques emerged with an observed gradual transition from central neuraxial blocks to peripheral and truncal blocks.[13] An additional advantage of the truncal blocks is the injection of the anesthetic agents in a muscle plane with no need to identify a certain plexus or nerve.[14] Among those are the thoracic PVB and ESPB.

Providing adequate analgesia for patients undergoing open renal surgeries or PCNL requires blocking both the visceral and somatic innervations to the kidney, ureter, muscle, and skin. This can be readily achieved by ipsilateral paravertebral block at the level of T10–L1.[15,16] In this context, thoracic PVB has been reported in many occasions to provide effective analgesia for open renal surgeries or PCNL procedures in pediatric patients.[4,5,17]

Shortly after its first description in 2016,[6] several case reports and series reported ESPB as part of the analgesia in pediatric patients undergoing numerous surgical procedures.[8] Holland et al.[18] reviewed the data of 164 children who received ESPB at a single institution, and reported encouraging results in the surgeries that involved incisions from T1–L4. Another retrospective observational study reported that ESPB was effective to achieve opioid-free analgesia after different surgical procedures in pediatric patients.[19] These initial promising findings encouraged the design of Randomized Clinical Trials (RCTs) that reported positive results in pediatric patients undergoing different surgical procedures in terms of reduced postoperative pain scores and decreased intraoperative and postoperative opioid and non-opioid analgesic consumption.[20-22] Furthermore, some trials reported ESPB to be more effective than caudal block in lower abdominal, renal, and hypospadias surgeries.[22-24]

In the literature, various studies evaluated using the ESPB for pain management in adult patients undergoing PCNL procedure. Liu et al.,[25] in a meta-analysis that included 456 adult patients in eight RCTs, described ESPB as a safe and effective technique for this purpose as compared to no block, local anesthetic infiltration, or conventional intravenous analgesia.

Table 2 Postoperative pain.

Parameters	ESPB group (n = 27)	Thoracic PVB group (n = 28)	RR (95% CI)	p-value
FLACC score < 4 without any rescue analgesia				
During the first 2 postoperative hours	21 (77.8)	24 (85.7)	0.907 (0.705–1.167)	0.446[a]
During the first 6 postoperative hours	19 (70.4)	22 (78.6)	0.896 (0.656–1.224)	0.485[a]
During the first 12 postoperative hours	16 (59.3)	20 (71.4)	0.830 (0.561–1.226)	0.343[a]
During the first 24 postoperative hours	16 (59.3)	19 (67.9)	0.873 (0.583–1.307)	0.508[a]
Rescue analgesia during the first 24 hours				
Total dose of nalbuphine (mg)	0 (0, 2)	0 (0, 1.65)		0.488[b]
Frequency of nalbuphine	0 (0, 1)	1 (0, 1)		0.479[b]

Data are presented as number (%) or median (Q1, Q2).
ESPB, Erector Spinae Plane Block; PVB, Paravertebral Block; RR, Relative Risk; CI, Confidence Interval; FLACC, Face, Legs, Activity, Cry, and Consolability.
[a] Chi-Square test.
[b] Mann-Whitney *U* test.

Table 3 Intraoperative data.

Parameters	ESPB group (n = 27)	Thoracic PVB group (n = 28)	95% CI	p-value
Patients with ≥ 20% increase in HR after nephroscopy	1 (3.7)	3 (10.7)		0.319[a]
HR (beats/min)				
Baseline	112.93 ± 19.62	109.57 ± 14.97	-12.77, 6.06	0.478[b]
5 minutes after intubation	113.15 ± 25.33	102.32 ± 13.73	-21.99, 0.37	0.057[b]
Before nephroscopy	100.48 ± 20.03	93.75 ± 10.69	-15.53, 2.07	0.345[b]
1 min after nephroscopy	101.63 ± 20.77	98.71 ± 14.51	-12.58, 6.75	0.893[b]
During skin closure	102.78 ± 19.25	97.21 ± 12.48	-14.31, 3.18	0.427[b]
MAP (mmHg)				
Baseline	71.62 ± 12.10	69.74 ± 17.86	-10.32, 6.57	0.226[b]
5 minutes after intubation	69.7 ± 12.50	64.68 ± 10.11	-11.24, 1.14	0.129[b]
Before nephroscopy	68.59 ± 12.92	71.50 ± 14.39	-4.50, 10.31	0.469[b]
After nephroscopy	70.15 ± 11.61	70.50 ± 11.45	-5.95, 6.65	0.913[b]
During skin closure	75.85 ± 14.67	74.82 ± 12.75	-8.45, 6.39	0.782[b]
Maximum inspired sevoflurane (%)	2.1 (1.8–2.7)	2 (1.9–2.4)		0.892[c]

Data are presented as mean ± SD, median (Q1, Q3), or number (%).
ESPB, Erector Spinae Plane Block; PVB, Paravertebral Block; HR, Heart Rate; MAP, Mean Arterial Pressure.
[a] Fisher's Exact test.
[b] Independent sample *t*-test
[c] Mann-Whitney *U* test.

To our knowledge, the current trial is the first to compare ESPB with thoracic PVB in pediatric patients undergoing PCNL procedure. Consistent with our findings, Khot et al.[26] compared both blocks in adult patients undergoing PCNL procedure and reported that both blocks were equally effective in providing postoperative analgesia. Similarly, Fan et al.[27] compared both blocks for pain management after laparoscopic nephrectomy in adult patients and reported that ESPB provided non-inferior analgesia within the first 24 hours postoperatively.

In PVB, the LA is injected into the Paravertebral Space (PVS) to block the spinal nerves in close proximity to their roots generating ipsilateral sensory, motor, and sympathetic block.[5,28] In ESPB, the target is to inject the LA into the erector spinae facial plane, a virtual space beneath the erector spinae muscle that communicates with the PVS. The exact mode of action of ESPB is still not fully understood. However, some imaging and cadaver models showed coverage of the dorsal rami with frequent extension towards the ventral rami and the PVS.[8,29] This relative similarity of the mode of action of ESPB and thoracic PVB may explain the comparable analgesic effects of both blocks that are noticed in the current study, and in various previous studies.[26,27,30]

In the current study, we used a single-shot technique. This technique has been widely accepted as in both thoracic PVB and ESPB, the injected local anesthetic agents tend to spread caudally and cranially to cover multiple levels.[8,16] Moreover, the single-shot technique is less time-consuming and carries less risk of complications. In addition, we found that the time to conduct the block was significantly shorter in the ESPB group. This is consistent with some previous results,[26,30] and can be explained by the relative ease to get the sono-anatomic view required to conduct the ESPB. Moreover, the site of injection is superficial compared to the paravertebral space which is deeper and has close proximity to the pleura.[8,28] Nevertheless, in the current study, the statistically significant difference in the time to conduct the block between the two studied groups should be interpreted cautiously as it did not reach a clinically important value. Moreover, the current study was not powered for this secondary outcome.

The safety profile of any regional block is a cornerstone that encourages or discourages considering it in clinical practice as part of the anesthetic and analgesic plan. In this study, no incidents of pneumothorax or LA toxicity were mentioned in the two studied groups. In this context, Vecchione et al.,[31] in their observational study that included 871 pediatric patients, described the thoracic PVB to have low risk of complications. With regard to the ESPB, different studies reported it as associated with no or low risk of complications in the pediatric population undergoing various types of surgeries.[8,24] Furthermore, De Cassai et al.[32] analyzed 45 RCTs that included 1,386 adult patients who received unilateral or bilateral ESPBs for different surgical procedures and reported no complications. Therefore, in general, the ESPB was described to have a better safety profile compared with other loco-regional techniques including the PVB,[29] and hence it can be advised as an alternative whenever epidural block or PVB are contraindicated or difficult to conduct.

This work had some limitations. First, postoperative pain was assessed by different nurses during the 24-hour period of follow-up. Nevertheless, all the involved nurses were well-trained to use the FLACC scale in pediatric patients. Second, as we assumed a power of 80% during sample size calculation and since no significant difference was detected in the primary outcome, type II error cannot be excluded and small, yet clinically significant, differences might be unrevealed. Third, the sample size might be insufficient to compare the incidence of complications in both blocks.

Finally, we recommend further RCTs with larger sample sizes to confirm the current findings or to detect small, yet clinically significant differences between both groups. We also suggest future RCTs with different volumes/concentrations of the local anesthetic, or with adding adjuvant agents to achieve optimum postoperative pain management.

Conclusion

ESPB was not found to be more effective than thoracic PVB for postoperative pain management in children undergoing PCNL procedure. Moreover, the intraoperative hemodynamics and maximum sevoflurane concentration were comparable. The time to conduct ESPB was significantly shorter; hence, it could be considered as an easy alternative to thoracic PVB for this procedure.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

The registry of the study

This study was registered on clinicaltrials.gov
Registration number: NCT05589649
Date of registration: October 18, 2022

Institutional review board approval

This study was approved from the Institutional Review Board (IRB) of Assiut University Faculty of Medicine, Egypt.
IRB n° 17300787
Date of approval: July 21, 2022

Authors' contributions

Fatma Nabil: Conceptualization; methodology; writing the original draft.
Ahmed M. Mandour: Methodology; data curation.
Amr M. Abdelgawad: Methodology; investigation.
Deiaaeldin M. Tamer: Methodology; data curation.
Ahmed A. Shahat: Investigation; software; writing the original draft.
Mohamed Anwar: Investigation; writing-review & editing; supervision.
Hany M. Osman: Formal analysis; writing-review & editing; project administration.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Randomized, double-blind trial of preoperative pregabalin versus placebo to improve quality of recovery after breast cancer surgery☆

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Abstract

Introduction: Surgery remains one of the most important treatments for breast cancer. In this context, the quality of postoperative recovery has become a key concern. Adequate control of acute pain is essential to optimize patient comfort and recovery. Pregabalin may contribute to this goal by preventing central sensitization and reducing perioperative anxiety.

Objectives: To evaluate the effect of perioperative pregabalin versus placebo on postoperative recovery quality in patients undergoing breast cancer surgery.

Method: In this randomized controlled trial, 92 patients received either pregabalin (150 mg orally, 1 hour before surgery) or a matching placebo, both prepared in identical capsules. The primary outcome was the QoR-15 score measured preoperatively, and at 24 and 48 hours postoperatively. The 24- and 48-hour assessments were conducted via telephone. The QoR-15 is a validated instrument that assesses the quality of recovery, with total scores ranging from 0 (very poor recovery) to 150 (excellent recovery). Secondary outcomes included opioid consumption, pain scores, incidence of nausea and vomiting, and lengths of stay in the Post-Anesthesia Care Unit (PACU) and hospital. An exploratory analysis of longitudinal changes in QoR-15 scores within each group was also performed. Analyses were performed per protocol.

Results: Eighty-four patients completed the study. There were no differences in overall QoR-15 score between the groups at any of the three assessment time points (preoperative, 24h, and 48h). In the exploratory longitudinal within-group analysis, better maintenance of recovery quality was observed in the pregabalin group compared with baseline, with medians (IQR) of 138 (122.3–145), 132.5 (125.8–135.3), and 134 (131.5–136) [$p = 0.006$ between 24h and 48h]. In the placebo group, the medians (IQR) were 140 (128–145.3), 129 (126–134.3), and 134 (126.8–136.3) [$p = 0.002$ between pre and 24h; $p = 0.026$ between pre and 48h].

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Conclusion: Although exploratory analysis showed a trend toward improvement within the pregabalin group, there was no significant difference in QoR-15 scores between groups.

Introduction

Breast cancer affects millions of women worldwide. In Brazil alone, 73.610 new cases were reported in 2023.[1] Surgery is widely recognized as one of the most important and frequently used treatments for breast cancer, particularly in cases diagnosed at early stages.[2-4] Consequently, the management of acute postoperative pain represents a fundamental component of care, as patients often experience a combination of nociceptive and neuropathic pain. In addition, preoperative anxiety influences the subjective perception of pain and may contribute to increased postoperative pain, morbidity, and mortality.[5] In this context, pregabalin has received attention due to emerging evidence supporting its benefit in the multimodal perioperative management of acute pain and anxiety.[6] Despite its limited formal indications, the off-label use of pregabalin has increased substantially, making it the tenth most prescribed medication in the United States in 2017.[7]

Therefore, it is essential to assess the effectiveness of such medications using instruments that capture a patient-centered perception of recovery.

Few studies in the literature have evaluated pregabalin's impact on the quality of recovery as a primary outcome, and none of them have specifically focused on breast cancer surgery.[8,9] Hence, a gap remains in the literature regarding a comprehensive evaluation of pregabalin use in the perioperative period, particularly in this surgical context.

We hypothesized that preoperative pregabalin, compared with placebo, would improve the perception of recovery in patients undergoing oncologic breast surgery, as assessed by the Quality of Recovery-15 (QoR-15) questionnaire. In addition, secondary outcomes such as the incidence of nausea and vomiting, opioid consumption, pain scores, and lengths of stay in the PACU and hospital were also assessed.

Methods

Study design and participants

This was a prospective, randomized clinical trial. Eligible patients were aged 20–65 years, classified as ASA I or II (American Society of Anesthesiologists), and scheduled for elective oncologic breast surgery at the University Hospital of the Jundiaí Medical School, São Paulo, between September 2022 and December 2023. All procedures were performed by the same surgical team. Patients initially enrolled in the study were subsequently excluded from the analysis if they had incomplete data or did not comply with the established protocols, such as failing to complete the postoperative assessment questionnaires.

Exclusion criteria included: patient refusal; altered level of consciousness or inability to communicate; any contraindication to the use of agents described in the study protocol; history of seizure disorder; current use of pregabalin or gabapentin; presence of chronic pain or current use of opioids; insulin-dependent diabetes mellitus; and renal insufficiency (estimated glomerular filtration rate < 60 mL/min/1.73 m^2). Patients were also excluded after randomization if there was any protocol violation, such as the use of non-protocol medications or refusal to complete the perioperative QoR-15 questionnaire.

Randomization

Patients were randomly assigned in a 1:1 ratio to receive either pregabalin or placebo by a researcher not involved in anesthesia management or questionnaire collection. Group allocation was determined on the morning of surgery using a computer-generated random sequence (www.random.org). The study medications were prepared in identical capsules to ensure blinding. For each patient, an opaque envelope containing a single capsule (150 mg pregabalin or placebo) was prepared, sealed, and labeled with an identification number (1 or 2) by an anesthesiologist who was not involved in the study. The envelopes were stored securely by a research assistant.

One hour before the start of surgery, the assigned capsule was administered orally by a member of the clinical staff who was not involved in anesthesia care. The randomization sequence was kept confidential by one investigator until completion of data analysis. The statistician, independent from the anesthesia team and data collection, conducted all analyses while blinded to group allocation. Patients, surgeons, anesthesiologists, and all personnel involved in anesthesia management or data collection were unaware of treatment assignment.

Outcomes

The primary outcome of the study was to evaluate the effect of perioperative pregabalin versus placebo on postoperative quality of recovery through the QoR-15 questionnaire. Additionally, an exploratory within-group (longitudinal) analysis was conducted to assess potential trends in recovery over time within each group.

Secondary outcomes included postoperative pain (at rest and during movement), opioid consumption, incidence of nausea and vomiting, length of stay in the PACU, and overall hospital length of stay.

Anesthesia

Patients were monitored according to standard ASA guidelines. General anesthesia was induced with fentanyl (4 $\mu g \cdot kg^{-1}$), propofol (2.0 $mg \cdot kg^{-1}$), rocuronium (0.6 $mg \cdot kg^{-1}$), and esketamine (0.3 $mg \cdot kg^{-1}$). Sevoflurane was used to maintain the desired anesthetic depth.

Intraoperative medications included dexamethasone (10 mg), ketoprofen (100 mg), dipyrone (2000 mg), and ondansetron (4 mg). At the end of the procedure, the surgical wound was infiltrated with local anesthetic (ropivacaine 0.75%, 20 mL). Neuromuscular blockade was reversed based on Train-Of-Four (TOF) monitoring, with atropine (0.01 $mg \cdot kg^{-1}$) and neostigmine (20–70 $\mu g \cdot kg^{-1}$) administered according to the degree of residual blockade.

Measurements and treatment of postoperative pain

Pain was assessed in the PACU every 15 minutes using a Verbal Numeric Rating Scale (VNRS) from 0 to 10, both at rest and during movement, where 0 represented no pain and 10 represented the worst possible pain. To assess pain during movement, patients were asked to perform a 90° arm abduction on the surgical side.

Intravenous morphine (1–2 mg) was administered every 10 minutes until a pain score below 4 was achieved (1 mg if pain < 7, 2 mg if pain ≥ 7). The occurrence of nausea and vomiting, as well as the number of vomiting episodes, was recorded. These symptoms were treated with intravenous dimenhydrinate (30 mg), and if needed, metoclopramide (10 mg) was administered subsequently.

After PACU discharge (Aldrete score $\geq$ 9), patients received ketoprofen 100 mg every 12 hours and oral dipyrone 500 mg every 6 hours. In the hospital ward, intravenous tramadol 100 mg was administered if the pain score exceeded 4.

Post-discharge follow-up was conducted by telephone at 24 and 48 hours, during which resting, and movement-related pain were recorded.

Assessment of patient's characteristics and perioperative data

Data collected included age, sex, ASA physical status, BMI, creatinine clearance (Cockcroft-Gault), duration of surgery, pain scores, and total consumption of morphine and tramadol.

The QoR-15 questionnaire was administered at three time points: 1-hour before surgery (in person) and at 24 and 48 hours postoperatively (by telephone). The QoR-15 is a short version of the QoR-40 and has been adapted into Portuguese following established guidelines (Fig. S1).[10]

It consists of 15 items divided into two parts: A and B. In Part A, the items reflect positive aspects of recovery and are rated on an 11-point numerical scale ranging from 0 ("none of the time") to 10 ("all of the time"). In Part B, the scoring is reversed: 10 corresponds to "none of the time" and 0 to "all of the time".

The QoR-15 evaluates five key dimensions of recovery: pain (2 items), physical comfort (5 items), physical independence (2 items), psychological support (2 items), and emotional state (4 items). The total score ranges from 0 (poor recovery) to 150 (excellent recovery).

Sample size

A sample size of 37 patients per group was estimated to achieve 85% power to detect a 12-point difference in the QoR-15 score, with a standard deviation of 17. This calculation was based on a 12-point difference in mean scores observed in a previous study using the QoR-15 in medium- and major-sized surgeries, as this reflects a realistic effect expected in our population. The Standard Deviation (SD) of QoR-15 scores in that study ranged from 17 to 18; therefore, an SD of 17 was considered acceptable.[11] Considering potential dropouts during the study, a total of 92 patients were recruited.

Ethics statement

This study was approved by the University Hospital of Jundiaí and the Ethics Committee (CAAE: 60819922.0.0000.5412, approved on 20/09/2022) at the Jundiaí Medical, registered on the Brazilian Clinical Trials Registry website (REBEC – U1111-1278-3266, approved on 14/03/2023), and all patients were informed and signed the Informed Consent Form.

Statistical analysis

After data collection, the distribution of the primary outcome was assessed using the Kolmogorov-Smirnov test and did not meet the assumption of normality; therefore, it was expressed as median and Interquartile Range (IQR). The groups (independent samples) were compared using the Mann-Whitney test for all quantitative factors. Categorical data and their frequencies were compared using the χ^2 test. Finally, for the exploratory analysis of QoR-15 evolution in each group (preoperative, 24 and 48 hours), since there were three measurement time points, the Friedman test was used, followed by the Wilcoxon test for pairwise post-hoc comparisons. Additionally, a subgroup analysis was performed excluding minor surgical procedures to assess whether surgery size influenced the results for both the primary outcome and pain scores.

The criterion for rejecting the null hypothesis was a $p < 0.05$ for both primary and secondary outcomes. Statistical analyses were performed using SPSS V26 (2019), Minitab 21.2 (2022), and Excel Office 2010.

Results

Initially, 92 patients were enrolled in the trial; however, 8 were excluded after randomization: 7 due to failure to reach patients by phone to complete the 24- and 48-hour questionnaires, and 1 for receiving a dose of tramadol in the PACU, which was not part of the study's analgesic regimen. Following the per-protocol analysis, 84 patients were included in the final analysis, with 44 in the pregabalin group and 40 in the placebo group (Fig. 1).

It was noted that both groups consisted mainly of patients classified as ASA 2. The most common surgery performed was segmental mastectomy without axillary dissection, resulting in a predominance of medium-sized surgeries in both groups. Four complications were observed, all of which were minor, occurring during the intraoperative and immediate postoperative periods: one intraoperative hypertensive peak in each group, one episode of delirium upon awakening in the placebo group, and one vascular injury related to the surgical procedure in the pregabalin group. There were no

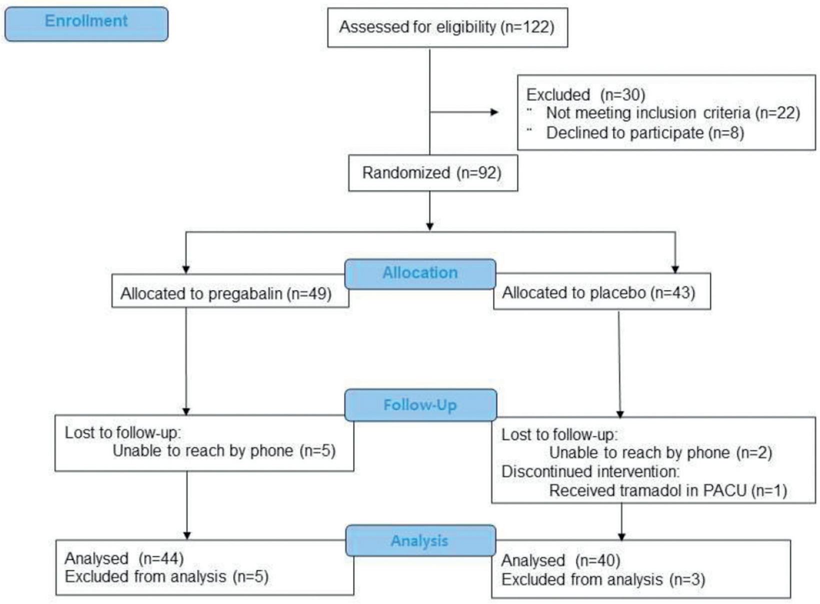

Figure 1 CONSORT Flow diagram of patient enrollment in the study.

statistically significant differences in demographic or clinical characteristics between the groups (Table 1 and S1).

A comparison of the QoR-15 scores at three time points (preoperative, 24 hours, and 48 hours) revealed no significant difference between the groups (Table 2 and Fig. 2).

Next, an exploratory longitudinal analysis of the QoR-15 was performed to evaluate changes in scores within each group. The three time points were first assessed, followed by pairwise post-hoc comparisons between assessment points. The p-values from Table 3 indicate a statistical difference in

Table 1 Demographic data and patient characteristics.

Variables	Placebo (n = 40)	Pregabalin (n = 44)	p-value
Age (years), Median (Q_1 – Q_3)	49 (43.3 – 57.5)	53 (44.7 – 59)	0.754[a]
Height (m), Median (Q_1 – Q_3)	1.6 (1.5 – 1.6)	1.6 (1.5 – 1.6)	0.896[a]
Weight (kg), Median (Q_1 – Q_3)	71 (62.8 – 83.3)	71.5 (64 – 78.5)	0.657[a]
BMI (kg.m^{-2}), Median (Q_1 – Q_3)	28.4 (25 – 31.5)	27.5 (25.1 – 30.2)	0.658[a]
ASA I:II, n	6:34	6:38	0.858[b]
Previous surgery, n (%)	28 (70%)	30 (68.2%)	0.857[b]
Surgical duration (min), Median (Q_1 – Q_3)	57.5 (40 – 75)	50 (40 – 60)	0.142[a]
Time to awakening (min), Median (Q_1 – Q_3)	12.5 (10 – 15)	10 (10 – 15)	0.732[a]
Surgery complexity, n (%)[c]			
Major	4 (10%)	6 (13.6%)	0.607[b]
Moderate	32 (80%)	33 (75%)	0.584[b]
Minor	4 (10%)	5 (11.4%)	0.840[b]
Complications	2 (5%)	2 (4.5%)	0.922[b]

Q1, First Quartile; Q3, Third Quartile.
[a] Mann-Whitney test.
[b] χ^2 test.
[c] Major, including unilateral or bilateral mastectomy, with or without prosthesis removal or placement; Moderate, segmental mastectomy or wide local excision; Minor, Unilateral excisional biopsy and nodulectomy.

Table 2 QoR-15 scores at the three time points in each group.

	Time points	Placebo	Pregabalin	p-value[b]
QoR-15[a]	Pre	140 (128 – 145.3)	138 (122.3 – 145)	0.616
	24 hours	129 (126 – 134.3)	132.5 (125.8 – 135.3)	0.495
	48 hours	134 (126.8 – 136.3)	134 (131.5 – 136)	0.634

[a] Median and Interquartile Range.
[b] Mann-Whitney test.

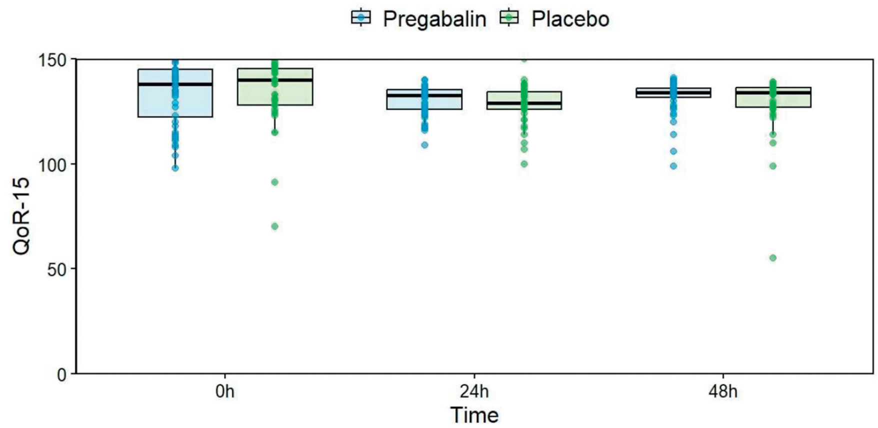

Figure 2 Comparison of QoR-15 scores between groups. Data are presented as median (interquartile range); points represent individual patients.

Table 3 Compares the evolution of QoR-15 score by Group and post-hoc p-values.

	QoR Pre	QoR 24 hours	QoR 48 hours	p-value			
				Total[b]	Pre/24[c]	Pre/48[c]	24/48[c]
Placebo[a]	140 (128 – 145.3)	129 (126 – 134.3)	134 (126.8 – 136.3)	0.002	0.002	0.026	0.054
Pregabalin[a]	138 (122.3 — 145)	132.5 (125.8 — 135.3)	134 (131.5 — 136)	0.008	0.176	0.398	0.006

[a] Median and Interquartile Range.
[b] Friedman test.
[c] Wilcoxon test.

the evolution of the QoR-15 score at different time points in both groups, with a p = 0.002 for the placebo group and a p = 0.008 for the pregabalin group. In the placebo group, the median started at 140 preoperatively, dropped to 129 at 24 hours, and then increased to 134 at 48 hours. Post-hoc analysis revealed a significant decrease in the QoR-15 score between the preoperative time and both postoperative time points (p = 0.002 for 24 hours and p = 0.026 for 48 hours). In the pregabalin group, the median started at 138, dropped to 132.5 at 24 hours, and ended at 134 at 48 hours. Post-hoc analysis showed only a significant difference between the 24-hour and 48-hour postoperative scores (p = 0.006), representing an

QoR-15 Items[a]	Pregabalin			Control		
	Pre	24 h	48 h	Pre	24 h	48 h
1.Able to breathe easy	9.00	9.93	9.93	9.70	9.83	9.95
2.Been able to enjoy food	8.86	9.52	9.68	9.43	9.60	9.65
3.Feeling rested	8.34	9.20	9.34	8.73	9.03	9.43
4.Have had a good sleep	8.34	8.09	8.50	7.78	8.23	8.43
5.Able to look after personal toilet and hygiene unaided	10.00	9.18	9.34	9.93	9.40	9.15
6.Able to communicate with family or friends	9.95	10.00	10.00	9.93	9.98	9.75
7.Getting support from hospital doctors and nurses	9.73	10.00	10.00	9.93	10.00	9.98
8.Able to return to work or usual home activities	8.89	0.82	0.82	8.63	0.73	0.25
9.Feeling comfortable and in control	9.11	9.93	9.80	9.40	9.88	9.75
10.Have a feeling of general well-being	8.80	8.66	8.80	9.00	8.70	8.73
11.Moderate pain	8.70	7.30	7.70	8.45	6.50	6.85
12.Severe pain	9.64	10.00	10.00	9.78	9.88	9.68
13.Nausea or vomiting	9.32	9.32	9.43	9.38	8.90	9.55
14.Feeling worried or anxious	6.16	8.30	8.84	5.63	8.65	8.78
15.Feeling sad or depressed	8.48	9.64	9.64	8.88	9.30	9.23

Figure 3 Heat map of the mean score for each QoR-15 item at the three perioperative time points. Part A (questions 1–10) and Part B (questions 11–15). Colors indicate score levels: dark green = high, yellow = medium, orange = low. Higher scores reflect better recovery. [a] Mean scores for each item.

improvement in the QoR-15 median during this interval (Table 3).

Analyzing Figure 3, which shows the heatmap of average QoR-15 item scores, it can be observed that "severe pain" was not a concern in the postoperative period for either group. The item with the lowest score in the preoperative period was the question "I felt worried or anxious", and in the postoperative period, the lowest scores were for "moderate pain" and "ability to return to work or domestic activities".

Postoperative pain scores, assessed using the Verbal Numerical Rating Scale (VNRS), did not differ between groups in the PACU, at 24 hours, or at 48 hours after surgery. Pain levels were low, with most median values in the PACU being 0 and interquartile ranges also at 0 (Table S2).

No significant differences were observed between the groups in the incidence of nausea and vomiting in the PACU and hospital ward, morphine consumption, or length of stay in the PACU and hospital (Table S3).

A subgroup analysis was performed, excluding minor surgeries (unilateral excisional biopsy and nodulectomy), evaluating both the primary outcome and pain. However, the null hypothesis could not be rejected, and the median values were very similar to those observed in the total study population (Table S4).

Discussion

The primary outcome of this study did not reveal significant differences in total QoR-15 scores between the pregabalin and placebo groups at 24 and 48 hours postoperatively. Similarly, no differences were observed in pain scores or opioid consumption. Exploratory longitudinal analyses within each group suggest that preoperative oral pregabalin may help maintain recovery quality over the postoperative period; however, these findings are hypothesis-generating and require confirmation using pre-specified longitudinal models in future studies.

Currently, both gabapentin and pregabalin are used to enhance postoperative recovery, serving as multimodal medication strategies for the control of acute pain and perioperative anxiety.[5,12-16] Several studies have been conducted evaluating pain and opioid consumption, and a recent meta-analysis demonstrated that pregabalin has modest efficacy in managing acute pain after breast cancer surgery, with greater efficiency in reducing chronic postoperative pain after 3 months. Acute pain at rest 24 hours after surgery was reduced by 0.31 points on a 0—10 VNRS (95% CI 0.05 to 0.57; p = 0.02).[17]

As demonstrated by Verret et al., it is crucial to consider a minimum difference of 10% on the pain scale to support the evidence that there is a clinically significant analgesic effect. Their meta-analysis found no relevant effects of gabapentinoids on postoperative pain – acute, subacute, or chronic – were found. This analysis included a wide range of surgical procedures, from endoscopic to major surgeries, with high heterogeneity, highlighting the variability of the included studies.[18,19]

It is known that determining whether a medication is effective or not depends on many factors, including the type of surgery performed and its extent. Mastectomies, in particular, are surgeries that involve nociceptive mechanisms, especially when the axillary region is involved.[15] Other studies have evaluated gabapentin specifically in oncologic breast surgery. For example, Jiang et al. demonstrated a reduction of 16.14 points (95% CI: 10.24—21.85; p < 0.001) and 27.33 points (95% CI: 3.63—51.03; p = 0.024) on the 110-point Visual Analog Scale (VAS) immediately after surgery and at 24 hours, respectively.[20]

Rai and colleagues also conducted a meta-analysis in the context of oncologic breast surgery, expanding the evaluation to include not only gabapentin but also pregabalin. A total of 516 patients were included in the gabapentin group and 209 in the pregabalin group. In the gabapentin group, using the 0—10 VNRS, pain in the PACU was reduced by 1.68 points (95% CI 0.77—2.59; p < 0.001), by 0.52 points (95% CI: 0.01—1.02; p = 0.04) at 24 hours, and morphine consumption on the first postoperative day decreased by 4.00 mg (95% CI 0.91—7.09; p = 0.01).[15]

In the same meta-analysis, only four pregabalin studies were included, and acute pain scores were reported in two trials. Pain in the PACU was reported in a single trial, showing a significant reduction in the pregabalin group (p = 0.01), while pain at 24 hours postoperatively was reported in both trials, with no significant reduction observed when pooled (p = 0.21). Three studies reported morphine consumption in the PACU, demonstrating a significant reduction of 4.8 mg (95% CI 0.83–8.76; p = 0.02) in the pregabalin group. It is noteworthy that two studies (accounting for nearly 60% of the patients in this subgroup) used a 75 mg pregabalin dose, one used 150 mg (16%), and the highest dose used was 300 mg (24%).[15] The use of multiple dosing regimens, in addition to the limited number of studies included in the analysis, may be the main reasons for the conflicting results reported in the literature.

However, the efficacy of a multimodal analgesic approach should not be assessed solely based on pain scores, as effective pain control methods with morphine or gabapentinoids may not reflect differences in final pain scores. In addition, postoperative opioid consumption is not considered a patient-centered outcome, as it may reflect both improved analgesia and decreased comfort or the occurrence of adverse events.[21] In this way, there is currently a growing concern regarding patients' perception and evaluation of the healthcare they receive. This perspective is often summarized by the expression "Through the Patient's Eyes".[22]

Borde et al. conducted a randomized clinical trial in patients undergoing off-pump coronary artery bypass surgery. Participants received 150 mg of pregabalin preoperatively, followed by 75 mg twice daily for 2 days after extubation. The primary outcome was the quality of recovery, assessed using the QoR-40 questionnaire. Patients in the pregabalin group had higher global QoR-40 scores 24 hours after extubation compared with the placebo group (177 $\pm$ 9 vs. 170 $\pm$ 9; p = 0.002). The pregabalin group also showed better scores in the emotional state, physical comfort, and pain dimensions.[9] Martins et al. also conducted an investigation in individuals undergoing bariatric surgery (non-laparoscopic); however, they did not find an improvement in recovery quality (assessed by QoR-40), raising the question of whether the lack of effect was due to the low pregabalin dose of 75 mg.[8]

Hetta et al. conducted a clinical trial in the context of oncologic breast surgery, aimed at predicting the optimal dose for achieving analgesic effects with minimal adverse effects. They compared placebo with three escalating doses of pregabalin (75, 150, and 300 mg) and found that a single preoperative dose of 150 mg pregabalin reduced pain and morphine consumption in the first 24 hours after mastectomies without increasing the incidence of pregabalin-related adverse events such as dizziness or visual disturbances.[23]

Based on these findings, our study selected a single preoperative dose of 150 mg pregabalin. However, we did not find statistically significant differences in pain scores (PACU, 24 and 48 hours) or opioid consumption. This result can partly be attributed to the multimodal analgesia employed both in the anesthetic technique and in the postoperative period for both groups (dexamethasone, ketoprofen, dipyrone, esketamine, local infiltration, and morphine rescue), which may have led to a redundant effect of pregabalin in this context of optimized multimodal analgesia.

Previous studies have shown that other agents, such as esketamine, can improve the quality of anesthetic recovery not only through analgesic effects and attenuation of hyperalgesia but also via their antidepressant properties. For instance, Gao et al. observed that esketamine contributed to better postoperative recovery in patients undergoing mastectomies, likely due to these multifaceted effects.[24] Considering that a significant proportion of women with breast cancer experience postoperative depression,[25] such pharmacological properties may enhance overall recovery.

Furthermore, most of the patients underwent small and medium-sized surgeries without axillary dissection, which are associated with lower nociceptive mechanisms.[15] To evaluate whether surgical extent could influence the results, we performed a subgroup analysis excluding minor procedures, such as nodulectomies and excisional biopsies. No differences in the primary outcome were observed at any time point between the groups. However, most of the included procedures were of moderate extent, such as segmental mastectomy without axillary dissection. It was not possible to perform an analysis exclusively on major surgeries, as the sample size for this type of procedure was small, which could compromise the validity of any conclusions.

As highlighted by Campfort et al., longitudinal analysis of individual patient trajectories can identify those with recovery below expectations, allowing more personalized perioperative management.[26] In our study, longitudinal analysis showed that pregabalin group-maintained baseline recovery scores in the first 24 hours, with an increase from 24 to 48 hours postoperatively. Conversely, the placebo group experienced a decline in recovery quality at 24 hours, which persisted at 48 hours. It was observed that the median in the placebo group decreased by 11 points 24 hours after surgery, which, according to Myles et al., represents a clinically relevant change of 8 points on the scale.[11]

This finding raises concern, as a reduced score within the first 24 hours after surgery is correlated with complications that can persist up to a month after the procedure.[26] Additionally, Chazapis et al. emphasized the importance of the 48-hour postoperative questionnaire approaching preoperative baseline levels. Failure to achieve this return may indicate undesirable recovery drift. This aspect was observed in the placebo group in our study, where the comparison of scores at 24 and 48 hours postoperatively was significantly lower than the preoperative baseline.[27]

In this study, most included procedures were segmental mastectomy without axillary dissection, generally associated with moderate complexity, lower pain levels, and faster recovery. This predominance of less extensive surgeries may limit the generalizability of our findings to mastectomies and other more extensive procedures, in which pregabalin could potentially have a greater impact. Therefore, many patients had high scores on the questionnaire, possibly reaching a ceiling effect, particularly on questions 11 and 12, which addressed pain. As a result, small differences in questionnaire scores may have gone undetected. The use of a robust multimodal analgesic regimen and local infiltration likely minimized detectable between-group differences in pain and overall QoR-15 scores. An additional limitation identified was the lack of Patient-Controlled Analgesia (PCA), which may have implications for pain perception and management in the postoperative period. Moreover, we did not assess pain during the period between PACU discharge and the first 24 hours post-procedure. We also did not systematically evaluate adverse effects such as visual disturbances or sedation using validated scales, which could have provided further insights into patient comfort and well-being. Finally, an important methodological limitation is the absence of pre-specified longitudinal modeling. Although exploratory within-group analyses in the pregabalin group suggest a more favorable recovery trajectory, these findings should be interpreted with caution. It is crucial to consider these limitations when interpreting the results and applying the conclusions of this study.

Conclusion

A single preoperative dose of 150 mg pregabalin did not produce significant differences in total QoR-15 scores between groups at 24 and 48 hours, nor in pain control or opioid consumption. In an exploratory longitudinal analysis, within-group trajectories suggest that pregabalin may help maintain recovery quality over the postoperative period, a finding that requires confirmation using pre-specified longitudinal models.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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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.2026.844749.

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ORIGINAL INVESTIGATION

Diagnostic accuracy of the Voluntary Breath-Hold Test to discriminate normal vs. abnormal spirometry: a two-gate study

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Abstract
Introduction: The Voluntary Breath-Hold Test (VBHT) is a simple, bedside, and rapid assessment that measures the duration of voluntary apnea. It has shown potential for clinical use, including as a triage tool prior to spirometry in primary care. However, its diagnostic accuracy in detecting abnormal pulmonary function before non-thoracic surgeries has not been established. This study aimed to determine the correlation between VBHT results, Maximal Voluntary Apnea Inspiratory Time (MVAIT) and Maximal Voluntary Apnea Expiratory Time (MVAET), and spirometry, the reference test for assessing pulmonary function.
Methods: This diagnostic-accuracy study included adults with normal spirometry and those with obstructive or restrictive ventilatory defects. Participants were divided into normal and abnormal spirometry groups. Maximal Voluntary Apnea Inspiratory Time (MVAIT) and Expiratory Time (MVAET) were evaluated using Receiver Operating Characteristic (ROC) curve analysis to assess their accuracy in distinguishing between normal and abnormal spirometry patterns.
Results: The study included 293 participants. MVAIT and MVAET were significantly lower for the abnormal (median: 29.32 s; 95% Confidence Interval [95% CI]: 25.99–32.35 s and median: 20.40 s; 95% CI: 18.66–22.88 s) than for the normal (median: 47.55 s; 95% CI: 43.93–51.87 s and median: 28.53 s; 95% CI: 26.74–30.63 s) group. For the prediction of normal spirometry, MVAIT $\geq$ 45.49 s and MVAET $\geq$ 32.86 s had sensitivity and specificity of (90.43%, 55.06%) and (90.43%, 33.71%), respectively.
Conclusion: VBHT is a bedside, low-cost, and safe method that shows moderate-to-good discriminative ability for identifying abnormal spirometry results. As an innovative adaptation of a long-known physiological maneuver, VBHT may serve as a rapid preliminary triage (rule-out) tool prior to formal spirometry, pending external validation in preoperative populations.

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Introduction

Pulmonary dysfunction is a major cause of morbidity and prolonged hospital stay after non-thoracic surgery, particularly among patients with Chronic Obstructive Pulmonary Disease (COPD).[1-3] Spirometry is the most widely used test for assessing lung function, especially through measurements such as Forced Vital Capacity (FVC). Identifying patients with abnormal spirometry before surgery is essential for optimizing perioperative management and reducing respiratory risk.[2]

Spirometry requires its own equipment, trained technicians, and interpretation by a specialist physician, which can limit its availability immediately before surgery, particularly in emergency abdominal, vascular and orthopedic surgeries.[4] The Voluntary Breath-Hold Test (VBHT) is a simple, inexpensive, bedside, and rapid assessment that may provide useful information about ventilatory function when spirometry is not readily available.

Apnea is defined as the temporary cessation of gas exchange between the lungs and the atmosphere.[5] In breath-holding, there is a period without respiratory sensation or electromyographic activity of the respiratory muscles after the onset of voluntary apnea. The period between the onset of apnea and the onset of the sensation of dyspnea can be considered a "comfort phase". After a few seconds, electromyographic activity of the diaphragm and sensation of dyspnea (uncomfortable awareness of difficulty breathing) evolve and progressively increase to the endpoint of apnea (breaking point), constituting the "struggle phase".[5] Expiration essentially involves passive recoil, but in voluntary breath-holding, voluntary muscles may contribute to keeping the chest open against the recoil force, which is not explained only by closure of the glottis and airways.[6]

VBHT is a simple and rapid procedure that measures the duration of voluntary apnea after a maximal inspiration, using a low-cost stopwatch. The maximum duration of voluntary apnea varies among individuals and depends on chemical and nonchemical stimuli.[7] Previous studies have evaluated VBHT in limited clinical contexts, suggesting potential usefulness[6] in the assessment and follow-up of patients with COPD.

This study aimed to determine whether the results of the VBHT are consistent with spirometry findings in healthy individuals and in patients with ventilatory disorders, assessing its diagnostic ability for identifying abnormal pulmonary function.

Methods

This was a two-gate (case-control) diagnostic-accuracy study conducted at a tertiary, university-affiliated hospital between January and December 2023. In the design, participants with known obstructive or restrictive ventilatory defects (cases) and healthy volunteers with normal spirometry (controls) were recruited through separate pathways, both from the same institution. Pulmonologists analyzing spirometry results were blinded to VBHT outcomes, and the technician conducting the VBHT had no access to spirometry data. The exclusion criteria were pregnancy; cognitive impairment and behavioral disorders; use of bronchodilators, stimulant and/or illicit drugs, or use of central nervous system depressant drugs within 24 h before the examination; pain or infectious symptoms that compromised the examination; hemoptysis; pneumothorax; cardiopulmonary instability; myocardial infarction or pulmonary embolism within the past six months; cerebral, thoracic, or abdominal aneurysm; eye surgery within the past two months; previous thoracic surgery; abdominal surgery within the past 2 months; or use of continuous home oxygen therapy.

The local ethics committee approved the study (CAAE 62652722.3.0000.5259), and all participants provided written informed consent. Each participant was interviewed, and data was collected using a standardized questionnaire that included demographic data, smoking history, comorbidities, use of medicines, and labor information.

The VBHT was performed by a trained investigator using a digital stopwatch AK68 (AKSO, Brazil). The maximal voluntary apnea inspiratory and expiratory times (MVAIT and MVAET, respectively) were measured. The VBHT was performed with participants seated, wearing a nose clip, and breathing through a mouthpiece to maintain tidal volume control. After two tidal cycles, participants were instructed to perform a maximal inspiration and hold their breath until intolerable discomfort (MVAIT), or a maximal expiration followed by breath-holding at residual volume (MVAET). Each participant received a brief demonstration and two practice trials before measurement. The test stopped if dizziness, coughing, or discomfort occurred. For MVAIT determination, participants inhaled from tidal volume to total lung capacity and then held their breath. For MVAET determination, participants breathed at tidal volume, inspired to total lung capacity, and exhaled to residual volume before holding their breath. Each maneuver was repeated twice within a 5-minute interval, and the best result was recorded. VBHT and spirometry were performed sequentially with a rest period between tests to avoid fatigue. Inter-operator reliability was evaluated in a pilot subset (n = 30), showing excellent agreement between technicians (ICC = 0.96 for MVAIT and 0.94 for MVAET). Spirometry was performed using a computerized spirometer (Spirom-3; Codax Medica, Brazil) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[7] and published reference values.[8] All spirometry results were independently analyzed by two experienced pulmonologists.

Data analysis was performed using GraphPad Prism version 10.0.2 for Windows (GraphPad Software, Boston, Massachusetts, USA). Continuous variables are presented as mean $\pm$ Standard Deviation (SD), median with interquartile range, or 95% Confidence Interval (95% CI), as appropriate.

Parametric data were analyzed using analysis of variance (ANOVA), whereas non-parametric data were analyzed using the Kruskal-Wallis test and Spearman's correlation. Categorical variables were compared using Fisher's exact test. The sample-size calculation was based on estimating an expected Area Under the ROC Curve (AUC) of approximately 0.75 with a precision of ± 0.05, using $\alpha = 0.05$ and 80% power, resulting in a minimum required sample of 245 participants. The quality of the spirometry results was assessed using Cohen's kappa coefficient. Diagnostic accuracy of MVAIT and MVAET for identifying normal and abnormal spirometry was assessed using Receiver Operating Characteristic (ROC) curve analysis, with internal validation by bootstrap resampling (1,000 iterations). Statistical significance was set at $p < 0.05$ for all analyses. This study adheres to STARD 2015 guidelines; the completed checklist is provided in Supplementary Material 1.

Results

A total of three hundred individuals met the inclusion criteria and provided written informed consent (Fig. 1). Seven participants were excluded due to low-quality spirometry (not meeting ATS/ERS quality standards) or inability to perform the Voluntary Breath-Hold Test (VBHT). The final analysis included 293 participants, of whom 185 (63.1%) were female. The demographic and clinical characteristics of the study population and the corresponding VBHT results are summarized in Table 1.

Participants were initially classified according to spirometry results into normal, obstructive ventilatory disorder, or restrictive ventilatory disorder groups, based on the consensus of two independent experts (Cohen's kappa = 0.881; 95% CI: 0.826–0.936). For patients with obstructive disorders, the median MVAIT and MVAET were 31.61 s (Interquartile Range [IQR], 22.71–37.88 s) and 20.96 s (IQR: 15.50–28.96 s), respectively. For those with restrictive disorders, the median MVAIT and MVAET were 26.74 s (IQR: 17.44–33.71 s) and 20.10 s (IQR: 15.93–25.04 s), respectively. No statistically significant differences were observed between the obstructive and restrictive groups in MVAIT ($p = 0.125$) or MVAET ($p = 0.479$) (Table 2). Similarly, there were no significant differences in sex, ethnicity, or BMI between these two groups. Therefore, participants with abnormal spirometry results (obstructive or restrictive) were combined into a single abnormal group for subsequent analyses. To complement the non-parametric comparisons, we estimated the Hodges-Lehmann median differences between groups. For MVAIT, the median difference between normal and abnormal spirometry was 14.6 s (95% CI 10.4–19.5 s). For MVAET, the Hodges-Lehmann difference was 6.6 s (95% CI 4.3–8.8 s), further supporting the marked separation between groups.

Participants in the abnormal spirometry group showed significantly lower MVAIT (median: 29.32 s; 95% CI: 25.99–32.35 s) than those in the normal group (median: 47.55 s; 95% CI: 43.93–51.87 s) ($p < 0.0001$). The MVAET was also significantly lower in the abnormal group (median: 20.40 s; 95% CI: 18.66–22.88 s) compared with the normal group (median: 28.53 s; 95% CI: 26.74–30.63 s) ($p < 0.0001$). These findings demonstrate the discriminative capacity of the VBHT to identify abnormal spirometry patterns (Table 1).

The correlations of MVAIT and MVAET with parameters of spirometry are shown in Table 3. Diagnostic accuracy was assessed by comparing the MVAIT and MVAET values between participants with normal and abnormal spirometry. The areas under the Receiver Operating Characteristic (ROC) curves were 0.791 (95% CI: 0.740–0.841) for MVAIT and 0.733 (95% CI: 0.675–0.787) for MVAET, validated by bootstrap resampling (1,000 iterations). Positive and negative predictive values (PPV and NPV) for the proposed cutoffs were 73.5% and 84.2% for MVAIT $\geq$ 45.49 s, and 65.9% and 80.7% for MVAET $\geq$ 32.86 s, respectively (Supplementary Table 1). These PPV and NPV estimates reflect the prevalence observed in this two-gate study sample and are therefore sample-dependent. For using VBHT as a diagnostic triage tool, a minimum sensitivity of 90% was established. An MVAIT $\geq$ 45.49 s yielded a sensitivity of 90.43% (95% CI:

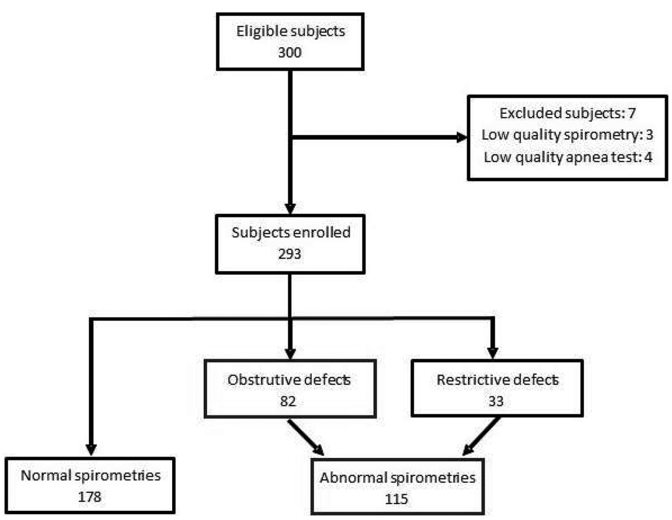

Figure 1 Study flowchart. A total of 300 eligible participants were screened. Seven were excluded due to low-quality spirometry (n = 3) or low-quality Voluntary Breath-Hold Tests (VBHT; n = 4). The final sample comprised 293 participants: 178 with normal spirometry and 115 with abnormal spirometry (82 obstructive and 33 restrictive ventilatory defects).

Table 1 Data of all groups.

	All participants (n = 293)	Normal spirometry (n = 178)	Abnormal spirometry (n = 115)	p-value
Sex: Female (%)	185 (63)	105 (59)	80 (70)	0.0824
Ethnicity: White (%)	145 (49)	90 (51)	55 (48)	0.7198
Age (years), median (95% CI)	55 (49–59)	50 (46–51)	55 (52–59)	0.004
BMI (kg/m^2), median (IQR)	27.18 (23.78–32.84)	27.50 (24.22–34.10)	26.77 (22.57–31.44)	0.033
MVAIT (s)				
Median (IQR)	38.06 (25.97–54.56)	47.55 (34.32–64.17)	29.32 (19.63–36.94)	< 0.0001
HL diff (95% CI)			14.6 (10.4—19.5)	
MVAET (s)				
Median (IQR)	25.62 (19.27–32.73)	28.53 (22.80–36.44)	20.40 (15.72–26.93)	< 0.0001
HL diff (95% CI)			6.6 (4.3—8.8)	

BMI, Body Mass Index; IQR, Interquartile Range; CI, Confidence Interval; MVAIT, Maximal Voluntary Apnea Inspiratory Time; MVAET, Maximal Voluntary Apnea Expiratory Time; HL diff, Hodges-Lehmann median difference (estimated difference in medians between normal and abnormal spirometry groups). Non-parametric variables were analyzed using the Mann-Whitney *U* test, and categorical variables using Fisher's exact test. Participants with obstructive or restrictive ventilatory disorders were grouped under "abnormal spirometry" for analysis.

Table 2 Data of the abnormal group.

Abnormal group (n = 115)	Obstructive disorder (n = 79)	Restrictive disorder (n = 36)	p-value
MVAIT (s)	31.61	26.74	0.1255
Median (IQR)	(22.71-37.88)	(17.44-33.71)	
MVAET (s)	20.96	20.10	0.4794
Median (IQR)	(15.50-28.96)	(15.93-25.04)	

MVAIT, maximal voluntary apnea inspiratory time; MVAET, maximal voluntary apnea expiratory time. IQR, interquartile range.
Observation: The Kruskal—Wallis test was used for non-parametric variables.

Table 3 Apnea test data and spirometry volumes and flows analysis.

	MVAIT		MVAET	
	r	p-value	r	p-value
CVF (L)	0.4806	< 0.0001	0.3799	< 0.0001
VEF$_1$ (L)	0.3304	< 0.0001	0.1409	0.0158
VEF$_1$/CVF (%)	0.0655	0.2641	-0.0228	0.6970
FEFmax (L/s)	0.3371	< 0.0001	0.1649	0.0047
VVM (L/min)	0.3253	< 0.0001	0.1352	0.0208

MVAIT, maximal voluntary apnea inspiratory time; MVAET, maximal voluntary apnea expiratory time; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; FEV1/FVC, FEV1/FVC ratio; FEFmax, maximal expiratory flow rate; VVM, maximum voluntary ventilation.
Observation: Spearman's correlation was used for non-parametric variables.

83.68—94.57) and specificity of 55.06% (95% CI: 47.72—62.18). An MVAET ≥ 32.86 s showed sensitivity of 90.43% (95% CI: 83.68—94.57) and specificity of 33.71% (95% CI: 27.17—40.93) for the diagnosis of normal spirometry (Figs. 2 and 3). Positive (LR+) and negative (LR-) likelihood ratios for MVAIT ≥ 45.49 s were 2.01 and 0.17, respectively, and for MVAET ≥ 32.86 s they were 1.36 and 0.28, respectively. The ROC-derived cutoffs for MVAIT (≥ 45.5 s) and MVAET (≥ 32.9 s) were established to maximize sensitivity for identifying normal spirometry. Internal validation was performed using bootstrap resampling (1,000 iterations). A multivariable logistic regression including age, sex, BMI, smoking status, MVAIT, and MVAET confirmed both variables as independent predictors of abnormal spirometry ($p < 0.001$). To further assess the diagnostic performance of VBHT, we evaluated the discrimination and calibration of the multivariable logistic regression model. The adjusted AUC was 0.74 (95% CI 0.69—0.80), obtained through bootstrap validation with 1,000 resamples, indicating preserved discriminative ability after adjustment for age, sex, BMI, smoking status, MVAIT, and MVAET. Model calibration was adequate, with a bootstrap-corrected calibration intercept of approximately 0.00 (95% CI: 0.25 to 0.26) and slope of 1.01 (95% CI: 0.73 to 1.33), demonstrating good agreement between predicted and observed probabilities. A detailed calibration curve is available in the Supplementary Material.

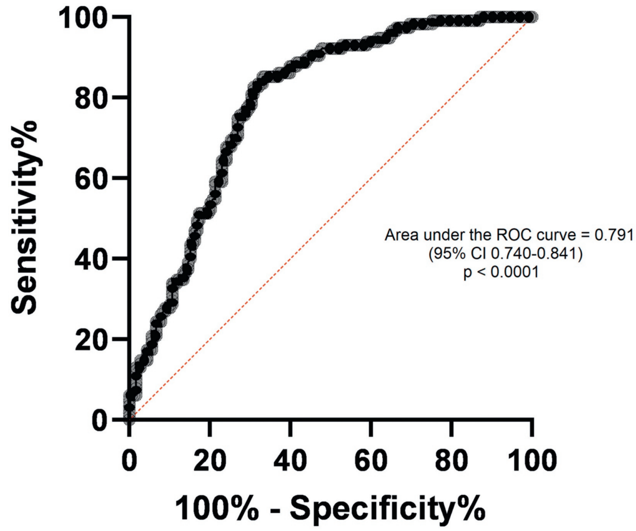

Figure 2 ROC curve of normal versus abnormal maximal voluntary apnea inspiratory time (MVAIT). Receiver Operating Characteristic (ROC) curve for Maximal Voluntary Apnea Inspiratory Time (MVAIT) in identifying normal spirometry results. Area Under the Curve (AUC) = 0.791 (95% CI: 0.740–0.841). The optimal cut-off (≥ 45.49 s) provided 90.43% sensitivity and 55.06% specificity. Internal validation was performed using bootstrap resampling (1,000 iterations).

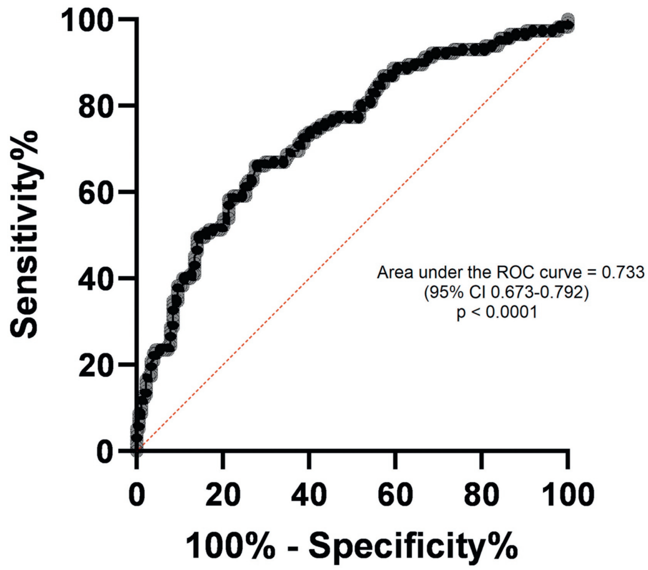

Figure 3 ROC curve of normal versus abnormal Maximal Voluntary Apnea Expiratory Time (MVAET). Receiver Operating Characteristic (ROC) curve for Maximal Voluntary Apnea Expiratory Time (MVAET) in identifying normal spirometry results. Area Under the Curve (AUC) = 0.733 (95% CI: 0.675–0.787). The optimal cut-off (≥ 32.86 s) provided 90.43% sensitivity and 33.71% specificity. Internal validation was performed using bootstrap resampling (1,000 iterations).

There were no major complications, such as desaturation, respiratory failure, or symptoms of myocardial ischemia. The overall incidence of minor, transient adverse signs and symptoms was 20.48%. Few participants experienced coughing (6.83%), tiredness (5.12%), headache (7.85%), blurred vision (1.36%), tachycardia (3.41%), and/or transient peak hypertension (0.34%). VBHT was safe and well tolerated, with only mild, self-limited symptoms observed in 21% of participants (e.g., transient dizziness, cough, or dyspnea). Participants were observed for at least two minutes after each test, and all symptoms resolved spontaneously without any medical intervention or test interruption. The complete dataset used for all analyses is provided as Supplementary Material.

Discussion

VBHT is a non-invasive, inexpensive, and easily reproducible bedside test with potential value as a triage ("rule-out") tool prior to spirometry for assessing ventilatory function.[10] During the procedure, individuals voluntarily hold their breath for as long as possible, beginning from total lung capacity (Maximal Voluntary Apnea Inspiratory Time, MVAIT) or from residual volume (Maximal Voluntary Apnea Expiratory Time, MVAET). Using a low-cost accessory device such as a stopwatch, trained staff can perform the measurements after a brief learning period. Our findings support the diagnostic ability of VBHT to discriminate normal from abnormal spirometry patterns.[7] In a pragmatic clinical pathway, individuals with VBHT values equal to or above the proposed cut-offs may be classified as "likely normal", whereas those with values below the cut-offs should undergo formal pulmonary function testing.

Statistical validation of VBHT by comparing the values of healthy patients with those of patients with obstructive and restrictive ventilatory disorders was necessary. The diagnosis was based on the results of spirometry and, when necessary, confirmed by whole-body plethysmography analyzed by two specialists based on pulmonary function tests.[8] Patients with obstructive and restrictive ventilatory disorders were included into a distinct group (abnormal group), because their MVAIT and MVAET values were not significantly different.

Given the two-gate (case-control) design, the contrast between normal and abnormal participants may be artificially amplified, which can lead to overestimation of diagnostic accuracy parameters, including sensitivity and the AUC. This phenomenon, known as spectrum bias, is intrinsic to case-control diagnostic studies. Therefore, although our results support the discriminative capacity of VBHT, they require confirmation in a single-gate, prospectively recruited consecutive cohort before clinical implementation.[9] Because participants were recruited from a pulmonary function testing environment and included healthy volunteers, the estimated diagnostic performance may not directly reflect that of a routine preoperative clinic population.

In this context, VBHT demonstrated high sensitivity but only modest specificity, a profile that aligns more closely with a triage ("rule-out") application rather than a diagnostic replacement for spirometry. The test may help identify individuals who are very unlikely to have abnormal ventilatory patterns, potentially reducing unnecessary spirometry evaluations in selected settings. However, VBHT should not be used as a standalone diagnostic tool, and any abnormal or borderline result must still be confirmed by conventional spirometry. Because the present two-gate design may overestimate discrimination, especially sensitivity and AUC, external validation using a single-gate, consecutively recruited cohort is essential before any clinical integration.[10] Because predictive values depend on disease prevalence, the PPV and NPV reported here are not directly transportable to routine preoperative settings, where the pretest probability of abnormal spirometry is typically lower.

The diagnostic performance of the VBHT was statistically validated by comparing values from participants with normal spirometry to those with obstructive or restrictive ventilatory disorders.[11] Spirometry was used as the reference standard, and, when clinically indicated, whole-body plethysmography was used for diagnostic confirmation.[8] Because MVAIT and MVAET values did not differ significantly between patients with obstructive and restrictive disorders, these participants were combined into a single abnormal group for analysis. These findings are consistent with the results reported by Barnai et al.,[12] who demonstrated that voluntary breath-holding times correlate with ventilatory limitation in patients with cystic fibrosis, supporting the physiological rationale for VBHT as a diagnostic screening tool.

Moreover, Hedhli et al.[5] conducted a cross-sectional study in 2021 including patients with stable COPD. Their results showed that MVAIT was significantly correlated with FEV_1 ($r = 0.686$; $p < 0.0001$), FVC ($r = 0.632$) and FEV_1/FVC ratio ($r = 0.645$). In addition, MVAIT demonstrated good discriminative power for severe forms of COPD with an area under the ROC of 0.822 (95% CI: 0.7—0.945). An MVAIT < 20.5 s allowed the detection of $FEV_1 < 50\%$ with 96% specificity and 72% sensitivity. In the present study, lower correlation coefficients were observed, and no statistically significant correlations were found between MVAIT or MVAET and the FEV_1/FVC ratio. These differences likely reflect the broader heterogeneity of our population, which included individuals without established COPD, rather than methodological discrepancies. This correlation likely reflects the integrative nature of VBHT, which assesses chemosensitivity and voluntary respiratory control, providing complementary, not redundant, information to spirometry volumes and flows.

Dankerk et al.[2] conducted a systematic review showing that, due to limited evidence and methodological variability, it remains unclear whether preoperative spirometry is sufficient to identify ventilatory impairment before non-thoracic surgery. The available literature remains inconclusive, with 65% of prospective studies supporting and 35% questioning the diagnostic contribution of preoperative spirometry. Nevertheless, spirometry prior to upper abdominal surgery is still recommended for individuals presenting typical symptoms of COPD according to GOLD key indicators. Our findings complement this discussion by suggesting that the VBHT may be a simple and accessible alternative for detecting abnormal spirometry patterns in the preoperative setting.

Tak et al.[3] reported that a lower preoperative FVC was associated with the occurrence of PPCs after laparoscopic abdominal surgery, whereas FEV_1 and the FEV_1/FVC ratio were not. This finding highlights the clinical relevance of FVC as an indicator of ventilatory limitation. In the present study, MVAIT and MVAET were both significantly correlated with FVC, suggesting that the VBHT may serve as a simple diagnostic tool for identifying reduced ventilatory capacity in the preoperative evaluation of non-thoracic surgical candidates.

No major complications occurred during the performance of the VBHT, confirming that the procedure is safe and well tolerated, supporting its feasibility for use in the preoperative setting.

The present study has limitations. All participants were recruited from a single pulmonary disease monitoring center, which may limit external generalizability and introduce selection bias. The age, sex, and BMI distribution of participants was not uniform, and the sample size was not powered for subgroup analyses. The pooling of obstructive and restrictive disorders may have masked subtle differences in VBHT performance between these patterns; future studies should analyze them separately. Excluding participants with recent surgery, cognitive impairment, or medication effects likely reduced variability and may underestimate challenges in real-world settings. Additionally, spirometry was used as the reference standard rather than an independent gold standard for diagnosis. Future research should include diffusing capacity of the lungs for carbon monoxide and cardiopulmonary exercise testing to refine diagnostic characterization and further validate the VBHT as a screening tool. Incorporating Diffusion Capacity (DLCO) and cardiopulmonary exercise testing variables may help clarify how VBHT reflects overall ventilatory reserve and gas exchange efficiency, supporting the future development of composite diagnostic or preoperative screening indices.

Conclusion

In conclusion, VBHT is a simple, reproducible, and low-cost test with potential utility as a preliminary triage tool to identify individuals unlikely to have abnormal spirometry. Its feasibility and minimal resource requirements make it appealing for preoperative screening or in settings with limited access to formal pulmonary function testing. Nevertheless, because VBHT showed high sensitivity but modest specificity and was evaluated in a two-gate design, it should not replace spirometry. Validation in a single gate, prospectively recruited population is required before VBHT can be recommended for routine clinical use.

Abbreviations

Postoperative Pulmonary Complication (PPC); Forced Vital Capacity (FVC); Chronic Obstructive Pulmonary Disease (COPD); Voluntary Breath-Holding Test (VBHT); Maximal Voluntary Apnea Inspiratory Time (MVAIT); Maximal Voluntary Apnea Expiratory Time (MVAET); Receiver Operating Characteristic (ROC); Standard Deviation (SD); Body Mass Index (BMI); Forced Expiratory Volume in the first second (FEV_1); Interquartile Range (IQR); Confidence Interval (CI); Perception of Dyspnea (POD); American Thoracic Society (ATS); European Respiratory Society (ERS).

Authors' contributions

The authors contributed equally as co-first authors.

AI assistance disclosure

No AI-assisted tools were used in the preparation, analysis, or writing of this manuscript.

Data availability statement

The datasets generated and/or analyzed during the current study are provided as Supplementary Material.

Declaration of competing 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.2026.844737.

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ORIGINAL INVESTIGATION

Impact of outpatient preanesthetic consultation on perioperative outcomes in 700 urological patients in a tertiary hospital: a retrospective observational study☆

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Abstract
Background: Outpatient preanesthetic consultation improves patient assessment and anesthetic planning, enhancing safety and reducing complications. Conducted in advance, it allows systematic, individualized planning. Uncontrolled hypertension, common in 60% of people over 60, is a major cause of surgery cancellation and increases cardiovascular risk. This study evaluates its impact on preventing perioperative complications and optimizing clinical and surgical outcomes in urological patients.
Methods: This retrospective observational study analyzed 700 patients (≥ 18 years) who attended outpatient preanesthetic consultation before urological surgery. Clinical conditions, systemic blood pressure, heart rate was analyzed during outpatient, preoperative, and intraoperative periods. Preoperative and intraoperative complications were recorded to evaluate consultation impact.

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Results: Among 700 patients (89.6% male, mean age 64.2), ASA II was most common classification. Hypertension was identified in 53.7% of patients during outpatient evaluation. All hypertensive patients received antihypertensive treatment until surgery, with blood pressure maintained within normal limits. Preoperative findings in the operating room included hypertension (2.0%), anemia (0.57%), atrial fibrillation (0.14%), and asthma (0.14%). Intraoperative events included hypertension (2.28%), hypotension (8.14%), bradycardia (1.14%), and inadequate neuraxial block (2.85%). One surgery was canceled due to hypertension. Blood pressure significantly decreased preoperatively and intraoperatively compared to outpatient values ($p < 0.0001$). Heart rate also decreased significantly intraoperatively. This single-center study has limitations, including absence of comparison groups assessed by other specialties or only day of surgery.

Conclusion: Reductions in systolic and diastolic blood pressure were documented upon operating room entry among patients evaluated in outpatient preanesthetic consultation, with a very low surgery cancellation rate.

Introduction

The outpatient preanesthetic consultation was first proposed in 1949 by Alfred Lee, who emphasized its role in preventive medicine. He noted many patients arrived for surgery in inadequate clinical condition, avoidable with earlier preparation.[1] A preoperative assessment conducted days before surgery is essential to understand clinical profile, perform evaluations, plan anesthesia, and educate patients. Its main goals are to reduce morbidity and mortality, improve awareness, and alleviate anxiety.[2-5] Preoperative education reduces anxiety across all age groups, highlighting the value of tailored preanesthetic information.[6,7]

Beyond preparation and education, outpatient preanesthetic consultation plays a central role in perioperative care by enabling early risk assessment and identification of comorbidities that may affect outcomes. More than a screening opportunity, it is also a moment for clinical adjustment of known or newly diagnosed conditions, contributing to safety and reducing complications.

A brief preanesthetic visit shortly before surgery does not replace a comprehensive assessment. In Brazil, Resolution n° 2.174/2017 of the Federal Council of Medicine recommends anesthesiologists know the patient's clinical condition before surgery. Assessment should be performed on an outpatient basis, except in urgent or emergency cases, when the anesthetist evaluates the patient immediately before entering the operating room. Preoperative evaluations by clinicians or cardiologists, while important, are not sufficient to address anesthetic-specific risks. The resolution requires anesthesia-specific informed consent before the procedure.[8]

Practice guidelines were adopted in France in 1994[9] and by the American Society of Anesthesiologists in 2001.[10] In countries like the USA, clinics exist solely for preoperative evaluation, with surgeons referring patients to anesthesiologists and nurses.[10] Many hospitals, including Brazil, use telemedicine for preanesthetic assessments, increasing convenience and satisfaction while reducing costs. Studies show telemedicine does not increase surgery cancellations, maintaining quality and safety.[11-13]

Shared decision-making has emerged, combining patients' preferences with medical expertise to determine personalized care. Perioperative professionals must develop guidelines and interventions promoting meaningful dialogue.[14]

In surgical specialties such as urology, where many procedures are elective and patients often have chronic conditions, outpatient consultation is essential. Common comorbidities – hypertension, uncontrolled diabetes, chronic respiratory diseases, obesity, and tobacco use – are risk factors for perioperative complications, including hemodynamic instability, delayed recovery, and infections. Inadequate preparation increases intra- and postoperative risks, while early management improves safety and outcomes.[15]

This study hypothesizes that outpatient preanesthetic consultation is the most appropriate method for preparing patients for surgery, potentially reducing perioperative complications and ensuring greater safety in urological procedures. The general objective was to demonstrate impact on preventing complications and optimizing clinical and surgical outcomes. Specific objectives were: (1) Describe baseline patient characteristics; (2) Assess cardiovascular abnormalities; (3) Analyze systemic blood pressure and heart rate across outpatient, preoperative, and intraoperative periods; and (4) Identify preoperative and intraoperative complications.

Methods

This retrospective observational study was based on the review of medical records of patients who underwent surgical procedures at Clementino Fraga Filho University Hospital (HUCFF), Federal University of Rio de Janeiro, Brazil. A convenience sample of 700 patients who underwent urological surgeries and completed outpatient preanesthetic consultation was included. These patients were selected from a broader surgical population involving multiple specialties.

Consultations at the Preanesthetic Outpatient Clinic (PAC) were conducted by anesthesia residents and medical students under the supervision of an anesthesiology professor. During these evaluations, patients received guidance on anesthetic techniques and intraoperative monitoring.

The study was approved by the HUCFF Research Ethics Committee (CAAE: 3973.3020.0.0000.5257) on February 2, 2021, and registered in the Brazilian Registry of Clinical Trials (ReBEC n° 3vxknd7) on August 10, 2022. It followed the Declaration of Helsinki and STROBE guidelines for observational studies. The Free and Informed Consent Form (FICF) was waived.

The inclusion criteria were patients over 18 years of age, of both sexes, and classified as ASA physical status I to III. No patients were excluded from the study (Fig. 1). Data were collected from HUCFF medical records (2022–2023), including outpatient Preanesthetic Consultation (PAC) forms, anesthesia and surgical reports, and documentation of preoperative and intraoperative complications. Baseline variables included age, sex, ethnicity, weight, height, and ASA physical status. Electrocardiography (ECG) and Echocardiography (ECHO) results were also recorded.

Information on comorbidities was obtained from clinical history, physical examination, and complementary tests, and was used to assess their frequency and relevance for anesthetic risk stratification. All data were collected according to a predefined study protocol and subsequently analyzed using appropriate statistical methods.

The preoperative period began with the patient's admission to the operating room for monitoring and venous access. Blood pressure and other physiological measurements were performed by anesthesiology staff and residents, trained in standardized measurement techniques. Monitoring was conducted using a Narcosul multiparametric monitor for all patients, including five-lead electrocardiography, pulse oximetry, noninvasive blood pressure, and capnography, following institutional protocols. Standardization of equipment and measurement procedures was adopted throughout the study to ensure consistency and reliability of collected data. The intraoperative period extended from anesthesia induction or anesthetic blockade to the end of the surgical procedure. Blood pressure and heart rate were recorded at three defined points: during the outpatient preanesthetic consultation and upon admission to the operating room (preoperative). Intraoperatively, three measurements were taken: at the beginning, middle, and end of surgery, and their average was used for analysis. Hypertension was defined as blood pressure > 140/90 mmHg, tachycardia as heart rate > 100 bpm, hypotension as blood pressure < 90/60 mmHg, and bradycardia as heart rate < 60 bpm.

As a retrospective study, no standardized anesthetic protocol was applied. The anesthetic technique was selected by the attending anesthesiologist, based on the patient's clinical condition and the surgical procedure. The distribution of techniques is detailed in the results. Complications were recorded during both preoperative and intraoperative periods. The study protocol remained unchanged throughout.

Sample size was calculated based on the rate of surgery cancellations for medical reasons (2%),[16] with a 5% alpha and a margin of error of 1.1%, resulting in a required sample of 622 patients. An additional 5% was added to account for potential losses to follow up, yielding a final sample size of 700 patients.

Selection was by convenience sampling. Univariate and multivariate analyses identified factors associated with preoperative and intraoperative complications. Descriptive results are shown in tables using measures of central tendency and dispersion for numerical variables, and frequencies for categorical ones. Data normality was tested using the Shapiro-Wilk test, with results expressed as mean ± standard deviation or median (interquartile range).

To assess Systolic (SBP), Diastolic (DBP), and Heart Rate (HR) variations across three time points, repeated-measures ANOVA with Bonferroni correction or Friedman's test with Dunn's post hoc was used, depending on normality. Associations between complications and ASA status, hypertension, and heart disease were tested using Chi-Square or Fisher's exact test. Binary logistic regression identified associations between patient characteristics and complications. A 5% significance level was adopted. Statistical analysis was performed using SPSS v26.

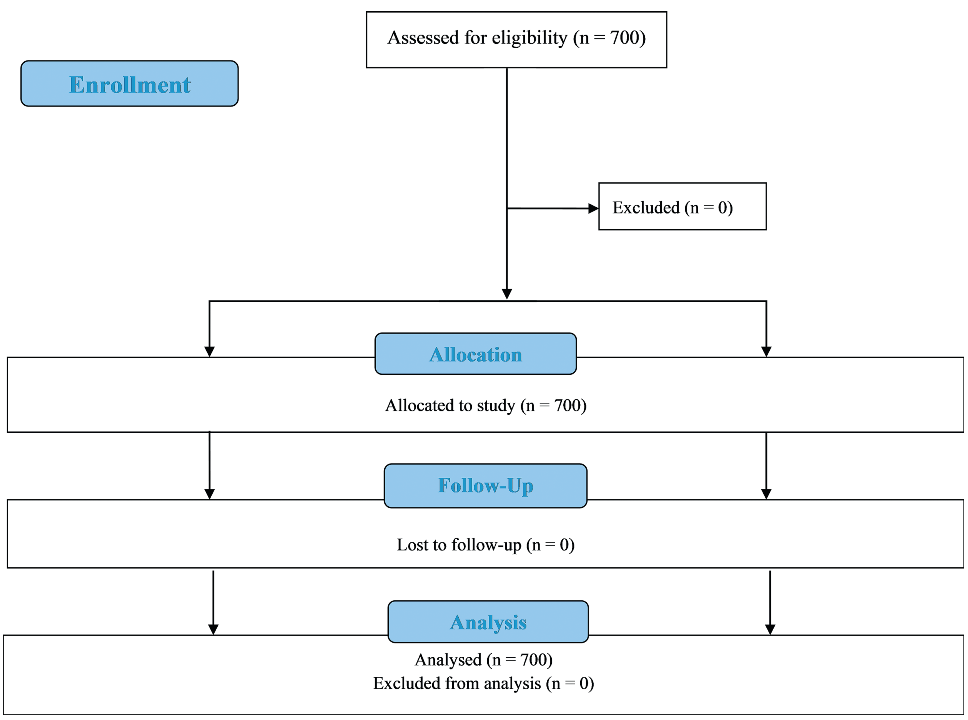

Figure 1 Flowchart of patient selection and inclusion.

Table 1 Baseline characteristics of the study participants.

Variable	Results (n = 700)					
Sex, n (%)						
Male	627 (89.6)					
Female	73 (10.4)					
Color, n (%)						
White	415 (59.3)					
Brown	201 (28.7)					
Black	84 (12.0)					
ASA, n (%)						
I	92 (13.1)					
II	426 (60.9)					
III	182 (26.0)					
	Mean	**SD**	**Median**	**IIQ**	**Minimum**	**Maximum**
Age (years)	64.2	12.7	67	59–73	18	93
Weight (kg)	70.1	11.7	69	62–78	42	114
Height (cm)	166.6	6.7	166	162–170	148	190

ASA, Physical Status Classification. Numerical data expressed as mean ± standard deviation; categorical data expressed as frequency (percentage) IIQ, Interquartile range (Q1–Q3).

Results

A total of 700 Urology Department patients were included. Table 1 summarizes baseline characteristics, and Table 2 reports comorbidities identified during outpatient consultations. The total number of comorbidities is 1,048, as some patients had more than one condition, so cumulative frequency exceeds participants. The most prevalent were hypertension (53.7%), tobacco use (40.6%), cardiovascular disease (17.7%), and diabetes mellitus (14.3%). Patients with any comorbidity were treated and stabilized in the outpatient setting and returned for preanesthetic reassessment and surgical clearance. A total of 376 hypertensive patients were identified; some had long-standing hypertension, others were newly diagnosed. All initiated antihypertensive treatment and remained on therapy until surgery, maintaining normal blood pressure. These factors influenced risk stratification, anesthetic management, and preoperative optimization. Table 3 shows variations in blood pressure and heart rate across outpatient, preoperative, and intraoperative periods for ASA I, II, and III physical status groups.

Table 2 Comorbidities and clinical risk factors detected in preanesthetic evaluation.

Variable	Results (n = 1048)[a]
Hypertension	376 (53.7)
Tobacco use disorder	284 (40.6)
Heart disease	124 (17.7)
Diabetes mellitus	100 (14.3)
Obesity	60 (8.6)
Lung disease	53 (7.6)
Anxiety	29 (4.1)
Cancer	22 (3.1)

Data presented as frequency (percentage).
[a] The same patient could present more than one comorbidity and risk factor.

Systolic and diastolic pressures significantly decreased from outpatient to preoperative and intraoperative phases in all ASA groups ($p < 0.0001$). Heart rate also decreased intraoperatively in ASA I ($p = 0.0012$) and III ($p = 0.0010$) patients.

Of the 700 patients, 650 were over 40 years old and underwent Electrocardiography (ECG). Sinus rhythm was observed in 341 patients (52.5%), while abnormalities were present in 47.5%. The most frequent findings were extrasystoles (18.2%), left ventricular hypertrophy (12.5%), right bundle branch block (8.4%), and signs of acute myocardial infarction (8.2%). Ninety-one patients with ECG abnormalities and suggestive clinical signs were referred for echocardiography. Structural or functional alterations were identified in 69 cases (10.6%), including hypertensive heart disease (3.5%), ischemic heart disease (3.1%), ventricular dysfunction (2%), diastolic dysfunction (1.4%), and mitral insufficiency (0.6%).

The main surgeries performed were Transurethral Resection (TUR) of the prostate (52.3%) and bladder tumor (6.9%), followed by pyelolithotomy (4.7%), nephrectomy (4.6%), radical prostatectomy (4.1%), and suprapubic prostatectomy (4.1%). Additional surgeries included orchiectomy, cystopexy, hydrocelectomy, and transgenitalization.

Spinal anesthesia was the predominant technique (77.9%), followed by general anesthesia (21%), epidural (9.4%), sedation (1%), and local anesthesia (0.7%). These percentages also account for cases in which anesthetic techniques were combined.

Table 4 presents preoperative and intraoperative complications according to ASA physical status. The preoperative findings refer to events observed upon entry into the operating room, during monitoring, before any anesthetic technique was initiated. This includes both patients with a previous history of hypertension and those without such a history who experienced a transient elevation in systemic blood pressure immediately prior to surgery.

Preoperative monitoring in the operating room revealed hypertension (2.0%), anemia (0.6%), atrial fibrillation (0.1%), and bronchospasm (0.1%). One case, a 77-year-old

Table 3 Blood pressure and heart rate by ASA class and perioperative timepoint.

	Outpatient	Preoperative	Intraoperative	p-value
ASA I (n = 92)				
SBP (mmHg)	129.1 ± 14.6^{a}	127.1 ± 15.9^{a}	116.3 ± 14.9^{b}	< 0.0001
DBP (mmHg)	80.7 ± 9.8^{a}	77.6 ± 9.4^{a}	73.1 ± 10.7^{b}	< 0.0001
HR (bpm)	75.9 ± 10.0^{a}	$75.7 \pm 9.1^{a,b}$	73.2 ± 8.9^{b}	0.0012
ASA II (n = 426)				
SBP (mmHg)	143.8 ± 19.8^{a}	139.3 ± 19.5^{b}	124.0 ± 19.9^{c}	< 0.0001
DBP (mmHg)	86.5 ± 11.4^{a}	82.9 ± 10.7^{b}	76.2 ± 12.14^{c}	< 0.0001
HR (bpm)	76.3 ± 10.6	76.04 ± 9.5	75.29 ± 9.2	0.2270
ASA III (n = 182)				
SBP (mmHg)	143.2 ± 18.7^{a}	139.6 ± 19.7^{a}	124.8 ± 21.4^{b}	< 0.0001
DBP (mmHg)	86.8 ± 11.0^{a}	82.4 ± 10.1^{b}	74.8 ± 12.7^{c}	< 0.0001
HR (bpm)	77.6 ± 10.5^{a}	75.3 ± 4.4^{b}	74.4 ± 8.9^{b}	0.0010

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; ASA, Physical Status Classification. Data presented as mean ± standard deviation. Different letters denote a significant difference ($p < 0.05$; repeated measures ANOVA test, with Bonferroni post-test). Different letters indicate statistically significant differences. In ASA I patients, both Systolic (SBP) and Diastolic Blood Pressure (DBP) were significantly lower intraoperatively compared to the outpatient and preoperative periods. Heart rate was also lower intraoperatively compared only to the outpatient measurement. In ASA II, SBP and DBP were lower intraoperatively than in both outpatient and preoperative periods, with preoperative values also lower than outpatient. In ASA III, SBP was lower intraoperatively compared to both outpatient and preoperative periods. DBP followed the same pattern, with preoperative values also lower than outpatient. Finally, heart rates in both preoperative and intraoperative periods were lower than in the outpatient setting.

Table 4 Preoperative and intraoperative complications according to ASA physical status classification.

Variable	ASA I (n = 92)	ASA II (n = 426)	ASA III (n = 182)	p-value
Preoperative				
Hypertension	1 (1.1)	12 (2.8)	1 (0.5)	0.1599
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.5)	0.2405
Intraoperative				
Hypotension	4 (4.3)	36 (8.5)	17 (9.3)	0.3371
Hypertension	0 (0.0)	12 (2.8)	4 (2.2)	0.2597
Bradycardia	1 (1.1)	6 (1.4)	1 (0.5)	0.6584

ASA, American Society of Anesthesiologists physical status classification. Data presented as frequency (percentage).

male (ASA II) with hypertension and heart disease, had surgery canceled due to severe blood pressure elevation (200/130 mmHg). Intraoperative complications included hypotension (8.1%), inadequate neuraxial block (2.6%), hypertension (2.3%), bradycardia (1.1%), dura mater perforation (0.1%), and allergic reactions (0.7%).

No preoperative or intraoperative deaths occurred. Hemodynamic parameters progressively declined from the outpatient to intraoperative periods across ASA groups. Both systolic and diastolic blood pressures decreased significantly ($p < 0.0001$), while heart rate declined significantly in ASA I and ASA III patients. These changes likely reflect anesthetic effects rather than instability. Even in ASA III, reductions were not excessive, suggesting effective preoperative optimization. Structured preanesthetic consultations may be associated with intraoperative stability by addressing modifiable risks, supporting the value of comprehensive assessment, especially in high-risk patients.

Binary logistic regression identified independent risk factors for preoperative and intraoperative complications, as shown in Table 5. Outpatient SBP ($p = 0.029$), preoperative SBP ($p < 0.001$), preoperative DBP ($p = 0.001$), and intraoperative heart rate ($p = 0.026$) were associated with an increased risk of preoperative complications. Additionally, age ($p = 0.008$) and preoperative SBP ($p = 0.029$) were associated with a higher risk of intraoperative complications. In contrast, intraoperative SBP ($p < 0.001$), DBP ($p < 0.001$), and heart rate ($p < 0.001$) were protective factors against intraoperative complications.

Discussion

In this retrospective study of 700 patients undergoing urological procedures, outpatient preanesthetic consultation conducted in advance played a key role in improving patient preparation and perioperative outcomes. Early evaluation allowed time for diagnostic testing, clinical optimization, and, when needed, multidisciplinary input. It also enabled individualized anesthetic planning, early risk identification, and reduced surgical cancellations. This structured approach enhances perioperative safety and supports efficient, patient-centered care.

Table 5 Multivariate logistic analysis to evaluate associations between patient characteristics and complications.

Patient characteristics	Preoperative adverse events			Intraoperative adverse events		
	OR	95% CI	p-value	OR	95% CI	p-value
Sex[a]	0.608	0.079–4.693	0.633	0.701	0.294–1.676	0.425
Color[b]	1.840	0.230–14.719	0.566	2.802	0.984–7.976	0.054
ASA	0.845	0.367–1.945	0.692	1.270	0.860–1.876	0.229
Age	1.010	0.968–1.055	0.640	1.031	1.008–1.054	0.008[c]
Weight	0.974	0.929–1.021	0.276	0.992	0.972–1.013	0.461
Height	0.963	0.891–1.040	0.336	0.979	0.944–1.014	0.235
Outpatient SBP	1.028	1.003–1.054	0.029[c]	1.008	0.996–1.021	0.169
Outpatient DBP	1.002	0.957–1.048	0.943	1.013	0.992–1.034	0.222
Outpatient HR	0.988	0.941–1.038	0.638	1.005	0.982–1.027	0.693
Preoperative SBP	1.062	1.035–1.088	< 0.001[c]	1.013	1.001–1.025	0.029[c]
Preoperative DBP	1.072	1.027–1.118	0.001[c]	1.008	0.986–1.031	0.472
Preoperative HR	1.018	0.963–1.077	0.525	1.012	0.986–1.038	0.377
Intraoperative SBP	1.018	0.994–1.043	0.139	0.961	0.948–0.974	< 0.001[c]
Intraoperative DBP	1.018	0.976–1.061	0.406	0.941	0.922–0.961	< 0.001[c]
Intraoperative HR	1.073	1.008–1.141	0.026[c]	0.904	0.879–0.931	< 0.001[c]

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; Reference variables were those that presented the highest frequency.
[a] Male sex as a reference variable.
[b] White color as a reference variable.
[c] Significant association ($p < 0.05$).

In contrast, same-day evaluations tend to be brief and reactive, focused on excluding immediate contraindications, which limit comprehensive assessment, risk stratification, and preventive or optimization strategies. According to the ASA's Practice Advisory for Preanesthesia Evaluation, assessments should preferably occur within 30 days before surgery and be updated within 48 hours, especially for high-risk or complex cases.[10]

In recent years, telemedicine has emerged as promising strategy for outpatient preanesthetic evaluations, particularly for ASA I and II patients, in accordance with ASA guidelines. The ASA emphasizes that remote consultations must maintain core elements such as clinical history, physical examination when feasible, and informed consent.[17] Studies such as Kamdar et al.[11] have demonstrated the safety, feasibility, efficiency, and patient satisfaction of this model in major academic centers. In Brazil, Machado et al.[12] and Freitas[13] reported similar positive outcomes in public hospitals, noting improved access, reduced costs, and no increase in surgical cancellations. These findings support telemedicine as a viable alternative for selected low-risk patients.

The most prevalent chronic conditions identified during outpatient consultations were hypertension, smoking, heart disease, diabetes, and obesity, all known to significantly increase perioperative risk. These findings are consistent with Klopfenstein et al.[18] and Zambouri,[19] who also reported high rates of hypertension, obesity, and tobacco use in surgical populations, reinforcing the importance of early identification and management of chronic conditions.

Hypertension was diagnosed in 53.7% of patients during the preanesthetic evaluation, aligning with prevalence rates of around 60% in individuals over 60, as reported by Dix et al.[20] and De Paula.[21] This is consistent with mean age of 64.2 years in this study. Early identification enabled therapeutic adjustments that may be associated with better perioperative management and surgical outcomes.

Patients received individualized care and anesthesia-focused guidance in outpatient setting. This facilitated early detection and control of hypertension. As a result, significant reduction in preoperative blood pressure was observed across all ASA classes (I, II, III) compared to outpatient values. Intraoperative heart rate also significantly decreased in ASA I and III patients. These results are consistent with Shirdel et al.,[22] who reported that qualified preoperative counseling and continued care until admission led to reductions in anxiety, systolic blood pressure, heart rate, and respiratory rate.

In the present study, causal inferences regarding the effect of preanesthetic consultation on blood pressure reduction cannot be drawn in absence of control group. Our project was to characterize the clinical trajectory of patients following the preanesthetic consultation rather than perform comparative analyses. Reductions in blood pressure were observed both upon entry into operating room and during intraoperative period; nevertheless, these findings warrant cautious interpretation. Preoperative changes may reflect the combined influence of pharmacologic optimization, preanesthetic medication, perioperative anxiolysis, or other contextual factors. Accordingly, conclusions were framed to reflect descriptive and observational design of study, avoiding unwarranted causal attribution.

Elective surgeries are often canceled due to uncontrolled hypertension, particularly in older adults, as noted by Dix et al.[20] and De Paula.[21] However, in this study, only one surgery was canceled, suggesting early outpatient evaluation allowed timely intervention and effective risk management. This emphasizes the role of preanesthetic assessment in clinical optimization, improving surgical scheduling, and reducing preventable cancellations.

Several studies, including Fischer et al.,[2] Kristoffersen et al.,[3] Tait et al.,[23] and Rosner,[24] show preanesthetic consultations reduce delays, cancellations, hospital costs, unnecessary tests, and complications. Among 700 scheduled procedures in this study, only one was canceled, reflecting the effectiveness of outpatient evaluations. Early consultations help identify and manage clinical issues in advance, enhancing care coordination and minimizing avoidable delays.

Conversely, Epstein et al.[25] reported high cancellation rates when patients were assessed only the night before surgery. Similarly, Zambouri[19] found many patients were examined only minutes before surgery. These scenarios highlight the benefits of a proactive, structured preanesthetic approach. In this study, patients were initially assessed in the outpatient clinic and re-evaluated the day before surgery by anesthesiology residents, who also prescribed preanesthetic medications as needed.

ECGs were performed in patients aged 40 and older, with 47.5% showing abnormalities, supporting findings from Alanzy et al.,[26] Correll et al.,[27] and Mossie et al.[28] regarding increased cardiovascular risk in older adults. Echocardiograms were requested only when ECG abnormalities were accompanied by clinical signs, aligning with Kristoffersen et al.[3] Fischer et al.[2] noted that preanesthetic assessments led to fewer unnecessary tests compared to surgeon-managed preoperative care. At HUCFF, tests were requested by surgeons but followed ASA-based recommendations jointly established with the Anesthesiology Outpatient Clinic, ensuring a standardized, clinically appropriate approach.

This study was carried out in a teaching hospital, where anesthesiology residents and medical students assumed a central role in outpatient consultations. This model aligns with Fischer,[2] who highlights the importance of active resident involvement in preanesthetic evaluations.

This study has limitations. Being conducted at a single center may limit external validity. Total surgical duration was not recorded, and the exact timing of intraoperative complications was not documented, preventing analysis of associations with specific phases or procedure length. The retrospective design and institutional constraints precluded inclusion of a control group or comparison with patients evaluated by other specialties or only on the day of surgery. Consequently, findings should be interpreted as exploratory, and observed blood pressure reductions may reflect multiple factors, including pharmacologic optimization, preanesthetic medication, perioperative anxiolysis, or clinical course. Future prospective comparative studies with control groups and standardized protocols are needed to confirm these observations and clarify their clinical significance.

In Brazil, where structural inequalities affect access to quality of healthcare, particularly in public system (SUS), cost-effective strategies that improve patient experience and optimize preoperative conditions are especially valuable. Preanesthetic consultation enables clinical assessment, builds trust, reduces anxiety, and enhances patient safety. In public healthcare, where time constraints and limited follow-up are common, this approach supports quality care, equity, and helps mitigate disparities.

Conclusion

The study population consisted mainly of older adults, with a high prevalence of chronic conditions such as hypertension, tobacco use, heart disease, diabetes, and obesity. Cardiovascular abnormalities, particularly ECG changes, were commonly detected during outpatient consultations, emphasizing the importance of early risk identification and timely treatment. Reductions in preoperative and intraoperative systolic and diastolic blood pressure were observed compared with outpatient values, while intraoperative heart rate was also significantly lower. Only one surgery was canceled due to hypertension. Preoperative and intraoperative complications were infrequent and manageable, suggesting early assessment helps prevent complications and promotes intraoperative stability.

Reductions in systolic and diastolic blood pressure were documented upon operating room entry among patients evaluated in outpatient preanesthetic consultation, with a very low rate of surgical cancellations, although further comparative and prospective studies are needed. This approach may also support better perioperative outcomes by enabling early risk identification, individualized planning, and reduced cancellations. Additionally, standardized test protocols based on clinical criteria, rather than those defined solely by surgical teams, proved appropriate and efficient.

In a healthcare system with structural inequalities and limited resources, such as Brazil's public system, cost-effective strategies optimizing preoperative preparation and enhancing patient experience are particularly relevant. These findings support broader implementation of outpatient preanesthetic assessments to improve surgical care quality and system efficiency.

Artificial intelligence use statement

The authors declare that an artificial intelligence tool [ChatGPT] was used exclusively for text organization. No AI tool was used for data analysis or interpretation of the results. The authors take full responsibility for the content of the manuscript.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

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Associate Editor

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ORIGINAL INVESTIGATION

Impact of mannitol on intracranial pressure assessed by optic nerve sheath ultrasonography during video-laparoscopic prostatectomy: a randomized clinical trial

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Abstract
Introduction: Intracranial pressure can increase during video-laparoscopic prostatectomy due to the Trendelenburg position and pneumoperitoneum, potentially leading to complications. The Optic Nerve Sheath Diameter (ONSD) has emerged as a reliable, non-invasive method to assess ICP. Mannitol is commonly used to reduce ICP, but its intraoperative effects in this surgical setting remain unclear. This study aimed to evaluate the impact of mannitol administration on ICP, as assessed by ONSD.
Methods: This single-center, randomized, parallel-group, non-blinded clinical trial, 1:1 allocation, included 48 patients undergoing video-laparoscopic prostatectomy at a tertiary hospital in Brazil. Participants were randomly assigned to either the Mannitol Group, receiving 0.5 $g.kg^{-1}$ of intravenous mannitol after 120 minutes in Trendelenburg, or the Control Group, which did not receive mannitol. ONSD was measured using ultrasonography at four intraoperative time points (T1—T4). Additional variables analyzed included hemodynamic and respiratory parameters, surgery duration, and extubation time. Statistical analysis was conducted using a linear mixed-effects model.
Results: ONSD increased in both groups between T1 and T3, followed by a reduction at T4. However, the decrease in ONSD in the Mannitol Group was not statistically significant compared to the Control Group. Regarding extubation, the mean extubation time was 24.04 ± 15.71 minutes in the Mannitol Group and 22.79 ± 15.37 minutes in the Control Group ($p = 0.782$).

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Conclusion: Mannitol administration during video-laparoscopic prostatectomy did not result in significant differences in ONSD trajectory or extubation time compared with the control group. At the dose and timing used, mannitol did not modify intraoperative surrogate measures of intracranial pressure.

Introduction

Prostate Cancer (PC) is the most common malignant neoplasm in men, with an estimated 1.6 million cases and 366,000 deaths annually, making it the second leading cause of cancer-related mortality in men.[1,2] There are various treatment options for PC, with radical video-laparoscopic prostatectomy being widely performed as a definitive treatment for localized disease. However, to establish an adequate surgical field, a pneumoperitoneum with dioxide of Carbon (CO_2) insufflation and Trendelenburg positioning (35–45°) is required. These specific conditions alter normal physiology, leading to increased intra-abdominal, intrathoracic, and intracranial pressure due to a reduction in cranial venous drainage. Additionally, CO_2 is known to cause cerebral vasodilation, leading to increased cerebral blood volume and flow. These factors collectively result in a significant increase in Intracranial Pressure (ICP).[3]

Intracranial pressure monitoring has traditionally relied on neuroimaging or invasive methods. Ultrasonographic measurement of the Optic Nerve Sheath Diameter (ONSD) has nevertheless emerged as a simple and practical surrogate for ICP assessment. Although several studies have suggested that an ONSD of approximately 5 mm may correlate with ICP values above 20 mmHg, these thresholds are context-dependent and show considerable heterogeneity across populations and methodologies.[4]

Intraoperative ICP elevation may lead to delayed or inadequate emergence from anesthesia, manifesting as delirium or disorientation.[5] However, postoperative neurological complications or visual dysfunction have not been observed.[6,7]

Among the various strategies available to reduce ICP during surgery, mannitol plays a significant role. It is an osmotic diuretic that is easy to administer and relatively safe, increasing cerebral blood flow, reducing cellular edema through its osmotic properties, and improving cerebral oxygenation and microcirculation.[3]

This study aims to analyze the author's hypotheses regarding the effect of mannitol in attenuating the increase in optic nerve sheath diameter compared with the control group, as well as its impact on extubation time in patients undergoing video-laparoscopic prostatectomy.

Methods

A randomized, controlled, non-blinded clinical trial was conducted to evaluate patients undergoing video-laparoscopic prostatectomy at a Brazilian tertiary university hospital between May 2023 and October 2024. The study protocol was submitted to and approved by the Ethics Committee of Hospital Universitário Onofre Lopes (protocol number CAAE 55520021.5.0000.5292) and was registered in the Brazilian Registry of Clinical Trials (ReBEC) under number 6.573.095 on September 3, 2022.

Participants

Male patients aged 20 to 79 years with a diagnosis of prostate cancer and willing to participate after signing the informed consent form were included in the study. Exclusion criteria comprised conditions that increase intracranial pressure, a history of neurosurgery, glaucoma, cardiac, hepatic, or renal insufficiency, an ASA classification greater than III, conversion of the surgery to an open modality, hemodynamic instability during surgery, and a surgical duration of less than 120 minutes.

Randomization and intervention

Simple randomization with a 1:1 allocation ratio was performed using sequentially numbered, opaque, sealed envelopes prepared by a researcher not involved in patient enrollment. After anesthesia induction, the anesthesiologist opened the envelope and allocated each patient to one of two groups: the Mannitol Group (MG) or the Control Group (CG).

Patients in the MG received intravenous mannitol after 120 minutes in the Trendelenburg position, at a dose of 0.5 $g.kg^{-1}$ infused over 30 minutes. Total body weight was used for dose calculation, with a maximum dose of 50 g. Patients in the CG did not receive mannitol, or any other intervention intended to reduce intracranial pressure. No changes to the study protocol or outcomes occurred after trial initiation. The timing of mannitol administration was standardized based on institutional workflow characteristics. As this is a teaching hospital where video-laparoscopic prostatectomies typically last 5 to 6 hours, and considering that approximately one-hour elapses between anesthetic induction and the beginning of the procedure itself, the authors selected this timing to ensure that mannitol would exert its osmotic effect during a substantial portion of the prolonged Trendelenburg period. This decision was supported by using the maximum dose of 50 g and the drug's half-life of approximately 90–120 minutes.

All ONSD measurements were performed by staff anesthesiologists with more than five years of clinical experience and specific training in optic nerve ultrasonography. The anesthesiologist performing the measurements was not involved in the anesthetic management of the case and remained blinded to group allocation. Blinding was ensured because, at the times when ONSD measurements were taken, mannitol infusion in the MG either had not yet begun or had already been completed. Nevertheless, the study is considered unblinded overall, as other team members were aware of group assignment, given that a placebo infusion for the control group was not feasible.

ONSD was measured once in each eye at each of the four predefined intraoperative time points (T1—T4), and the mean value of both eyes was used for statistical analysis. According to the protocol, measurements would be repeated if the inter-eye difference at the same time point exceeded 0.5 mm; however, this threshold was never reached, and no repeated measurements were required. Using a GE HealthCare Logiq® ultrasound system with a 7.5 MHz high-frequency linear probe, ONSD was assessed 3 mm posterior to the globe at the following time points: T1 (10 minutes after induction), T2 (Trendelenburg position with 15 mmHg pneumoperitoneum), T3 (immediately before returning to horizontal position at the end of surgery), and T4 (10 minutes after resuming the supine position and pneumoperitoneum deflation). All measurements were performed by trained anesthesiology staff experienced in optic nerve ultrasonography.

The strategy was designed to minimize the risk associated with excessive ocular globe compression during surgery. Considering that each patient underwent four measurement time points per eye, performing three repeated measurements per eye at every time point would have resulted in 12 measurements per eye throughout the procedure, significantly increasing examination duration and potential risks without adding meaningful clinical benefit.

Anesthetic management, data collection and outcomes

Patients underwent balanced general anesthesia, and the anesthesiologist determined whether neuraxial anesthesia would also be used. Pre-oxygenation was performed using a face mask at 8 $L.min^{-1}$. Following orotracheal intubation, patients were ventilated in controlled mode with a tidal volume of 6—8 $mL.kg^{-1}$, a Positive End-Expiratory Pressure (PEEP) of 5 cm H_2O, and an inspired oxygen fraction of 50%. Depth of anesthesia is routinely monitored in our service. All patients were monitored with processed EEG (BIS®), and values were maintained between 40 and 60 throughout the procedure.

The primary outcome was the effect of mannitol administration on the trajectory of Optic Nerve Sheath Diameter (ONSD), measured in millimeters, across four intraoperative time points (T1—T4). Secondary outcomes included time to extubation, intraoperative hemodynamic parameters (e.g., mean arterial pressure), respiratory parameters (e.g., $EtCO_2$ and peak inspiratory pressure), surgical duration, and intraoperative fluid volume.

Statistical analysis

Sample size was calculated using Stata version 15 (StataCorp, College Station, TX, USA) to detect a mean difference of 0.3 mm in ONSD between groups, assuming a standard deviation of 0.3 mm, 80% statistical power, and a two-sided alpha of 0.05. Allowing for an anticipated 20% attrition rate, the final sample size was set at 24 patients per group. No missing data were observed for the outcomes evaluated.

The Minimal Clinically Important Difference (MCID) was defined as 0.3 mm based on prior perioperative ONSD studies showing that intraoperative changes during pneumoperitoneum and Trendelenburg typically range from 0.3 to 0.5 mm, and that mannitol-related effects fall within a similar magnitude.[3] Additionally, studies correlating ONSD with invasively measured intracranial pressure indicate that differences of this magnitude may reflect clinically relevant changes around the ICP threshold of 20 mmHg.[4] Published data also show intra- and inter-observer variability of approximately ± 0.1 to 0.3 mm, suggesting that a 0.3 mm difference exceeds expected measurement noise and likely represents a true physiological change. Therefore, a 0.3 mm difference was considered the smallest clinically meaningful effect of mannitol in this setting.[2-4]

Baseline characteristics were described using means and standard deviations for continuous variables and frequency distributions for categorical variables. Data normality was assessed using the Shapiro-Wilk test. Pre-intervention differences between groups were evaluated using Student's *t*-test or Wilcoxon test for continuous variables and Pearson's Chi-Square test or Fisher's exact test for categorical variables. In addition, between-group differences in ONSD variation at each time point were analyzed using Student's *t*-test, with a significance level set at $p < 0.05$.

A linear mixed-effects model was used to compare changes in ONSD between the Mannitol and Control groups. ONSD was considered the dependent variable. Time points (T1, T2, T3, and T4), group assignment, and their interaction were included as fixed effects. The model was additionally adjusted for Body Mass Index (BMI), surgery duration, and extubation time. Intra-individual variability was incorporated as a random effect to account for repeated measurements within subjects. The covariance structure for repeated measures was modelled as autoregressive of order 1 [AR(1)], assuming that measurements closer in time are more strongly correlated. The model included a random intercept for each subject to account for intra-individual variability across time points; random slopes were not included. Fixed effects comprised group, time, and group vs. time interaction, along with BMI, surgery duration, and extubation time as covariates. A p-value < 0.05 was considered statistically significant. Sample size calculation and statistical analyses were performed using Stata V 15 software. There were no missing data for the outcomes assessed. No subgroup or sensitivity analyses were performed.

Results

The study included 51 patients, with 48 patients randomized between the Mannitol Group (n = 24) and the Control Group (n = 24). None of them were excluded after randomization, as shown in Figure 1. All patients allocated to the mannitol group received the full dose as described, and no patient in the control group received mannitol.

No significant differences were observed in baseline characteristics, including age (p = 0.830) and BMI (p = 0.085), as demonstrated in Table 1.

The analysis of intraoperative parameters showed that mean arterial pressure and end-$ETCO_2$ levels were similar between groups at all time points ($p > 0.05$). The duration of surgery was slightly longer in the Mannitol Group (6.51 ±

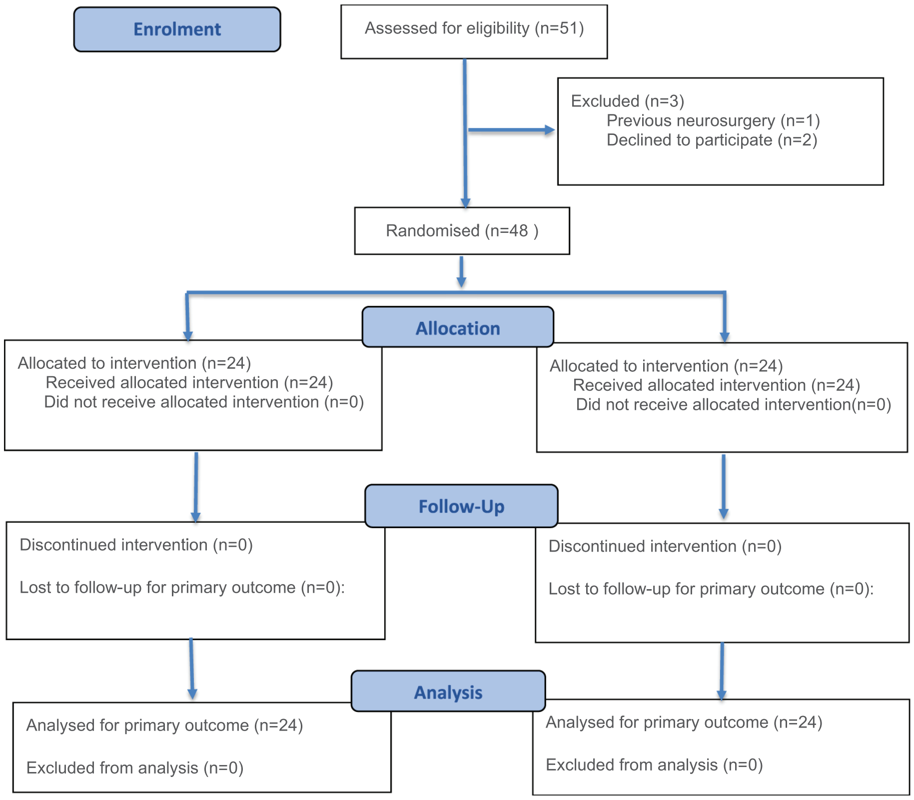


Figure 1 CONSORT flow diagram.

Table 1 Demographic characteristics and results.

Variable	Mannitol Group	Control Group	Difference between means (95% CI)	p-value
Age (years)	64.71 ± 7.13	64.33 ± 4.63	−0.38 (−3.93 – 3.18)	0.83
BMI (kg.m^{-2})	24.95 ± 3.60	26.58 ± 2.76	1.63 (−0.12 – 3.38)	0.08
Surgery duration (hours)	6.51 ± 1.27	5.98 ± 1.30	−0.52 (−1.14 – 0.10)	0.16
Extubation time (minutes)	24.04 ± 15.71	22.79 ± 15.37	−1.25 (−10.56 – 8.06)	0.78
Infused volume (mL)	2161.78 ± 655.04	2120.03 ± 584.87	−41.67 (−265.08 – 181.175)	0.81
$ETCO_2$ (mmHg) – T1	32.63 ± 4.47	33.33 ± 8.06	0.71 (−2.57 – 3.99)	0.70
$ETCO_2$ (mmHg) – T2	34.88 ± 5.01	36.42 ± 6.12	1.54 (−1.99 – 5.08)	0.34
$ETCO_2$ (mmHg) – T3	37.88 ± 5.09	37.75 ± 3.91	−0.13 (−2.52 – 2.27)	0.92
$ETCO_2$ (mmHg) – T4	35.42 ± 5.19	35.92 ± 4.13	0.50 (−2.38 – 3.38)	0,71
MAP (mmHg) – T1	70.58 ± 14.27	69.33 ± 11.52	−1.25 (−9.39 – 6.89)	0,74
MAP (mmHg) – T2	87.29 ± 16.78	88.08 ± 15.58	0.79 (−10.03 – 11.61)	0.87
MAP (mmHg) – T3	76.54 ± 9,91	76.17 ± 10.56	−0.38 (−6.88 – 6.13)	0.90
MAP (mmHg) – T4	72.21 ± 7.72	73.75 ± 10.74	1.54 (−3.16 – 6.25)	0.57
Peak inspiratory pressure (cmH_2O) – T1	18.58 ± 4.28	19.25 ± 5.70	0.66 (−2.53 – 3.87)	0.65
Peak inspiratory pressure (cmH_2O) – T2	27.00 ± 3.63	26.92 ± 5.68	−0.08 (−2.57 – 2.41)	0.95
Peak inspiratory pressure (cmH_2O) – T3	25.46 ± 5.62	24.96 ± 6.1	−0.50 (−3.62 – 2.62)	0.77
Peak inspiratory pressure (cmH_2O) – T4	19.67 ± 3.94	19.79 ± 3.61	0.13 (−1.93 – 2.18)	0.90
Mean eyes diameters (mm) – T1	3.90 ± 0.56	3.57 ± 0.7	−0.33 (−0.73 – 0.08)	0.08
Mean eyes diameters (mm) – T2	4.06 ± 0.93	3.93 ± 0.8	−0.13 (−0.67 – 0.40)	0.60
Mean eyes diameters (mm) – T3	4.34 ± 0.85	4.39 ± 0.78	0.05 (−0.36 – 0.47)	0.83
Mean eyes diameters (mm) – T4	3.95 ± 0.75	4.34 ± 0.95	0.39 (−0.04 – 0.83)	0.12

BMI, Body Mass Index; $ETCO_2$, End-tidal Carbon Dioxide; MAP, Mean Arterial Pressure.

1.27 hours) compared to the Control Group (5.98 ± 1.30 hours), but the difference was not statistically significant (p = 0.163). The volume of crystalloid infused during surgery also did not differ between the groups. No significant adverse events were recorded in either group.

Regarding extubation, the mean extubation time was 24.04 ± 15.71 minutes in the Mannitol Group and 22.79 ± 15.37 minutes in the Control Group (p = 0.782). The relative extubation time as a percentage of total surgical duration also did not differ significantly between groups (p = 0.650).

Analysis of ONSD revealed a progressive increase from T1 to T3 in both groups, followed by a reduction at T4. The Mannitol Group showed a more pronounced decrease at T4 compared to the Control Group. However, between-group differences at each time point were not statistically significant, as shown in Figure 2. The figure displays mean ONSD values with 95% Confidence Intervals for each time point, along with results from univariate comparisons between groups.

In the mixed-effects linear regression model (Table 2), mannitol administration was not significantly associated with changes in ONSD (β = 0.206; 95% CI: -0.180 to 0.592; p = 0.984). None of the covariates included in the model – BMI, surgery duration, or extubation time – showed significant associations with ONSD variation. Only the intraoperative time points (T1, T2, T3 and T4) remained significantly associated with ONSD (β = 0.001; 95% CI: 0.000 to 0.002; p = 0.001).

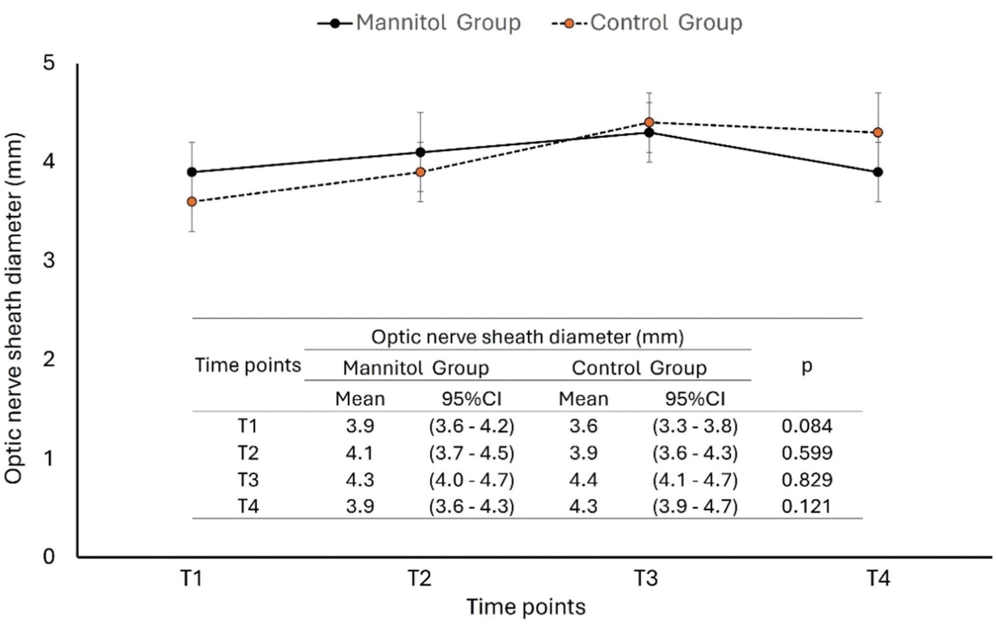
Discussion

The main findings of our study indicate that the Trendelenburg position is associated with an increase in the ONSD during video-laparoscopic prostatectomy. However, the administration of mannitol did not significantly alter the variation in ONSD, nor did it affect extubation time.

Several studies have demonstrated the use of ONSD measurement as an indirect indicator of ICP in surgeries requiring pneumoperitoneum and prolonged Trendelenburg positioning, such as conventional and robotic-assisted videolaparoscopic prostatectomies. Kim and colleagues assessed the extent of ICP elevation caused by CO_2 pneumoperitoneum combined with the Trendelenburg position in patients undergoing robot-assisted laparoscopic radical prostatectomy. ONSD measurements and cerebral oximetry were recorded at five different time points during surgery. Their study, which included 20 patients, revealed a significant 12.5% increase in ONSD compared to post-induction values. Among these patients, three showed ONSD values corresponding to an ICP greater than 20 mmHg.[6]

Chin and co-investigators evaluated the sonographic measurement of ONSD as a surrogate marker for ICP in 21 anesthetized patients in the Trendelenburg position. Their findings demonstrated that ONSD measured three minutes after positioning was significantly higher ($p < 0.001$) than the value recorded after anesthesia induction (5.1 ± 0.3 mm vs. 4.5 ± 0.4 mm). This effect was also observed when Trendelenburg positioning was combined with pneumoperitoneum (4.9 ± 0.4 mm vs. 4.5 ± 0.4 mm). However, the final ONSD measurement after desufflation of pneumoperitoneum was comparable to the post-induction value.[8]

Balkan and collaborators investigated the effects of Trendelenburg positioning (35°–45° tilt) and CO_2 insufflation on ONSD and hemodynamic parameters in patients undergoing robot-assisted laparoscopic radical prostatectomy to assess potential correlations between these variables. A total of 34 patients were included. ONSD was measured using ultrasound at four time points: T1 (5 minutes after intubation in the supine position), T2 (30 minutes after CO_2 insufflation), T3 (120 minutes in the Trendelenburg position), and T4



Time points	Optic nerve sheath diameter (mm)				p
	Mannitol Group		Control Group		
	Mean	95%CI	Mean	95%CI	
T1	3.9	(3.6 - 4.2)	3.6	(3.3 - 3.8)	0.084
T2	4.1	(3.7 - 4.5)	3.9	(3.6 - 4.3)	0.599
T3	4.3	(4.0 - 4.7)	4.4	(4.1 - 4.7)	0.829
T4	3.9	(3.6 - 4.3)	4.3	(3.9 - 4.7)	0.121

Figure 2 Variation in Optic Nerve Sheath Diameter (ONSD) at four intraoperative time points (T1 to T4) in the Mannitol and Control groups. Data are presented as mean values with 95% Confidence Intervals (95% CI). Between-group comparisons at each time point were performed using Student's *t*-test; $p < 0.05$ were considered statistically significant.

Table 2 Mixed-effects linear regression model assessing the influence of mannitol on Optic Nerve Sheath Diameter (ONSD).

Optic nerve sheath diameter (mm)	Adjusted[a]		p
	β (SE)	95% CI	
Mannitol	0.206 (0.197)	−0.180 – 0.592	0.984
BMI ($kg.m^{-2}$)	−0.024 (0.029)	−0.081 – 0.033	0.409
Surgery duration (hours)	−0.069 (0.076)	−0.219 – 0.080	0.364
Extubation time (minutes)	0.005 (0.006)	−0.007 – 0.018	0.389
Intraoperative time points (T1, T2, T3 and T4 in minutes)	0.001 (0.001)	0.000 – 0.002	**0.001**

[a] The dependent variable was the variation in optic nerve sheath diameter (ONSD, in mm). Fixed-effect independent variables included mannitol use, Body Mass Index (BMI), surgery duration, extubation time, and intraoperative time points. Time was modeled as a continuous fixed-effect variable. Intra-individual variability was included as a random effect to account for repeated measures within subjects. Estimates (β), Standard Errors (SE), 95% Confidence Intervals (95% CI), and p-values are reported.

(after abdominal desufflation in the supine position). Systolic and diastolic blood pressure, heart rate, and end-tidal CO_2 were also recorded. The mean ONSD values were 4.87 mm at T1, 5.21 mm at T2, 5.30 mm at T3, and 5.08 mm at T4. A statistically significant increase in ONSD was observed between T1 and T3, followed by a significant decrease at T4. Additionally, a positive correlation was identified between ONSD and diastolic blood pressure, whereas no significant correlations were found between ONSD and mean arterial pressure, heart rate, or end-tidal CO_2.[5]

The potential of mannitol as an intraoperative ICP-lowering agent has been explored with mixed results. Jun et al. reported a reduction in ONSD following mannitol administration in patients positioned in Trendelenburg during robotic prostatectomy, suggesting a potential benefit in mitigating ICP elevation.[3] However, their study lacked a control group and was not randomized, limiting the generalizability of the findings. In contrast, our controlled data suggest that mannitol administration does not confer additional benefit in reducing ONSD or improving immediate postoperative outcomes in this specific surgical setting.

It is important to note that mannitol's pharmacological effects may be more pronounced in settings of sustained or pathological ICP elevation, rather than the transient increases seen during laparoscopic procedures in otherwise healthy individuals. Moreover, factors such as baseline intracranial compliance, the duration of surgical positioning, and individual variation in cerebrovascular autoregulation may modulate the impact of osmotic therapy on ICP and its surrogates.

Our study has several limitations. First, the potential variability in ultrasonographic technique could introduce measurement bias, including the possibility of intra-observer variation despite standardized training. Second, we did not assess perioperative neurocognitive outcomes, such as postoperative delirium or cognitive dysfunction. Although initially considered, these evaluations were not feasible in our institutional setting, particularly because standardized preoperative assessments could not be performed. Third, the relatively small sample size may limit the detection of subtle differences in secondary outcomes and affect the overall precision of our estimates. Finally, because this was a single-center study conducted in a teaching hospital with specific workflow characteristics, the generalizability of our findings to other settings may be limited.

Conclusion

In this randomized trial, intraoperative mannitol administration during video-laparoscopic prostatectomy did not produce statistically significant between-group differences in ONSD trajectory, hemodynamic or respiratory parameters, or extubation time. Under the specific conditions, dose, and timing used in this study, mannitol did not modify surrogate measures of intracranial pressure. These findings should be interpreted cautiously as their generalizability to other populations, surgical durations, and dosing strategies may be limited.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI assistance disclosure

The authors declare that no Artificial Intelligence (AI) tools were used in the conception, design, data analysis, or writing of this manuscript.

Brazilian Registry of Clinical Trials (ReBEC)

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Ethics Committee approval

Ethical approval was granted by the Onofre Lopes University Hospital Research Ethics Committee, under the Ethical Appreciation Presentation Certificate number CAAE 55520021.5.0000.5292 on May 4, 2022.

Authors' contributions

George Pereira Barreto contributed to the study conception, conducted the study execution, and participated in manuscript drafting. Fernanda Cunha Soares and Rand Randall Martins contributed to statistical analysis and manuscript drafting. Paulo José de Medeiros contributed to the critical revision of the manuscript. Ygor Paulion Bezerra Pereira, Isabelle França Bezerra Machado, and Elkanah Marinho de Araujo were involved in the execution of the study. Wallace Andrino da Silva led the study, developed the original idea, coordinated all phases of the project, and was responsible for writing and revising the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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REVIEW ARTICLE

Early tracheostomy in severe traumatic brain injury: an umbrella systematic review

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Abstract
Background: Tracheostomy is an option to ensure airway safety in patients with severe traumatic brain injury. However, the optimal timing for tracheostomy remains unclear based on current evidence.
Methods: Umbrella systematic review to determine the effectiveness of early tracheostomy in TBI. Databases: PubMed, Embase, Scopus, Web of Science, Lilacs, Cochrane, Open Grey, and clinical trials. Inclusion criteria: Meta-analysis of early tracheostomy in severe TBI patients. Exclusion criteria: if there was no data regarding the time of death or the follow-up period. Data extraction: Selection, risk of bias evaluation, and data extraction were performed by two independent authors.
Results: Four meta-analyses were included from 5673 initial records, and a new meta-analysis was performed from data obtained in primary studies. The evidence included in this umbrella review showed that early tracheostomy reduced ICU (MD = -5.69 days; 95% CI [-7.78, -3.59]) and Hospital (MD = -3.53 days; 95% CI [-4.44, -2.62]) length of stay, time in mechanical ventilation (MD = -5.08; 95% CI [-7.12, -3.05]) and risk of ventilator associated pneumonia (RR = 0.78; 95% CI [0.70, 0.86],). These studies cannot determine the effectiveness of early tracheostomy on mortality (RR = 1.32; 95% CI [0.89, 1.96],) or neurological prognosis.

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Conclusions: This umbrella review suggests that early tracheostomy is effective in reducing ICU and Hospital length of stay, time in mechanical ventilation, and ventilator-associated pneumonia.
Inplasy protocol: 202280096.

Introduction

Traumatic Brain Injury (TBI) is any injury that affects the skull, brain tissue, and its associated vessels, and it's a major public health issue worldwide. The overall incidence of TBI is estimated at 1299 cases in North America, 1012 cases in Europe, and 801 cases in Africa (per 100,000 people).[1] In Brazil, there were one million hospitalizations of TBI patients between 2010 and 2019, and 45,42% of those were in patients aged 20 to 49 years old.[2]

TBI can be classified by the Glasgow Coma Scale (GCS) as mild (13–15), moderate (9–12), and severe (< 9) (TEASDALE, 1974).[3] One of the aims in assisting patients with severe TBI is the hemodynamic and airway management to avoid secondary injuries as hypoxemia and hypercapnia.[4,5]

Extubating in neurological patients remains a challenge. Waiting for full neurological recovery is not mandatory. However, the ability to cough, swallow, and maintain eye contact during evaluation can be assessed.[6] This strategy can result in prolonged time in mechanical ventilation, and it has increased hospital morbidity and mortality.[7,8] The prolonged hospital care is associated with complications, such as pneumonia, thromboembolic events, and mortality.[9]

In this scenario, tracheostomy is one of the options to guarantee a safer airway, promote early patient mobilization, progression of the diet, reduction of airway resistance, and complications ratio.[10] Although the time to perform tracheostomy still remains unclear in the light of current evidence.[6,11]

Hence, the aim of this umbrella review was to determine the effectiveness of early tracheostomy in severe patients with traumatic brain injury.

Methods

The Preferred Reporting Items for Systematic Review and Meta-analysis Protocols[12] was used to design a protocol, which was registered on Inplasy — International Platform of Registered Systematic Review and Meta-analysis Protocols (ID number: 202280096).[13]

The inclusion criteria were: (P) Patients above 18 years old with a severe traumatic brain injury and advanced airway support; (I) Early tracheostomy (< 10 days of intubation); (C) Late tracheostomy (> 10 days) or prolonged intubation; (O) Mortality, time on ICU stay, on Hospital stay and in mechanical ventilation, complications (pneumonia, pressure ulcers, thromboembolic events and time using antibiotics), and quality of life (scores regarding neurological functions); and (S) Systematic reviews with meta-analysis. No language restrictions were applied. A study would be excluded if there was no data regarding the time of death and follow-up period in hospital stay or after discharge.

Online databases were searched on August 22nd, 2022, using the MESH terms of Craniocerebral Trauma and tracheostomy: Medline by PubMed, Lilacs, Cochrane, Scopus by Elsevier, Web of Science, and Embase by Elsevier. The references of the selected studies were also analyzed. Grey literature was sought with SIGLE by Open Grey and Clinical Trial Register at the International Clinical Trials Registry Platform (Supplementary Material).

Two independent reviewers (RRA and IHAA) selected the studies and performed data extraction using pre-established forms.[13] Then, disagreements were solved by consensus meetings with a third and more experienced reviewer (OBON).

Risk of bias was assessed using the ROBIS tool. This evaluation was performed by two reviewers, independently (RRA and EVSP). Cohen's kappa statistic was used to measure the level of agreement between reviewers for the selection of eligible studies and for the risk of bias assessment. MetaXL 5.3 (Epigear, Queensland, Australia) was used to perform meta-analyses. The Relative Risk (RR) was calculated for dichotomic outcomes and the Mean Difference (MD) for continuous outcomes (Confidence Interval 95%). Predicting a possible heterogeneity between studies, the random effects model was used.

To avoid the results being inflated by overlap of primary studies in the included meta-analyses, we performed our own meta-analyses with the primary studies' data (Supplementary Material). The presence of heterogeneity was analyzed by the Cochrane Q statistic and was measured using the Higgins Test (I^2). To explore heterogeneity, we performed a sensitivity analysis by excluding studies with a high risk of bias, and a subgroup analysis by comparing prospective versus retrospective cohorts and late tracheostomy versus prolonged intubation in the control group. The publication bias was assessed with the DOI-plot and LFK index. We also checked and didn't find any retractions in the selected studies.

GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was used to assessing certainty of the evidence.

Results

In total, 5491 registers were identified from the search strategy across all online databases. Then, 22 articles were identified as potentially relevant to this umbrella review. In the selection process, 18 articles failed to meet the inclusion criteria, as 11 articles were duplicated, six papers included TBI with other causes of mechanical ventilation in the analysis, and one publication did not discriminate outcomes from early versus late tracheostomy. We did not identify new studies in

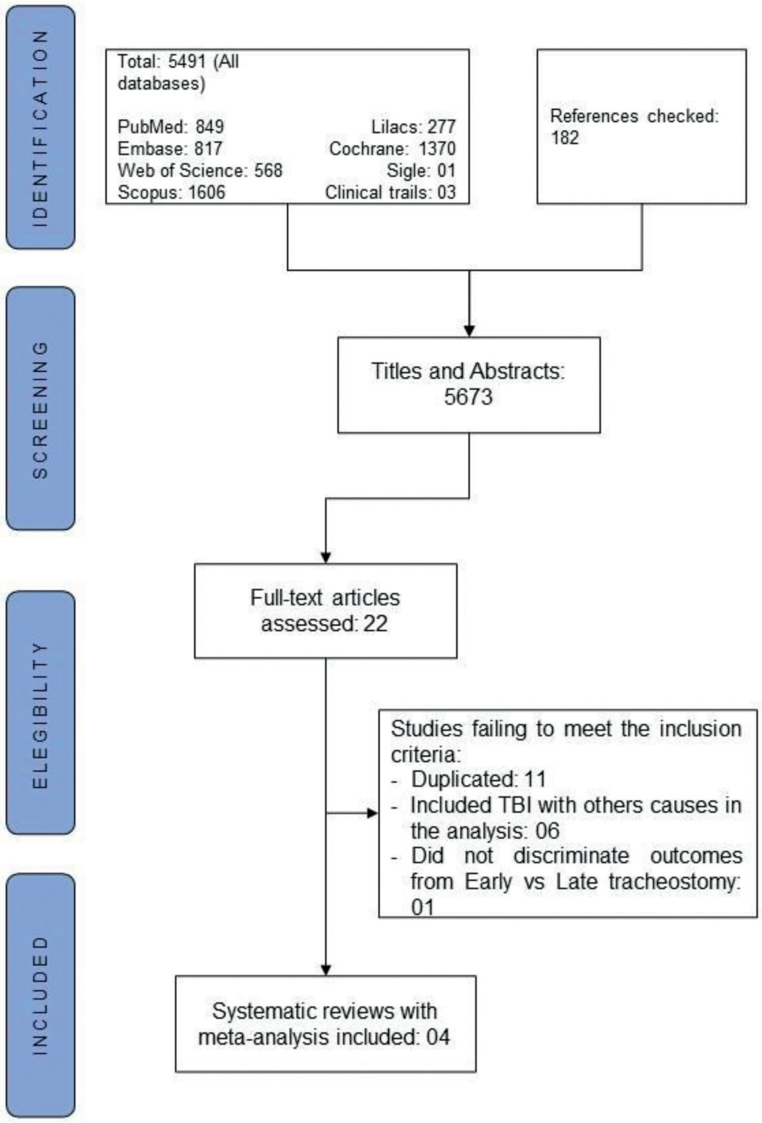

Figure 1 Flowchart of the selection process.

the screening process of references (Fig. 1). Thus, four articles[14-17] were included in this umbrella review (agreement: 91.3%; Kappa = 0.774, 95% CI 0.41–1.00) (Table 1).

Risk of bias

There were 70% of agreement on this stage (Kappa = 0.400, 95% CI 0.166–0.684). Disagreements were solved by a third reviewer (OBON):

Domain 1: Only McCredie et al. (2017)[14] published a priori protocol, nonetheless Lu et al. (2018),[15] Franca et al. (2020)[16] and Marra et al. (2021)[17] had describe satisfactory the eligibility criteria and outcomes; Domain 2: Franca et al. (2020)[16] and Marra et al. (2021)[17] presented high concerns regarding the selection process because was restrict to one database (PubMed) and the search strategy was not clear enough to replicate; Domain 3: all of the included studies[14-17] had low risk of bias because data extraction and risk of bias was performed by two reviewers independently; Domain 4: Franca et al. (2020)[16] and Marra et al. (2021)[17] didn't take the high heterogeneity in consideration in their results and conclusions, Lu et al. (2018)[15] wasn't clear about the synthesis and just McCredie et al. (2017)[14] had low concerns for executed what was planned in protocol.

Mortality

The meta-analyses results by McCredie et al. (2017),[14] Lu et al. (2018),[15] Franca et al. (2020)[16] and Marra et al. (2021)[17] reported no difference in mortality between early and late tracheostomy groups (Table 1). In our meta-analysis we also found no difference between groups with three RCTs[18-20] and this data showed no heterogeneity (RR = 1.86 [0.90, 3.84], I^2 = 0%, Q = 1.06, p = 0.59). The same result was presented with eight cohorts,[20-27] but this data reported a moderate heterogeneity (RR = 1.32 [0.89, 1.96], I^2 = 56%, Q = 16.06, p = 0.02) (Table 2).

Table 1 Results of meta-analyses included with primary studies.

Outcome	Meta-analysis	Selected primary studies	Results
Mortality	McCredie et al. (2017)[14]	**RCT** Sugerman et al. (1997)[18] Bouderka et al. (2004)[19] Dunhan et al. (2014)[20] Barquist et al. 2006[32]	RCT: RR = 1.2 [0.44, 3.30], I^2 = 37%
	Lu et al. (2018)[15]	**RCT** Sugerman et al. (1997)[18] Bouderka et al. (2004)[19] Dunhan et al. (2014)[20]	RCT: OR = 2.58 [0.96, 6.96], I^2 = 0%
		Observational Siddiqui et al. (2015)[22] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27] Wang et al. (2012)[28]	Cohort: OR = 1.15 [0.81, 1.63], I^2 = 0%
	Franca et al. (2020)[16]	**RCT** Dunhan et al. (2014)[20] **Observational** Shibahashi et al. (2017)[21] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27]	RCT and Cohort: Risk = 0.03 [-0.02, 0.07], I^2 = 69%
	Marra et al. (2021)[17]	**RCT** Sugerman et al. (1997)[18] Dunhan et al. (2014)[19]	RCT: OR = 3.154 [0.456, 21.695], I^2 = 0%
		Observational Shibahashi et al. (2017)[21] Robba et al. (2020)[23] Kahlili et al. (2017)[24] Rizk et al. (2011)[25] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27]	Cohort: OR 1.505 [0.993, 2.279], I^2: 49.435%
VAP	McCredie et al. (2017)[14]	**RCT** Sugerman et al. (1997)[18] Bouderka et al. (2004)[19] Dunhan et al. (2014)[20] Barquist et al. (2006)[32] Blot et al. (2008) Fayed et al. (2012)	RR = 0.89 [0.65, 1.21], I^2 = 54%
	Lu et al. (2018)[15]	**RCT** Sugerman et al. (1997)[18] Bouderka et al. (2004)[19] Dunhan et al. (2014)[20]	RCT: OR = 0.89 [0.47, 1.68], I^2 = 0%
		Observational Siddiqui et al. (2015)[22] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27] Wang et al. (2012)[28]	Cohort: OR = 0.62 [0.51, 0.77], I^2 = 0%
	Franca et al. (2020)[16]	**RCT** Dunhan et al. (2014)[20] **Observational** Shibahashi et al. (2017)[21] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27]	RCT and Cohort: RR = 0.78 [0.70, 0.88], I^2 = 0%
	Marra et al. (2021)[17]	**Observational** Shibahashi et al. (2017)[21]	Cohort: OR = 0.623 [0.518, 0.750], I^2 = 0%

Table 1 (*Continued*)

Outcome	Meta-analysis	Selected primary studies	Results
		Robba et al. (2020)[23] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27] Wang et al. (2012)[28]	
Time in MV	McCredie et al. (2017)[14]	**RCT** Sugerman et al. (1997)[18] Bouderka et al. (2004)[19] Dunhan et al. (2014)[20] Barquist et al. (2006)[32] Blot et al. (2008) (NO TBI) Terragni et al. (2010) (NO TBI) Fayed et al. (2012) (NO TBI) Bösel et al. (2013) (NO TBI) Youngi et al. (2021) (NO TBI)	MD = -2.72 [-4.15, -2.19], I^2 = 0%
	Lu et al. (2018)[15]	**RCT** Bouderka et al. (2004)[19] Dunhan et al. (2014)[20] **Observational** Siddiqui et al. (2015)[22] Robba et al. (2020)[23] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27] Wang et al. (2012)[28]	RCT and Cohort: MD = -4.92 [-6.82, -3.02], I^2 = 51%
	Franca et al. (2020)[16]	**RCT** Dunhan et al. (2014)[20] **Observational** Shibahashi et al. (2017)[21] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27]	RCT and Cohort: MD = -4.15 [-6.30, -1.99], I^2 = 85%
	Marra et al. (2021)[17]	**RCT** Dunhan et al. (2014)[20] **Observational** Shibahashi et al. (2017)[21] Robba et al. (2020)[23] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27]	RCT and Cohort: MD = -4.866 [-6.981, -2.751], I^2 = 93.203%
LOS (ICU)	McCredie et al. (2017)[14]	**RCT** Sugerman et al. (1997)[18] Blot et al. (2008) (NO TBI) Terragni et al. (2010) (NO TBI) Bösel et al. (2013) (NO TBI) Youngi et al. (2021) (NO TBI)	MD = -2.55 [-4.59, -0.50], I^2 = 0%
	Lu et al. (2018)[15]	**RCT** Sugerman et al. (1997)[18] Bouderka et al. (2004)[19] Dunhan et al. (2014)[20] **Cohorts** Siddiqui et al. (2015)[22] Kahlili et al. (2017)[24] Ahmed, Kuo et al. (2007)[27] Wang et al. (2012)[28]	RCT and Cohorts: MD = -3.08 [-3.75, -2.41], I^2 = 38%
	Franca et al. (2020)[16]	**Cohorts** Shibahashi et al. (2017)[21] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27]	Cohorts: MD = -5.87 [-8.74, -3.00], I^2 = 83%

Table 1 (*Continued*)

Outcome	Meta-analysis	Selected primary studies	Results
	Marra et al. (2021)[17]	**Cohorts** Shibahashi et al. (2017)[21] Robba et al. (2020)[23] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27]	Cohorts: MD = -5.96 [-7.99, -3.92], I^2 = 88.661%
LOS (Hospital)	Lu et al. (2018)[15]	**Cohorts** Siddiqui et al. (2015)[22] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27] Wang et al. (2012)[28]	Cohorts: MD = -4.79 [-8.63, -0.94]; I^2 = 59%
	Franca et al. (2020)[16]	**Cohorts** Shibahashi et al. (2017)[21] Kahlili et al. (2017)[24] Alali et al. (2014)[26]	Cohorts: MD = -6.68 [-8.03, -5.32]; I^2 = 0%
	Marra et al. (2021)[17]	**Cohorts** Shibahashi et al. (2017)[21] Robba et al. (2020)[23] Kahlili et al. (2017)[24] Alali et al. (2014)[26] Ahmed, Kuo et al. (2007)[27]	Cohorts: MD = -6.97 [-8.25, -5.68]; I^2 = 0%

RR, Risk Ratio; OR, Odds Ratio; MD, Mean Difference; RCT, Randomized Control Trial; VAP, Ventilator-Associated Pneumonia; Time in MV, Duration (in days) of mechanical ventilation; LOS (ICU), ICU Lenght of stay; LOS (Hospital), Hospital Lenght of stay; ET, Early Tracheostomy; LT, Late Tracheostomy; PI, Prolonged Intubation.

Ventilator-associated pneumonia

Franca et al. (2020)[16] and Marra et al. (2021)[17] reported a decrease in the risk of ventilator-associated pneumonia in the ET group. Otherwise, McCredie et al. (2017)[14] and Lu et al. (2018)[15] reported no difference between groups. Our meta-analyses found no difference between early and late tracheostomy on the risk of pneumonia (RR = 0.94 [0.70, 1.27]; I^2 = 0%, Q = 0.07, p = 0.97) across three RCTs.[18-20] The ET group reduced in 22% the risk of ventilator-associated pneumonia in seven cohort studies[21-27] (RR = 0.78 [0.70, 0.86]; I^2 = 0%, Q = 2.75, p = 0.84). Meta-analyses with RCTs and cohort studies did not show statistical heterogeneity (Fig. 2).

Duration of mechanical ventilation

All included meta-analyses[14-17] reported that the ET group was significantly associated with reduced duration of mechanical ventilation. In our analysis, there was no difference in the Mean Difference in days of mechanical ventilation between groups in two RCTs[18,20] (MD = -2.95 [-6.16, 0.26]; (I^2 = 0%, Q = 0.00, p = 0.98). In our meta-analysis of five cohorts,[21,23,26-28] the ET group was associated with fewer days in mechanical ventilation, although this result was based on high heterogeneity (MD = -5.08 [-7.12, -3.05]; I^2 = 85%, Q = 26.84, p = 0.00) (Fig. 2).

ICU length of stay

Four meta-analyses[14-17] reported that the ET group was significantly associated with reduced ICU length of stay. In our analysis, just one RCT[18] evaluated this outcome. The ET group was associated with fewer days in mechanical ventilation in six cohorts[21,23,24,26-28] (MD = -5.69 [-7.78, -3.59]; I^2 = 73%, Q = 18.37, p = 0.00) (Fig. 2).

Hospital length of stay

McCredie et al. (2017),[14] Lu et al. (2018),[15] and Franca et al. (2020)[16] reported that the ET group was significantly associated with reduced hospital length of stay. In our meta-analysis, we also reported that the ET group was associated with fewer days in mechanical ventilation in six cohorts[21,23,24,26-28] (MD = -3.53 [-4.44, -2.62]; I^2 = 0%, Q = 3.47, p = 0.63) (Fig. 2).

Quality of life

None of the included meta-analyses reported this outcome. However, five cohort studies presented some types of scores for this outcome. Two cohorts[21,22] demonstrated by GOS (Glasgow Outcome Scale), Shibahashi et al. (2017)[21] reported no statistical difference between groups, and Siddiqui et al. (2015)[22] showed a better result in the early tracheostomy group, but without a statistical analysis.

Two cohorts[23,24] evaluated GOSE (Glasgow Outcome Scale-Extended) at 6 months of follow-up. Robba et al. (2020)[23] reported a worse result (OR = 1.69 [1.07—2.67], p = 0.018). Khalili et al. (2017)[24] showed no statistical difference between groups. One study[25] evaluated FIM (Functional Independence Measure) with better results in the ET group (FIM > 10, ET: 43% vs. LT: 29%, p < 0.0001).

Table 2 GRADE.

Outcome	Study	ET group	LT/PI group	Day of ET	N° of participants (studies)	Certainty of the evidence (GRADE)	Meta-analysis
Mortality	**RCT**						
	Bouderka et al. (2004)[19]	12/31	7/31	5–6 days	153 (3 RCTs)	⊕⊕x̂x̂ Low[a]	RR = 1.86 [0.90, 3.84], I^2 = 0%
	Dunhan et al. (2014)[20]	0/15	0/9	3–5 days			
	Surgerman et al. (1997)[18]	5/35	1/32	3–5 days			
	Cohorts						
	Ahmed & Kuo et al. (2007)[27]	4/27	1/28	≤ 7 days	5043 (7 Cohorts)	⊕x̂x̂x̂ Very Low[a]	RR = 1.32 [0.89, 1.96], I^2 = 56%
	Alali et al. (2014)[26]	48/571	39/571	≤ 8 days			
	Shibahashi et al. (2017)[21]	1/40	4/51	≤ 72 hours			
	Rizk et al. (2011)[25]	238/1577	111/1527	≤ 7 days			
	Wang et al. (2012)[28]	2/16	4/50	≤ 7 days			
	Siddiqui et al. (2015)[22]	4/49	9/51	≤ 7 days			
	Khalili et al. (2017)[24]	10/53	18/99	≤ 6 days			
VAP	**RCT**						
	Bouderka et al. (2004)[19]	12/31	7/31	5–6 days	213 (3 RCTs)	⊕⊕x̂x̂ Low[a]	RR = 0.94 [0.70, 1.27]; I^2 = 0%
	Dunhan et al. (2014)[20]	0/15	0/9	3–5 days			
	Surgerman et al. (1997)[18]	5/35	1/32	3–5 days			
	Cohorts						
	Ahmed & Kuo et al. (2007)[27]	11/27	14/28	≤ 7 days	2039 (7 Cohorts)	⊕⊕x̂x̂ Low[b]	RR = 0.78 [0.70, 0.86]; I^2 = 0%
	Alali et al. (2014)[26]	238/571	301/571	≤ 8 days			
	Shibahashi et al. (2017)[21]	13/40	21/51	≤ 72 hours			
	Wang et al. (2012)[28]	7/16	38/50	≤ 7 days			
	Siddiqui et al. (2015)[22]	22/49	32/51	≤ 7 days			
	Khalili et al. (2017)[24]	28/53	59/99	≤ 6 days			
	Robba et al. (2020)[23]	49/180	100/253	≤ 7 days			
Time in MV	**RCT**						
	Bouderka et al. (2004)[19]	14.5 ± 7.3d / 31p	17.5 ± 10.6d / 31p	5–6 days	86 (2 RCTs)	⊕⊕x̂x̂ Low[a]	
	Dunhan et al. (2014)[20]	14.1 ± 5.7d / 15p	19 ± 11.3d / 32 p	3–5 days			MD = -2.95 [-6.16, 0.26]; I^2 = 0%
	Retrospective cohorts						
	Ahmed & Kuo et al. (2007)[27]	15.7 ± 6d / 27p	25.8 ± 11.8d / 28p	≤ 7 days	1288 (3 cohorts)	⊕⊕⊕x̂ Moderate[c]	
	Alali et al. (2014)[26]	21.4 ± 10.45d/571p*	24.9 ± 5.95d/ 571p*	≤ 8 days			MD = -3.26 [-3.94, -2.57]; I^2 = 0%
	Shibahashi et al. (2017)[21]	5 ± 1.54d / 40p*	8 ± 3.05d/ 51p*	≤ 72 hours			
	Prospective cohorts						
	Wang et al. (2012)[28]	13.7 ± 7.3d / 16p	23.4 ± 11d / 50p	≤ 7 days	499 (2 cohorts)	⊕⊕⊕⊕ High[d]	MD = -7.53 [-9.05, -6.01]; I^2 = 0%
	Robba et al. (2020)[23]	12.35 ± 6.73d/180p*	19.63 ± 10.29d/253p*	≤ 7 days			

Table 2 (*Continued*)

Outcome	Study	ET group	LT/PI group	Day of ET	N° of participants (studies)	Certainty of the evidence (GRADE)	Meta-analysis
ICU lenght of stay	**RCT**						
	Surgerman et al. (1997)[18]	16 ± 5.9d / 35p	19 ± 11.3d / 32p	3–5 days			
	Retrospective cohorts						
	Ahmed & Kuo et al. (2007)[27]	19 ± 7.7d / 27p	25.8 ± 11.8d / 28p	≤ 7 days			
	Alali et al. (2014)[26]	13.7 ± 5.95d / 571p*	19.7 ± 7.43 / 571p*	≤ 8 days	1288 (3 Cohorts)	⊕⊕⊕x̂ Moderate[e]	MD = -4.67 [-7.85, -1.5]; I^2 = 0%
	Shibahashi et al. (2017)[21]	10 ± 4.61d / 40p*	12.06 ± 3.81d / 51p*	≤ 72 hours			
	Prospective cohorts						
	Wang et al. (2012)[28]	14.9 ± 8.9d / 16p	22.1 ± 7.6d / 50p	≤ 7 days	651 (3 Cohorts)	⊕⊕⊕x̂ Moderate[f]	MD = -7.34 [-9.76, -4.92]; I^2 = 0%
	Khalili et al. (2017)[24]	26.79 ± 13.16d/ 53p	34.92 ± 20.07d/ 99p	≤ 6 days			
	Robba et al. (2020)[23]	19.6 ± 19.9d / 180p	26.7 ± 12.5d / 253p	≤ 7 days			
Hospital lenght of stay	**Cohorts**						
	Ahmed & Kuo et al. (2007)[27]	24.36 ± 5.48d / 27p*	28 ± 6,25d / 28p*	≤ 7 days	1939 (6 Cohorts)	⊕⊕⊕x̂ Moderate[f]	MD = -3.53 [-4.44, -2.62]; I^2 = 0%
	Alali et al. (2014)[26]	21.4 ± 10.41d/571p*	24.9 ± 5.95/571p*	≤ 8 days			
	Shibahashi et al. (2017)[21]	52.64 ± 19.22d/40p*	56.29 ± 16.78d/51p	≤ 72 hours			
	Wang et al. (2012)[28]	38.0 ± 21.4d/ 16p	46.8 ± 22d / 50p	≤ 7 days			
	Robba et al. (2020)[23]	35.1 ± 34.4d /180p	34.7 ± 33.6d / 253 p	≤ 7 days			
	Khalili et al. (2017)[24]	38.58 ± 20.18d/ 53p	46.40 ± 24.56d/ 99p	≤ 6 days			

[a] Small number of events, Large IC.
[b] LFK index: -2,10 (Major asymmetry), I^2 = 0%.
[c] High magnitude of effect, I^2 = 0%, LFK index: -2,71 (Major asymmetry).
[d] No asymmetry, I^2 = 0%, high magnitude of effect.
[e] High magnitude of effect, High heterogeneity.
[f] High magnitude of effect, I^2 = 0% (Major asymmetry).
ET, Early Tracheostomy; LT, Late Tracheostomy; PI, Prolonged Intubation; p, Participants.
Data in Mean ± Standard Deviation / participants.
* Data converted of Median and Interquartile interval from primary studies by Wan et al. (2014).[39]

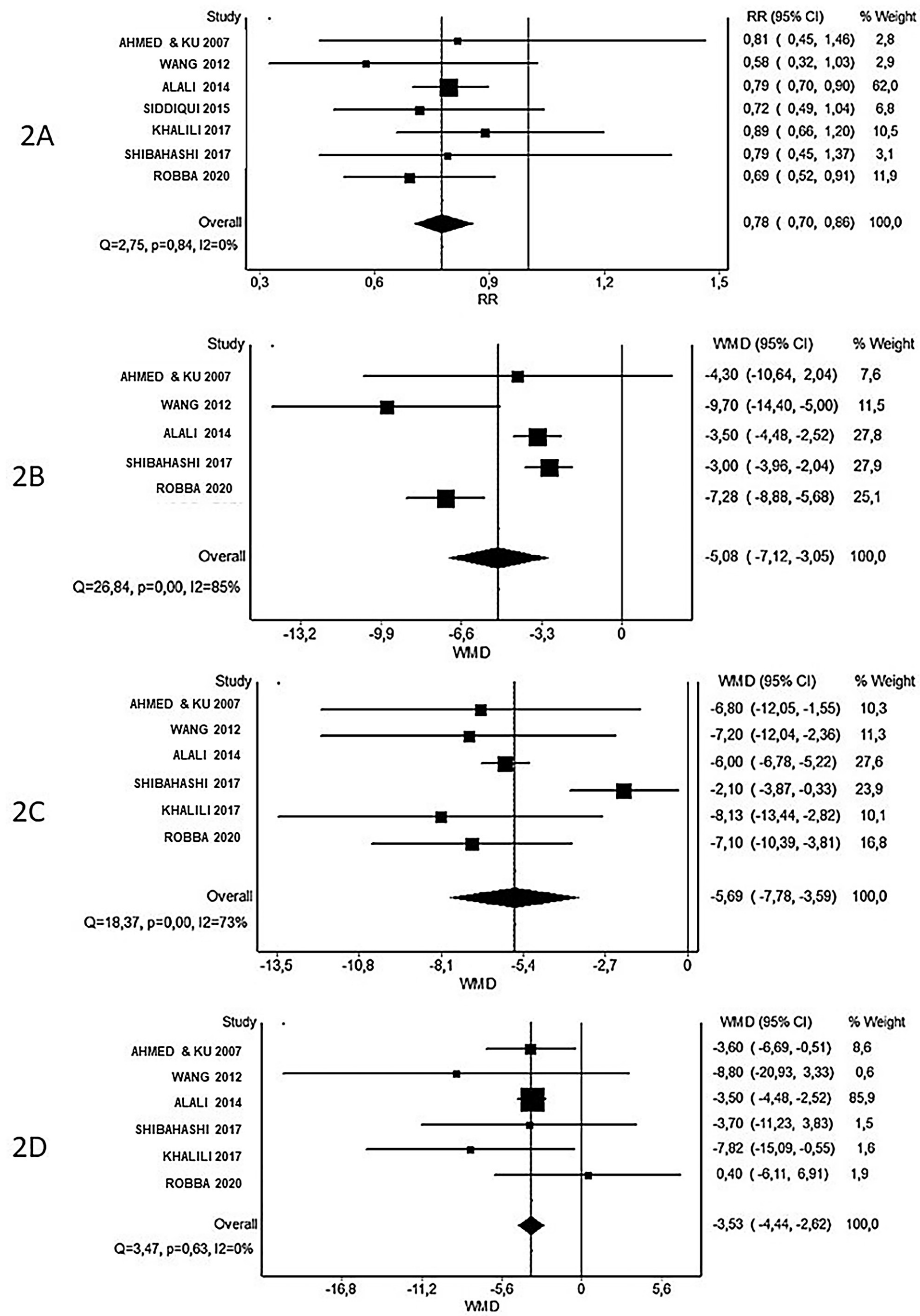

Figure 2 Forest plot of early tracheostomy in severe TBI patients: (A) Ventilator-associated pneumonia, (B) Time in mechanical ventilation, (C) ICU length of stay, (D) Hospital length of stay.

Other health care related outcomes

None of the meta-analyses selected reported these outcomes. One cohort[26] reported fewer events of decubitus ulcer (ET: 4.03% vs. LT: 8.93%), deep venous thrombosis (ET: 8.23% vs. LT: 14.36%), and pulmonary embolism (ET: 1.75% vs LT: 3.33%) in the ET group. Another cohort[25] showed more infectious events (sepsis, septicemia, and acute sinusitis) in the LT group (ET: 24.35% vs. LT: 34.9%). Moreover, Robba et al. (2020)[23] presented a higher need for antibiotics in the LT group (ET: 88.33% vs. LT: 95.65%).

Publication bias

The risk of publication bias was analyzed in mortality and VAP from RCTs.[18-20] In the mortality meta-analysis, we found no asymmetry in publication bias (LFK index: -0.59). In the VAP meta-analysis, we reported a minor asymmetry on publication bias (LFK index: 1.94). Otherwise, there was a major asymmetry in risk of publication bias in cohort meta-analysis about mortality (LFK index: -4.56), ventilator-associated pneumonia (LFK index: -2.10), duration in mechanical ventilation (LFK index: -4.51), ICU length of stay (LFK index: -2.82), and Hospital length of stay (LFK index: -3.83) (Supplementary Material).

Homogeneity and sensitivity

To address heterogeneity in observational studies, we separated prospective from retrospective cohorts and excluded the only study[22] that used prolonged intubation as the control group. This analysis showed an increase in mortality in the ET group in prospective cohorts, although this result was based on a major asymmetry in publication bias analysis (RR = 1.74 [1.25, 2.41], I^2 = 23%, Q = 3.87, p = 0.28, LFK index = -4.65). The retrospective cohorts presented no difference between groups and no asymmetry in publication bias (RR = 1.21 [0.50, 2.93], I^2 = 28%, Q = 2.77, p = 0.25, LFK index = -0.20). The benefit of ET in reducing the risk of ventilator-associated pneumonia was sustained when we removed the Siddiqui et al. (2015)[22] study, and the data were presented with minor asymmetry (LFK index = -1.81) (Supplementary Material).

GRADE

The force of evidence was considered moderate in cohort studies on ICU length of stay, hospital length of stay, and duration of mechanical ventilation. However, mortality and ventilator-associated pneumonia were low or very low (Table 2).

Discussion

The impact of early tracheostomy does not appear to be significant on mortality in patients on mechanical ventilation due to neurological involvement. Our results showed that both randomized clinical trials and cohort studies did not provide enough data to define the effectiveness of ET in preventing deaths in severe TBI patients, and these results were also the same as those found for other neurological causes, such as stroke,[29] acute brain injury,[30] and spinal cord trauma.[31]

Regarding the incidence of Ventilator-Associated Pneumonia (VAP), the literature reports highly discordant results, not only for TBI. For example, in critically ill patients in the ICU, some studies indicate no difference between early and late tracheostomy.[33-35] Other studies showed benefit from performing an ET in neurological patients;[29,30,36] however, in non-neurological patients, they did not maintain that benefit.[37]

There was a difference in the data on pneumonia cases in the Alali et al. (2014)[26] study. Franca et al. (2020)[16] used a propensity-matched analysis excluding deaths; as a result, 213/516 cases were reported in the ET group and 281/516 in the LT group. However, two meta-analyses[15,17] used a propensity-matched analysis with deaths; therefore, the number of events was 238/571 in the ET group and 301/571 in the LT group. In our meta-analyses, we used a propensity-matched analysis with deaths and found that early tracheostomy reduced the risk of ventilator-associated pneumonia by 22%.

Time on mechanical ventilation is highly relevant in critically ill care. As in VAP, neurological patients[29-31,38] show better outcomes with early tracheostomy than critically ill patients in general[34] or non-neurological patients.[37] This umbrella supports the results in neurological patients, with moderate-high certainty, and the evidence from cohorts, mainly due to the magnitude of the effect, with an average reduction of 7.53 days in mechanical ventilation time in the ET group. However, the clinical trials failed to confirm that benefit.

Although some studies fail to demonstrate a benefit of early tracheostomy in critically ill patients in reducing ICU length of stay 33,37, most of the literature indicates that patients undergoing ET spend less time in the ICU.[30,31,35,36,38] The Umbrella result followed the same direction as the time in mechanical ventilation. It showed a benefit with moderate certainty of evidence, with a mean reduction of 7.34 days in patients undergoing ET, based on an evaluation of 651 patients.

This Umbrella review indicated an average mean reduction of 3.53 days in hospital length of stay in the ET group, with moderate certainty of evidence evaluating 1939 patients. Bertini et al. (2023)[38] also reported this benefit, but with a smaller magnitude, reducing the average by 1.26 days with PT. As in VAP, ET seems to be better indicated in neurological patients[29-31,38] than in non-neurological patients.[37]

Outcomes as complications (pneumonia, septicemia, candidemia, pressure ulcers, thromboembolic events, and time on antibiotics), and quality of life (scores regarding neurological function) lacked sufficient data to assess the effectiveness of early tracheostomy, and this should be taken into consideration for future trials.

Our results were limited by lower concordance among reviewers in the risk of bias analysis, although divergences were resolved in consensus meetings, and the selection showed satisfactory concordance among reviewers. Another limitation was the risk of bias analysis in the primary studies, which we did not perform, but the four meta-analyses included did not report major issues in their analyses.

Conclusions

The evidence included in this umbrella review suggests that early tracheostomy is associated with reduced ICU and Hospital length of stay, time on mechanical ventilation, and ventilator-associated pneumonia. These studies cannot determine the effectiveness of early tracheostomy on mortality and neurological prognosis.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

Raul Ribeiro de Andrade: Conceptualization (Lead), Data curation (Lead), Formal analysis (Lead), Investigation (Lead), Methodology (Lead), Project administration (Lead), Writing-original draft (Lead).

Edla Vitória Santos Pereira: Data curation (Equal), Formal analysis (Equal).

Igor Hudson Albuquerque e Aguiar: Investigation (Equal).

Olavo Barbosa de Oliveira Neto: Data curation (Supporting), Formal analysis (Supporting), Writing-review & editing (Supporting).

João Gustavo Rocha Peixoto dos Santos: Visualization (Supporting), Writing-review & editing (Supporting).

Fabiano Timbó Barbosa: Conceptualization (Equal), Project administration (Equal), Supervision (Equal), Writing-review & editing (Equal).

Célio Fernando de Sousa-Rodrigues: Formal analysis (Supporting), Investigation (Supporting), Methodology (Supporting), Project administration (Supporting), Supervision (Lead), Writing-review & editing (Supporting).

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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.2026.844727.

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REVIEW ARTICLE

Remimazolam compared with propofol, dexmedetomidine, and midazolam for adult sedation in flexible bronchoscopy: a systematic review and meta-analysis

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Abstract

Background: Remimazolam, a short-acting benzodiazepine, has emerged as a potential safer alternative for sedation in Flexible Bronchoscopy (FB). This meta-analysis compares its efficacy and safety with Propofol, Dexmedetomidine, and Midazolam in adult patients undergoing FB.

Methods: PubMed, Embase, and Cochrane databases were searched on July 17, 2025, for trials comparing Remimazolam with other sedatives. Primary outcomes included hypotension, bradycardia, and intraprocedural opioid consumption; secondary outcomes were hypoxia, respiratory depression, patient satisfaction, induction time, and recovery time. Pooled Risk Ratios (RR), Mean Differences (MD), and Standardized Mean Differences (SMD) were calculated using a random-effects model in R (4.4.0). Risk of bias was assessed using the RoB2 tool, and subgroup analyses were conducted for each comparator.

Results: Eleven trials (1,884 patients) were included. Remimazolam reduced respiratory depression (RR = 0.44 [95% CI 0.29; 0.67]; p = 0.0002; I^2 = 0%), hypoxia incidence (RR = 0.60 [95% CI 0.39; 0.93]; p = 0.0227; I^2 = 64.7%), bradycardia (RR = 0.39 [95% CI 0.20; 0.77]; p = 0.0069; I^2 = 52.3%), and hypotension (RR = 0.61 [95% CI 0.40; 0.95]; p = 0.0289; I^2 = 74.0%) compared to all sedatives. Compared to Propofol, Remimazolam reduced the incidence of hypotension (RR = 0.42 [95% CI 0.31; 0.58]; p < 0.0001; I^2 = 0%), respiratory depression (RR = 0.41 [95% CI 0.25; 0.68]; p = 0.0005; I^2 = 12.3%), but increased induction time (MD = 0.61 min [95% CI 0.23; 0.99];

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$p = 0.002$; $I^2 = 90.9\%$). Compared to Dexmedetomidine, it improved satisfaction (SMD = 0.23 [95% CI 0.07; 0.39]; $p = 0.004$; $I^2 = 0\%$) and reduced recovery time (MD = -1.79 min [95% CI -2.66; -0.92]; $p < 0.001$; $I^2 = 90.7\%$), hypoxia incidence (RR = 0.49 [95% CI 0.28; 0.88]; $p = 0.0162$; $I^2 = 60.3\%$), and induction time (MD = -2.21 min [95% CI -2.41; -2.00]; $p < 0.001$; $I^2 = 0\%$). Compared to Midazolam, Remimazolam increased sedation success (RR = 2.03 [95% CI 1.40; 2.95]; $p = 0.0002$; $I^2 = 50\%$), shortened induction time (MD = -0.69 min [95% CI -1.37; -0.01]; $p = 0.047$; $I^2 = 81.5\%$), and recovery time (MD = -4.49 min [95% CI -7.06; -1.92]; $p < 0.001$; $I^2 = 40.9\%$).
Conclusions: Remimazolam reduced respiratory depression overall and demonstrated improved safety, faster recovery, and greater efficacy compared to Propofol, Dexmedetomidine, and Midazolam, respectively, supporting its potential as an effective alternative for sedation in FB. Nonetheless, substantial heterogeneity in certain outcomes and the relatively small sample size in some comparisons limit the generalizability of our findings.
Systematic review protocol: PROSPERO (CRD 42024568148).

Introduction

Flexible Bronchoscopy (FB) is a widely performed procedure for diagnosing and treating pulmonary diseases.[1-3] In the United States alone, over 500,000 FB procedures are done annually, underscoring the clinical importance of optimizing sedation strategies in high-volume settings.[4] This high procedural burden is also reflected globally, where FB remains a cornerstone in the diagnosis and management of respiratory conditions, with utilization having expanded significantly worldwide over the past two decades.[5] Ensuring optimal sedation during this procedure is critical to patient safety, comfort, and procedural success. Propofol, Dexmedetomidine and Midazolam are commonly employed to guarantee adequate sedation during FB, and Remimazolam has emerged as a promising alternative.[6,7]

Remimazolam is a novel short-acting benzodiazepine that enhances $GABA_A$ receptor activity and is rapidly hydrolyzed by nonspecific esterases, forming an inactive metabolite.[8] Propofol is an intravenous hypnotic agent that acts as a γ-aminobutyric acid-A ($GABA_A$) receptor agonist and has been widely used over the past three decades.[9] Dexmedetomidine, a selective α-2 adrenoceptor agonist approved in the United States in 1999, is commonly used for sedation.[10] Midazolam, a benzodiazepine, is one of the most frequently used sedatives, primarily modulating $GABA_A$ receptors.[11]

Due to Remimazolam's pharmacological properties, it has emerged as an alternative for bronchoscopy sedation, highlighting its clinical relevance due to its quick onset, high procedure success rate, minimal residual effect, hemodynamic and respiratory stability.[7,12,13] Additionally, traditional sedatives used for FB are associated with various adverse effects. Propofol is linked to hypotension, bradycardia, and respiratory depression.[6,7,14] Dexmedetomidine may prolong recovery time.[15] Midazolam is known to cause prolonged post-procedure sedation and delayed recovery.[6,14] Although Remimazolam has shown promising results, there is a lack of comprehensive evidence comparing its efficacy and safety with these sedatives for FB procedure.

This systematic review and meta-analysis compares Remimazolam versus Propofol, Dexmedetomidine and Midazolam in terms of efficacy and safety outcomes – hypotension, bradycardia, intraprocedural opioid consumption, hypoxia, respiratory depression, patient satisfaction, induction time, and recovery time – with subgroup analyses comparing Remimazolam with each sedative individually.

Methods

This systematic review and meta-analysis were performed and reported following the Cochrane Collaboration Handbook for Systematic Review of Interventions[16] and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement guidelines.[17] This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database on July 22, 2024 (registration number CRD 42024568148), https://www.crd.york.ac.uk/PROSPERO/view/CRD42024568148. There were no deviations from the pre-specified protocol in this systematic review and meta-analysis, including eligibility criteria, outcome definitions, data extraction, and statistical methods.

Systematic literature search

We conducted a comprehensive systematic search on July 17, 2025 across PubMed, Embase, and Cochrane Library databases to identify all relevant studies. A combination of the following terms was used to search all databases: Remimazolam; Byfavo; "CNS 7056". The complete search strategy for each database is provided in the Supplementary Appendix. Only studies in the English language were included; no further restrictions were applied to the search, and the grey literature was not searched, in order to enhance methodological rigor and ensure the reliability of the synthesized evidence.

Selection criteria and data extraction

We included only Randomized Controlled Trials (RCTs) in English in this systematic review and meta-analysis. Two authors independently assessed the titles and abstracts using Rayyan, assessed the full texts of potentially eligible studies and removed the duplicates.[18] We consulted a third author to reach a consensus in cases of unresolved disagreement and included studies based on the Population, Intervention, Control, and

Outcomes (PICO) guidelines.[19,20] The inclusion criteria were: 1) Population: Adult patients undergoing flexible bronchoscopy; 2) Intervention: use of intravenous Remimazolam for sedation; 3) Comparison: intravenous Propofol, Dexmedetomidine, or Midazolam for sedation; and 4) Outcomes: incidence of hypotension during the procedure, bradycardia, intraprocedural opioid consumption, respiratory depression, patient satisfaction, success of sedation, time to complete recovery of consciousness, hypoxia and induction time to sedation.

We excluded: 1) Studies with overlapping populations, defined as the same institutions and recruitment periods; 2) Studies reporting no outcomes of interest; 3) No control group; 4) Non-RCTs; 5) Patients undergoing rigid bronchoscopy; 6) Conference abstracts; and 7) Patients under conscious sedation. There were no restrictions based on the publication date. We did not search the grey literature and contacted the corresponding author for specific study results, in cases of missing data from individual studies. All included and cited studies will be systematically screened for potential retractions using the PubMed/MEDLINE and Retraction Watch databases.

Two reviewers independently collected data using a predesigned Excel datasheet. The following variables were collected: publication year; country; enrollment period; baseline characteristics; Remimazolam dosage; comparator sedative dosages; analgesic regimen; sedation level; incidence of adverse events (hypotension, respiratory depression, bradycardia, hypoxia); intraprocedural opioid consumption; patient satisfaction, sedation success; recovery time; and induction time.

Quality and risk assessment

Two reviewers independently evaluated the risk of bias using version 2 of the Cochrane Risk of Bias tool (RoB2) for randomized controlled trials. They assigned a judgment of "low risk", "some concerns", or "high risk" for each of the five domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported results. Any disagreements were resolved through consensus.[21]

To assess the robustness of the obtained estimates and evaluate heterogeneity, a leave-one-out analysis (Supplemental Fig. 1) was performed for all outcomes. When an outcome included at least 10 studies, we assessed publication bias through the funnel plot and Egger's test (Supplemental Fig. 2). Additionally, Baujat plots were used to identify individual studies that contributed substantially to heterogeneity in cases where I^2 was 50% or higher (Supplemental Fig. 3).[22]

Primary and secondary outcomes

Our primary outcomes were the incidence of hypotension, bradycardia and intraprocedural opioid consumption. Hypotension was defined as Systolic Blood Pressure (SBP) < 90 mmHg or 20% lower than baseline,[23,24] or a Mean Arterial Pressure (MAP) reduction > 20% of baseline.[23-26] Bradycardia was defined as a Heart Rate (HR) < 60 Beats Per Minute (BPM) or a reduction greater than 20% compared with baseline or an HR < 50 BPM.[25,26] Intraprocedural opioid consumption was expressed in intravenous morphine equivalents, calculated using the method proposed by Kane et al., following the guidelines of the American Pain Society.[27]

We pooled results whenever three or more studies reported the same outcome. The secondary outcomes included respiratory depression, defined as < 10 breaths per minute or < 8 breaths per minute;[25] hypoxia, defined as oxygen saturation < 90%.[23-26] Patient satisfaction score was assessed by a standardized 5-point or 10-point scale, where lower scores indicate lower satisfaction; induction time; sedation success, defined as successful completion of the FB procedure; and time to complete recovery of consciousness, defined as the interval from the bronchoscopy completion to full awakening.

Statistical analysis

We analyzed the data using R software, version 4.4.0. We computed Risk Ratios (RR) with 95% Confidence Intervals (95% CI) for each binary endpoint. We defined statistical significance as $p < 0.05$. We reported continuous outcomes as Mean Differences (MD) with 95% CI when studies used the same scale and as Standardized Mean Differences (SMD) with 95% CI when different scales were used to measure the same outcome. When continuous data were reported as medians with IQR or range, we calculated the mean and SD using the methods proposed by Luo et al. and Wan et al.[28,29] Considering the anticipated clinical and methodological heterogeneity across studies, including variability in patient populations, dosing regimens, and comparators, a random-effects model was deemed the most suitable approach for synthesizing the pooled results.[28,29] Additionally, we assessed heterogeneity among the trials using the I^2 statistic, with $I^2 > 50\%$ indicating significant heterogeneity and explored heterogeneity sources with leave-one-out sensitive analysis and Baujat plot.[22,30] We conducted subgroup analyses for each comparator (Propofol, Dexmedetomidine and Midazolam) to distinguish their individual effects on the pooled results. The data and analytical code supporting the findings of this study are available from the corresponding author upon reasonable request.

Results

Search results

We identified a total of 3,696 reports through our search strategy, with 1,548 duplicates. We screened the titles and abstracts of the remaining 2,148 reports, excluding 2,129. We assessed the full text of nineteen trials, excluding eight (Fig. 1). The remaining eleven RCTs were included in this systematic review and meta-analysis.

Study characteristics

We included eleven RCTs with 1,884 patients.[23-26,31-37] Of these, 1,057 received Remimazolam, while 827 received comparator sedatives, including Dexmedetomidine, Propofol, and Midazolam. All patients were classified as ASA I–III. Nine studies were conducted in China. The dose of Remimazolam varied across the RCTs. Details of the individual studies, like drug dosages and relevant characteristics, are summarized in Table 1.

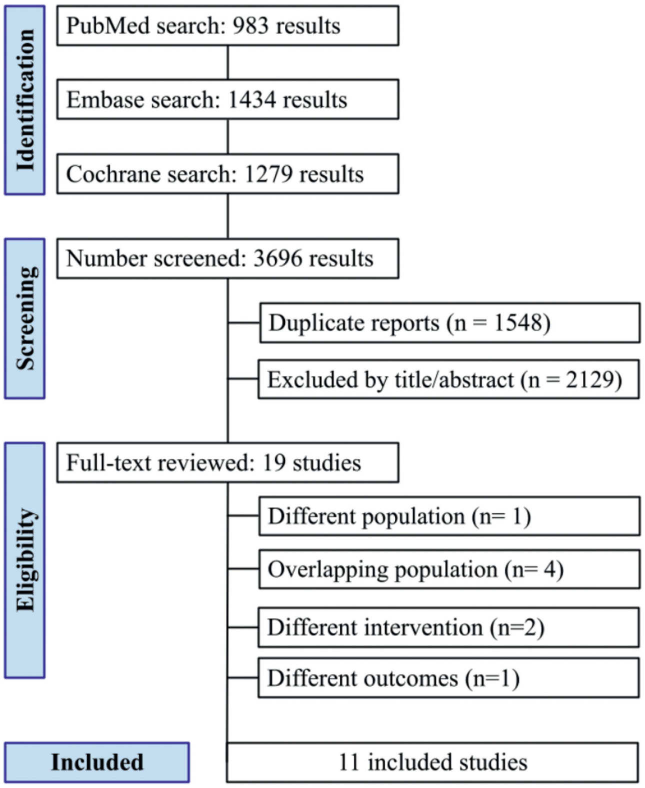

Figure 1 PRISMA-compliant flow diagram of study screening and selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Risk of bias

Among the eleven included studies in this systematic review and meta-analysis, two were assessed as having an overall low risk of bias, while the remaining nine were classified as presenting "some concerns", predominantly due to limitations in the domain of selective reporting of results. Importantly, no study was deemed to have a high overall risk of bias. A summary of the assessment for each specific domain is provided in Figure 2.

The primary source of bias concerns was incomplete or unclear reporting of prespecified outcomes, which may introduce a risk of reporting bias. Nevertheless, all studies provided sufficient data for the extraction and analysis of primary and secondary outcomes. Moreover, domains critical to internal validity, including the randomization process, adherence to intended interventions, completeness of outcome data, and outcome measurement, were predominantly judged to be at low risk, thereby enhancing the overall reliability of the evidence base.

Outcomes

Primary outcomes

The Remimazolam group demonstrated a statistically significant reduction in the incidence of hypotension (RR = 0.61 [95% CI 0.40; 0.95]; p = 0.0289, I^2 = 74.0%, 11 trials, 1,883 patients, Fig. 3A). When individually compared to Propofol, the Remimazolam group was associated with a significantly lower incidence of hypotension (RR = 0.42 [95% CI 0.31; 0.58]; p < 0.0001, I^2 = 0%, 5 trials, 688 patients, Fig. 3A). No significant differences were observed between Remimazolam and Dexmedetomidine or Midazolam in the subgroup analysis for this outcome. The certainty of evidence was deemed low for the hypotension incidence outcome.

Remimazolam showed a statistically significant reduction in the incidence of bradycardia in the overall analysis (RR = 0.39 [95% CI 0.20; 0.77]; p = 0.0069, I^2 = 52.3%, 9 trials, 1479 patients, Fig. 3B). The certainty of evidence was deemed low for the bradycardia incidence outcome. The subgroup analysis showed no significant difference between Remimazolam and any individual comparator for this outcome.

Similarly, intraprocedural opioid consumption did not significantly differ between Remimazolam and the overall sedative group (MD = -0.58 mg of intravenous morphine [95% CI -1.31; 0.14]; p = 0.114, I^2 = 95%, 6 trials, 1,451 patients, Fig. 3C), with no statistical differences found in the subgroup comparisons. The certainty of evidence was deemed low for the intraprocedural opioid consumption outcome.

Secondary outcomes

The Remimazolam group showed a statistical reduction in respiratory depression compared to the overall analysis (RR = 0.44 [95% CI 0.29; 0.67]; p = 0.0002, I^2 = 0%, 5 trials, 1080 patients, Fig. 4A) and when individually compared to Propofol (RR = 0.41 [95% CI 0.25; 0.68]; p = 0.0005, I^2 = 12.3%, 3 trials, 562 patients, Fig. 4A). No significant differences were observed with the other sedatives. The certainty of evidence was deemed moderate for the respiratory depression incidence outcome.

Our analysis revealed no statistically significant difference between the Remimazolam group and the overall analysis on the patient satisfaction score (SMD = 0.15 [95% CI -0.03; 0.33]; p = 0.109, I^2 = 46.7%, 7 trials, 1041 patients, Fig. 4B). However, Remimazolam sedation was associated with higher patient satisfaction compared to the Dexmedetomidine individual group (SMD = 0.23 [95% CI 0.07; 0.39]; p = 0.004, I^2 = 0%, 3 trials, 629 patients, Fig. 4B). There was no significant difference between Remimazolam and the other comparators. The certainty of evidence was deemed moderate for the patient satisfaction score outcome.

No significant difference was observed for sedation success between Remimazolam and the overall analysis (RR = 1.18 [95% CI 0.94; 1.47; p = 0.1557, I^2 = 82.3%, 7 trials, 1168 patients, Fig. 4C). However, subgroup analysis showed a significantly higher success rate with Remimazolam compared to Midazolam (RR = 2.03 [95% CI 1.40; 2.95]; p = 0.0002, I^2 = 50%, 2 trials, 466 patients, Fig. 4C), but no significant difference with Propofol or Dexmedetomidine. The certainty of evidence was deemed low for sedation success outcome.

Overall, there was no difference in induction time (MD = -0.77 minutes [95% CI -1.83; 0.29]; p = 0.156, I^2 = 99.2%, 6 trials, 929 patients, Fig. 5A), although our subgroup analysis demonstrated Remimazolam had a significant shorter induction time compared to Midazolam (MD = -0.69 minutes [95% CI -1.37; -0.01]; p = 0.047, I^2 = 81.5%, 2 trials, 194 patients, Fig. 5A) and Dexmedetomidine (MD = -2.21 minutes [95% CI -2.41; -2.00]; p < 0.001, I^2 = 0%, 2 trials, 483 patients, Fig. 5A). The comparison with Propofol demonstrated a longer induction time (MD = 0.61 minutes [95% CI 0.23; 0.99] p = 0.002, I^2 = 90.9%, 2

Table 1 Characteristics of the included studies.

Study (Author, Year)	Country	Enrollment Period	ASA	Sample Size (Remimazolam/ Control)	Age (years), mean ± SD	Body Weight (kg), mean ± SD	Remimazolam Details	Control Details	Analgesia Protocol	Procedure Details	Benzodiazepine antagonists	Outcomes assessed	Level of Sedation
Chen, 2022	China	December 2020 to November 2021	I–II	73/73	56.55 ± 5.80	Remimazolam group: 68.97 ± 5.33. Dexmedetomidine group: 69.64 ± 6.20	First 10 min: 2000 μg.kg^{-1} Maintenance: 16.7 −33.3 μg.kg^{-1}.min^{-1}	First 10 min: Dexmedetomidine 0.5 μg.kg^{-1} Maintenance: Dexmedetomidine 0.003−0.012 μg.kg^{-1}.min^{-1}	Single dose: Fentanyl 1 μg.kg^{-1}, Dexamethasone 0.1 mg.kg^{-1} Infusion: Remifentanil 0.05−0.2 μg.kg^{-1}.min^{-1}	Endobronchial inspection, bronchoscopic biopsy and lavage	All patients: flumazenil (200 μg)	Sedation success, respiratory depression, time to complete recovery of consciousness, patient satisfaction, hypoxia, hypotension, bradycardia	Moderate
Xu, 2024	China	April to September 2023	I–II	60/60	60.80 ± 4.23	Remimazolam group: 67.2 ± 6.2 Dexmedetomidine group: 67.6 ± 7.4	First 10 min: 1000 μg.kg^{-1} Maintenance: 16.7−33.3 μg.kg^{-1}.min^{-1}	First 10 min: Dexmedetomidine 0.5 μg.kg^{-1} Maintenance: Dexmedetomidine 0.003 −0.012 μg.kg^{-1}.min^{-1}	5 min before induction: Alfentanil 10 μg.kg^{-1} During procedure: Alfentanil 0.5−2 μg.kg^{-1}.min^{-1}	Endobronchial inspection, bronchoscopic biopsy and lavage	N/A	Sedation success, time to complete recovery of consciousness, patient satisfaction, intraprocedural opioid consumption, induction time, hypoxia, hypotension, bradycardia	Moderate
Gao, 2023	China	January 2021 to August 2021	I–III	30/30	59.4 ± 9.15	N/A	Induction: 100 μg.kg^{-1}.min^{-1} Maintenance: 10−33.3 μg.kg^{-1}.min^{-1} Rescue: 100 μg.kg^{-1}	Induction: Propofol 2000 μg.kg^{-1} Maintenance: Propofol 66.7−100 μg.kg^{-1}.min^{-1} Rescue: 500 μg.kg^{-1}	5 min prior: Sufentanil 0.15 μg.kg^{-1}	Elective bronchoscopy	N/A	Time to complete recovery of consciousness, patient satisfaction, induction time, hypoxia, hypotension, bradycardia	Deep
Zhang, 2023	China	N/A	I–III	96/96	64.37 ± 13.38	Remimazolam group: 56.72 ± 12.37 Propofol group: 58.72 ± 11.31	Single dose: 200 μg.kg^{-1} Rescue: Remimazolam 50 μg.kg^{-1}	Single dose: Propofol 1500 μg.kg^{-1} Rescue: Propofol 500-1000 μg.kg^{-1}	Prior anesthesia: Alfentanil 10 μg.kg^{-1}	Bronchoscopy with preserved spontaneous breathing	N/A	Respiratory depression, time to complete recovery of consciousness, patient satisfaction, intraprocedural opioid consumption, induction time, hypotension, bradycardia	Moderate
Zhou, 2022	China	N/A	I–III	155/155	50.76 ± 12.65	Remimazolam group: 60.8 ± 9.57 Propofol group: 62.0 ± 9.71	Single dose: 200 μg.kg^{-1} Rescue: 100 μg.kg^{-1}	Initial dose: Propofol 2000 μg.kg^{-1} Rescue: Propofol 750 μg.kg^{-1}	Single dose: Fentanyl 2 μg.kg^{-1}	Check the airways, biopsy, EBUS-TBNA, bronchoalveolar lavage, bronchial foreign body removal	N/A	Sedation success, respiratory depression, time to complete recovery of consciousness, intraprocedural opioid consumption, hypoxia, hypotension,	Moderate
Wu, 2024	China	May 2022 to July 2022	I–III	46/48	69.78 ± 3.86	Remimazolam group: 59.33 ± 11.91 Midazolam group: 60.67 ± 10.53	Single dose: 135 μg.kg^{-1} Rescue: titrated Propofol, until RSS = 4	Single dose: Midazolam 45 μg.kg^{-1} Rescue: titrated Propofol, until RSS = 4	Single dose: Alfentanil 1.8 μg.kg^{-1}	Diagnostic flexible bronchoscopy	Flumazenil (05 μg.kg^{-1}) and naloxone (3 μg.kg^{-1})	Sedation success, intraprocedural opioid consumption, induction time, hypoxia, hypotension	Deep
Kim, 2023	South Korea	April 2022 to 2023	I–III	49/51	66.29 ± 13.53	N/A	< 60 years or > 50 kg, single dose: 5000 μg ≥ 60 years or f < 50 kg, single dose: 3000 μg Rescue: Remimazolam 2500 μg	< 60 years or > 50 kg, single dose: Midazolam 3000 μg ≥ 60 years or < 50 kg, single dose: Midazolam 2000 μg Rescue: Midazolam 500 μg	N/A	Diagnostic or therapeutic flexible bronchoscopy	N/A	Time to complete recovery of consciousness, patient satisfaction, induction time, hypoxia, hypotension, bradycardia	Moderate
Pastis, 2019	USA	N/A	I–III	303/69	62.32 ± 12.46	Remimazolam group: 80.9 ± 20.21 Midazolam group: 83.0 ± 22.10	Initial dose: 5000 μg Top-up dose: 2500 μg	Initial dose: < 60 years Midazolam 1750 μg. > 60 years or debilitated Midazolam 1000 μg top-up dose: < 60 years Midazolam 1000 μg; > 60 years or debilitated Midazolam 500 μg	Initial dose: Fentanyl 25−75 μg Top-up dose: Fentanyl 25−200 μg	Diagnostic or therapeutic flexible bronchoscopy	N/A	Sedation success, respiratory depression, time to complete recovery of consciousness, intraprocedural opioid consumption, hypoxia, hypotension, bradycardia	Moderate

Table 1 *(Continued)*

Study (Author, Year)	Country	Enrollment Period	ASA	Sample Size (Remimazolam/ Control)	Age (years), mean ± SD	Body Weight (kg), mean ± SD	Remimazolam Details	Control Details	Analgesia Protocol	Procedure Details	Benzodiazepine antagonists	Outcomes assessed	Level of Sedation
Chai, 2025	China	March 2023 to April 2024	I–II	30/30	69.95 ± 4.22	Remimazolam group: 60.2 ± 10.0 Propofol group: 61.8 ± 8.9	Initial dose: 200 μg.kg^{-1} Maintenance: 16.7 μg.kg^{-1}.min^{-1}	Initial dose: 2000 μg.kg^{-1} of propofol Maintenance: 66.7 μg.kg^{-1}.min^{-1} of propofol.	0.15 μg.kg^{-1} sufentanil over 30 seconds	Fibreoptic bronchoscopy	N/A	Sedation success, respiratory depression, time to complete recovery of consciousness, patient satisfaction, hypotension, bradycardia	Deep
Luo, 2025	China	April 2024 to June 2024.	II–III	33/33	71.4 ± 3.83	Remimazolam group: 68.6 ± 6.8 Propofol group: 67.9 ± 7.8	Initial dose: 200 μg.kg^{-1} Additional dose: 50 μg.kg^{-1}	Initial dose: 1500 μg.kg^{-1} of propofol Additional dose: 500 μg.kg^{-1} of propofol	10 μg.kg^{-1} of alfentanil over 30 seconds	Flexible fibreoptic bronchoscopy	N/A	Sedation success, time to complete recovery of consciousness, hypoxia, hypotension, bradycardia	Deep
Zhou, 2024	China	April 2021 to September 2022.	I–III	182/182	59.8 ± 9	Remimazolam group: 61.7 ± 11.9 Dexmedetomidine group: 60.3 ± 11.1	Initial dose: 100–200 μg.kg^{-1} Maintenance dose: to 1.7–8.3 μg.kg^{-1}.min^{-1}	Initial dose: 0.4–0.8 μg.kg^{-1} of dexmedetomidine Maintenance dose: 0.0067 –0.0333 μg.kg^{-1}.min^{-1} of dexmedetomidine	0.1 μg.kg^{-1}.min^{-1} of remifentanil and ideally shouldn't be > 0.2 μg.kg^{-1}.min^{-1}	Flexible fibreoptic bronchoscopy	N/A	Time to complete recovery of consciousness, patient satisfaction, intraprocedural opioid consumption, induction time, hypoxia, hypotension, bradycardia	Deep

trials, 252 patients, Fig. 5A). The certainty of evidence was deemed low for induction time outcome.

No significant difference was observed between the Remimazolam and the pooled comparator group in the time to complete recovery of consciousness (MD = -0.67 minutes [95% CI -2.38; 1.04], p = 0.440, I^2 = 98.8%, 10 trials, 1789 patients, Fig. 5B). However, we noted a significant faster recovery with Remimazolam compared to Midazolam (MD = -4.49 minutes [95% CI -7.06; -1.92], p < 0.001, I^2 = 40.9%, 2 trials, 472 patients, Fig. 5B) and Dexmedetomidine (MD = -1.79 minutes [95% CI -2.66; -0.92], p < 0.001, I^2 = 90.7%, 3 trials, 629 patients, Fig. 5B). In contrast, no difference was found with Propofol for this outcome (MD = 1.32 minutes [95% CI -0.53; 3.17] p = 0.161, I^2 = 97.2%, 5 trials, 688 patients, Fig. 5B). The certainty of evidence was deemed low for the time to complete recovery of consciousness outcome.

Furthermore, Remimazolam's incidence of hypoxia was statistically lower when compared with the overall sedatives (RR = 0.60 [95% CI 0.39; 0.93]; p = 0.0227, I^2 = 64.7%, 9 trials, 1631 patients, Fig. 5C). When compared specifically with dexmedetomidine, Remimazolam also presented a significant reduction in hypoxia events (RR = 0.49 [95% CI 0.28; 0.88]; p = 0.0162, I^2 = 60.3%, 3 trials, 629 patients, Fig. 5C). No significant difference was found in the comparison of Remimazolam and Midazolam or Propofol. The certainty of evidence was deemed low for the hypoxia outcome.

Sensitivity analysis

The robustness of the finding regarding hypotension was further evaluated through a leave-one-out sensitivity analysis and a Baujat plot. The pooled RRs ranged from 0.54 to 0.67 (95% CI 0.35 to 1.09). However, statistical significance was not maintained in most analyses, with a loss of significance observed upon exclusion of Zhou et al. (2024), Gao et al. (2023), Zhang et al. (2023), Zhou et al. (2022), Chai et al. (2025), and Luo et al. (2025). Heterogeneity remained relatively stable across exclusions, ranging from 64.8% to 76.4. (Supplemental Fig. 1A) The Baujat analysis revealed Zhou et al. (2024) and Pastis et al. (2019) as the studies with the largest contribution to both heterogeneity and influence on overall result (Supplemental Fig. 2A).

The bradycardia overall pooled analysis demonstrated consistent results across the leave-one-out sensitivity analysis, with RR ranging from 0.33 to 0.54 (95% CIs between 0.16 and 0.95). Notably, the exclusion of Zhou et al. (2024) resulted in a substantial reduction in heterogeneity (I^2 = 0%). However, the omission of any single study did not alter the direction or significance of the pooled effect, reinforcing the robustness of the findings (Supplemental Fig. 1B). The Baujat analysis reinforced Zhou et al. (2024) as the study with the highest contribution to both heterogeneity and influence on the overall result (Supplemental Fig. 2B).

Intraprocedural opioid consumption heterogeneity was not statistically influenced by any single study, with MD ranging from -0.81 to -0.35 milligrams of intravenous morphine (95% CIs between -1.64 and 0.39). Statistical significance favoring Remimazolam was observed only when Zhou et al. (2022) was excluded (MD = -0.81, [95% CI -1.52; -0.10], I^2 = 92.3%). Overall heterogeneity remained high throughout the analysis (I^2 = 78.3% to 96.0%), indicating that no single study disproportionately influenced between-study

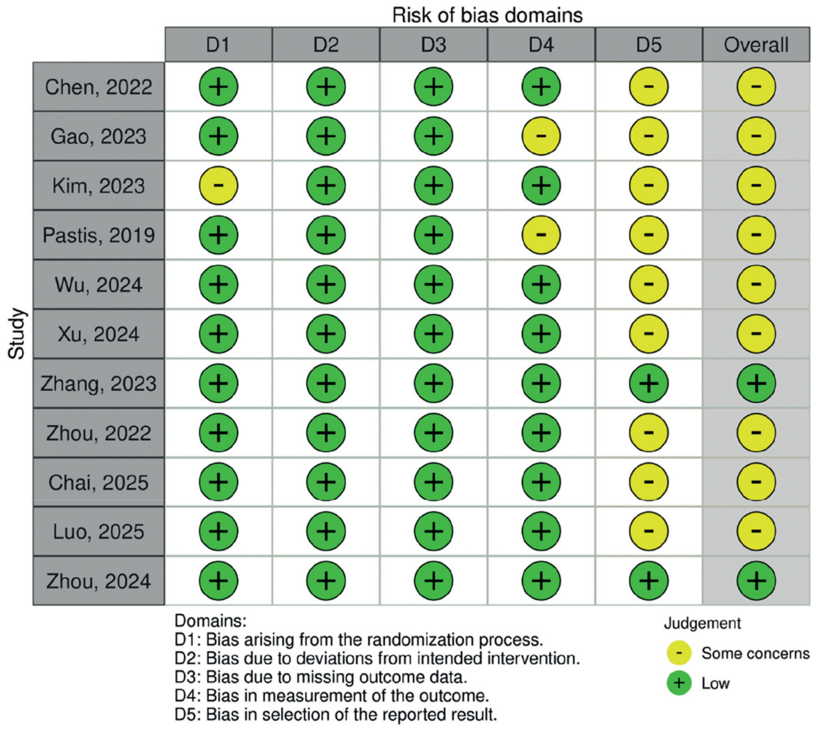

Figure 2 Risk of bias assessment with Cochrane's risk of bias tool for randomized trials.

variability (Supplemental Fig. 1C). However, the Baujat plot revealed Zhang et al. (2023) as the study with the largest contribution to both heterogeneity and influence on the overall result (Supplemental Fig. 2C).

The respiratory depression overall pooled analysis had low heterogeneity (I^2 = 0%), with individual studies' RR ranging from 0.38 to 0.56 (95% CIs between 0.24 and 1.02). Leave-one-out showed that omitting Zhang et al. (2023) led to the loss of statistical significance (RR = 0.56 [95% CI 0.31; 1.02], I^2 = 0%), indicating its substantial contribution to the observed effect. In contrast, removing Pastis et al. (2019) slightly increased heterogeneity (I^2 = 2.5%), but did not affect statistical significance (Supplemental Fig. 1D). As the heterogeneity for this outcome was considerately low, a Baujat plot was not generated in accordance with our predefined methodological strategy.

Patient satisfaction score leave-one-out analysis revealed that removing Zhang et al. (2023) reduced heterogeneity substantially from 46.7% to 0% and led to statistical significance favoring Remimazolam (SMD = 0.22 [95% CI 0.09; 0.36], I^2 = 0%). Overall SMD ranged from 0.11 to 0.22 (95% CIs between -0.09 and 0.37) (Supplemental Fig. 1E). Since the heterogeneity for this outcome was below 50 percent, a Baujat plot was not assessed, consistent with our predefined methodological strategy.

Hypoxia had a RR range from 0.52 to 0.70 (95% CIs between 0.34 and 1.07). Loss of statistical significance occurred when excluding Zhou et al. (2024), Luo et al. (2025), or Gao et al. (2023), indicating these studies contributed meaningfully to the overall significance. Heterogeneity remained relatively stable across exclusions, with I^2 values ranging from 40.0% to 68.9% (Supplemental Fig. 1F). The Baujat plot revealed Zhou et al. (2024) as the study with the largest contribution to both heterogeneity and influence on the overall result (Supplemental Fig. 2D).

For induction time, high heterogeneity persisted regardless of which studies were excluded. Notably, exclusion of Gao et al. (2023) resulted in a statistically significant reduction in induction time favoring the Remimazolam group (MD = -1.09 [95% CI -2.14; -0.03] I^2 = 98.8%) (Supplemental Fig. 1G). The Baujat plot revealed Gao et al. (2023) as the study exerting the greatest influence on the pooled effect, whereas Zhou et al. (2024) accounted for the largest contribution to heterogeneity (Supplemental Fig. 2E).

Leave-one-out sensitivity analysis for sedation success revealed no significant changes in either heterogeneity or effect estimates, with RR range from 1 to 1.22 (95% CIs between 0.90 and 1.60) (Supplemental Fig. 1H). The Baujat plot revealed Zhou et al. (2022) as the study exerting the greatest influence on the pooled effect, whereas Pastis et al. (2019) accounted for the largest contribution to heterogeneity (Supplemental Fig. 2F).

For time to complete recovery of consciousness, high heterogeneity persisted regardless of which studies were excluded, with no impact on the direction or significance of the combined effect, with MD range from -1.18 to -0.21 (95% CIs between -2.77 and 1.40) (Supplemental Fig. 1I). The Baujat plot revealed Zhou et al. (2022) as the study with the largest contribution to both heterogeneity and influence on the overall result (Supplemental Fig. 2G).

Funnel plot analysis and Egger's test were performed for the outcomes of hypotension and time to complete recovery of consciousness, as both included at least 10 studies. The funnel plots demonstrated symmetrical distributions around the pooled effect estimates, and Egger's test did not indicate evidence of publication bias for either outcome (Supplemental Fig. 3).

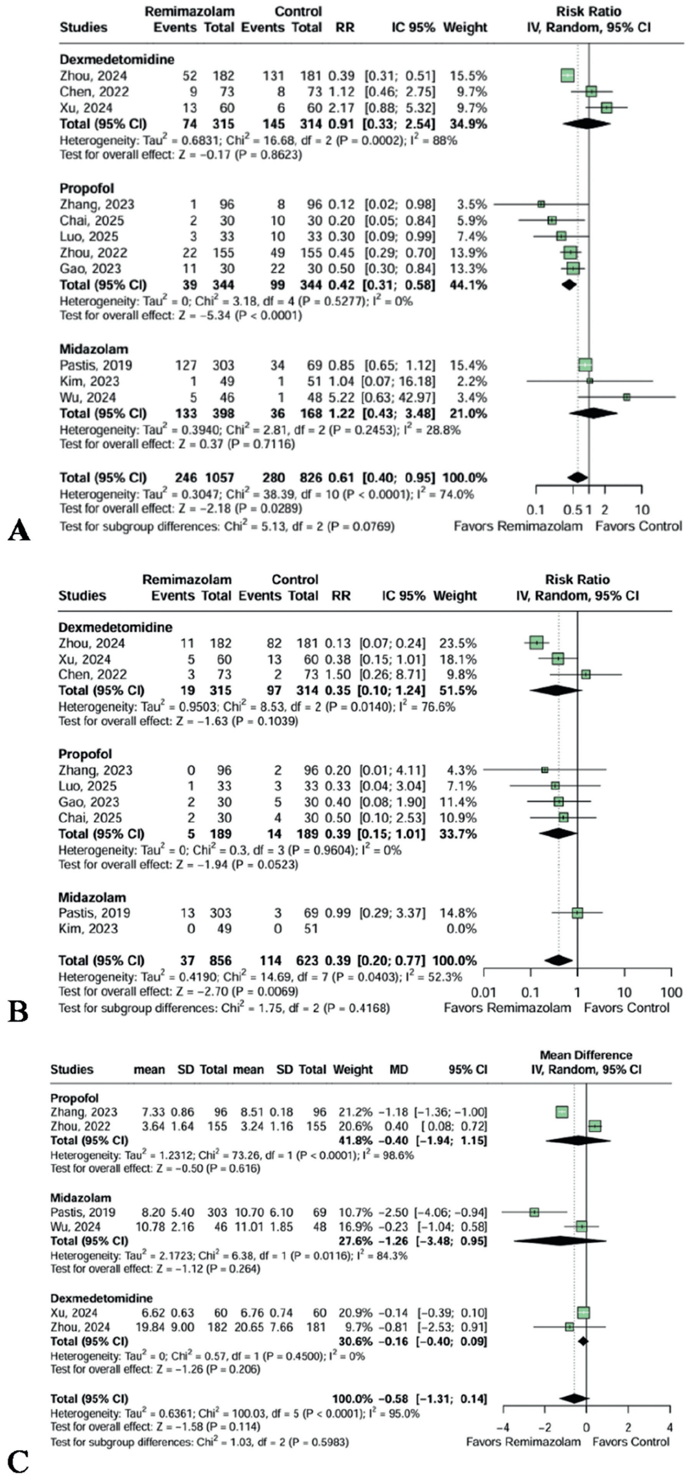

Figure 3 (A) The incidence of hypotension was significantly reduced in the Remimazolam group compared to Propofol and in the overall analysis. (B) The Remimazolam group showed a significant reduction in bradycardia in the overall analysis. (C) Intraprocedural opioid consumption, in milligrams of intravenous morphine, did not present a statistical difference between Remimazolam and studied groups.

Certainty of evidence

According to the GRADE approach, the initial certainty of the evidence was considered high, as all included studies were randomized controlled trials. The certainty was subsequently downgraded based on the assessment of risk of bias, inconsistency, imprecision, and potential publication bias. Respiratory depression incidence, and patient's satisfaction score

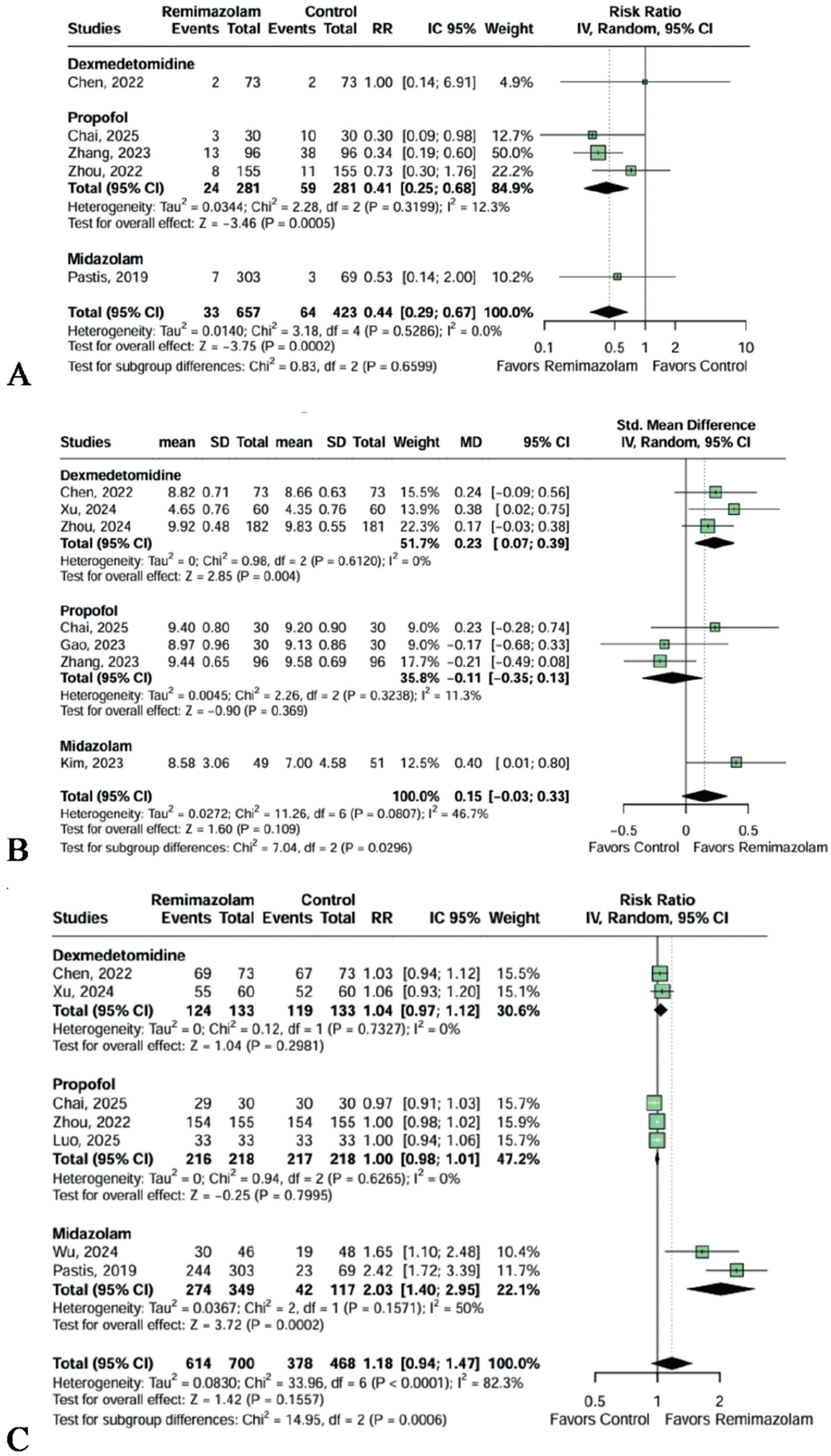

Figure 4 (A) Respiratory depression was statistically decreased in the Remimazolam group compared to the overall analysis and compared to Propofol. (B) The Remimazolam group demonstrated a significantly higher patient satisfaction score, in comparison to Dexmedetomidine. (C) The Remimazolam group presented a statistically higher success of sedation compared to Midazolam.

were judged to have moderate certainty, whereas hypotension, bradycardia, intraprocedural opioid consumption, success of sedation, induction time, time to complete recovery of consciousness, and hypoxia were classified as low certainty. A detailed GRADE assessment and summary of findings are presented in Table 2.

Discussion

In this systematic review and meta-analysis, including 1,884 patients from 11 RCTs, we found that Remimazolam was associated with a significantly lower risk of respiratory depression, hypoxia, hypotension, and bradycardia

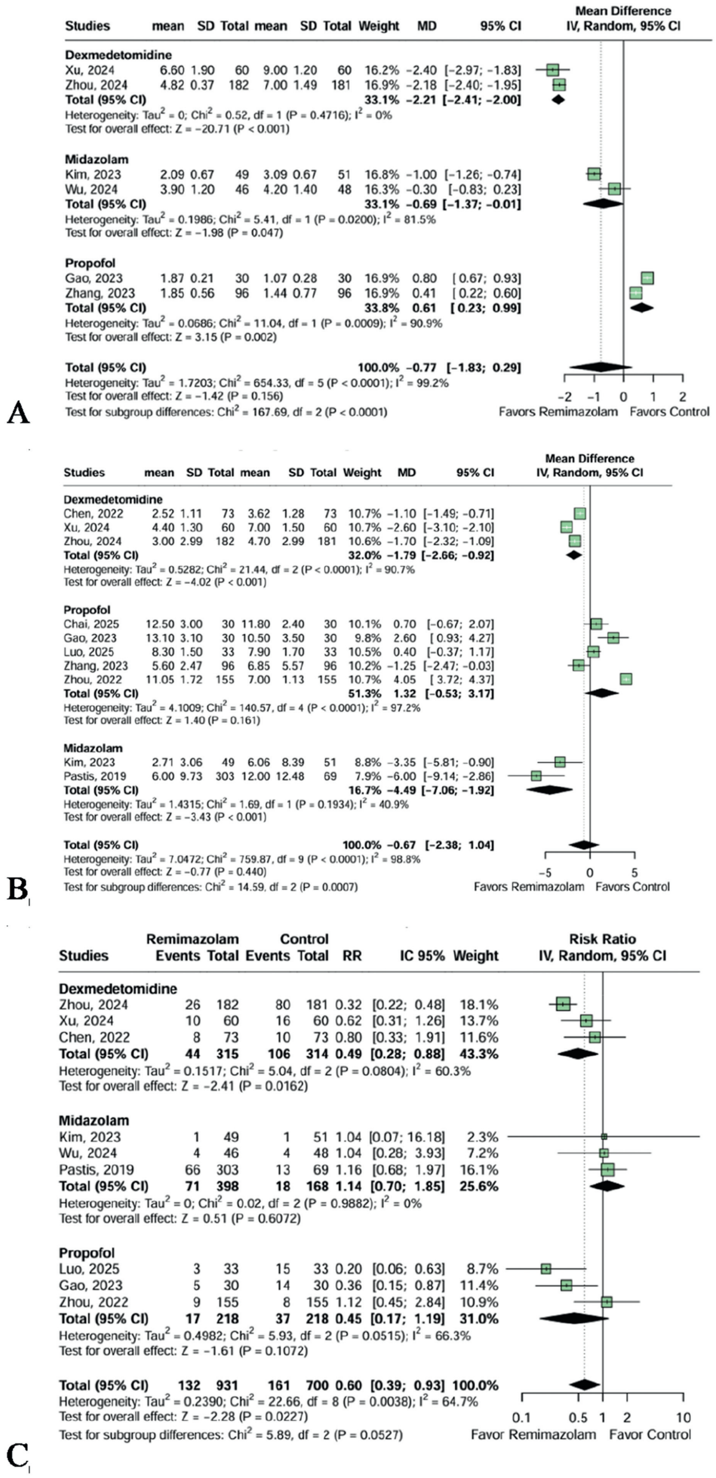

Figure 5 (A) Induction time, in minutes, was significantly reduced in the Remimazolam group compared to Midazolam and Dexmedetomidine. Remimazolam sedation presented a statistically higher induction time compared with Propofol. (B) Time to complete recovery of consciousness, in minutes, was statistically faster in the Remimazolam group, in comparison to Midazolam and Dexmedetomidine. (C) Hypoxia was significantly reduced in the Remimazolam group compared to Dexmedetomidine and in the overall analysis.

compared to commonly used sedatives. Subgroup analyses showed that 1) Compared to Propofol, Remimazolam reduced the incidence of hypotension and respiratory depression, and increased induction time; 2) Compared to Dexmedetomidine, it resulted in higher patient satisfaction, faster recovery of consciousness, and induction time, as well as a statistically lower hypoxia incidence; and 3) Compared to Midazolam, it achieved higher sedation success,

Table 2 GRADE assessment and summary of findings. Author(s): Question: Remimazolam compared to Dexmedetomidine, Midazolam and Propofol for bronchoscpy Setting: Bibliography.

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Intervention]	[Comparison]	Relative (95% CI)	Absolute (95% CI)		
Hypotension												
11	Randomized trials	Serious[a]	Serious	Not serious	Not serious	None	246/1057 (23.3%)	280/826 (33.9%)	**RR 0.61** (0.40 to 0.95)	132 fewer per 1.000 (from 203 fewer to 17 fewer)	⊕⊕○○ Low[a]	Important
Bradycardia												
9	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None	37/856 (4.3%)	114/623 (18.3%)	**RR 0.39** (0.20 to 0.77)	112 fewer per 1.000 (from 146 fewer to 42 fewer)	⊕⊕○○ Low[a,b]	Important
Intraprocedural opioid consumption												
6	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None	842	609	–	MD **0.58 mg of IV morphine equivalent lower** (1.31 lower to 0.14 higher)	⊕⊕○○ Low[a,b]	Important
Respiratory depression												
5	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	33/657 (5.0%)	64/423 (15.1%)	**RR 0.44** (0.29 to 0.67)	85 fewer per 1.000 (from 107 fewer to 50 fewer)	⊕⊕⊕○ Moderate[a]	Important
Patient satisfaction score												
7	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	520	521	–	SMD **0.15 SD higher** (0.03 lower to 0.33 higher)	⊕⊕⊕○ Moderate[a]	Important
Success of sedation												
7	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None	614/700 (87.7%)	378/468 (80.8%)	**RR 1.10** (0.04 to 1.47)	81 more per 1.000 (from 775 fewer to 380 more)	⊕⊕○○ Low[a,b]	Important
Induction time												
6	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None	463	466	–	MD **0.77 minutes lower** (1.83 lower to 0.29 higher)	⊕⊕○○ Low[a,b]	Important
Time to complete recovery of consciouness												
10	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None	1011	778	–	MD **0.67 minutes lower** (2.38 lower to 1.04 higher)	⊕⊕○○ Low[a,b]	Important
Hypoxia												
9	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None	132/931 (14.2%)	161/700 (23.0%)	**RR 0.60** (0.39 to 0.93)	92 fewer per 1.000 (from 140 fewer to 16 fewer)	⊕⊕○○ Low[a,b]	Important

CI, Confidence Interval; MD, Mean Difference; RR, Risk Ratio; SMD, Standardized Mean Difference.
Explanations:
[a] Outcome significantly carried out by studies with “some concerns” risk of bias. Downgraded by one level.
[b] High heterogeneity ($I^2 > 50\%$). Downgraded by one level for inconsistency.

shorter induction time, and faster recovery. No significant differences were observed between groups regarding bradycardia, or intravenous morphine consumption.

The reduced incidence of hypotension and bradycardia associated with Remimazolam, compared to the general sedative group and reduced hypotension compared to Propofol, can be attributed to its selective action on $GABA_A$ receptors while maintaining a negligible effect on sympathetic tone.[38,39] In contrast, Propofol induces a dose-dependent decrease in blood pressure through the suppression of sympathetic activity, resulting in vasodilation and a reduction in peripheral vascular resistance.[40] Furthermore, Remimazolam experiences rapid biotransformation by tissue esterases into a pharmacologically inactive metabolite (CNS 7054) and is characterized by a brief context-sensitive half-life, which reinforces its swift recovery profile in contrast to Midazolam and Dexmedetomidine.[38] The reduction in respiratory depression in the Remimazolam group compared to both the overall, and Propofol groups can be explained by its higher respiratory depression threshold compared to Propofol.[12]

The advantageous pharmacokinetic attributes of Remimazolam likely enhance patient satisfaction, promote a quicker induction, and facilitate a more rapid recovery when compared with Dexmedetomidine, alongside superior sedation outcomes and reduced induction and recovery times when contrasted with Midazolam. Overall, the differences in pharmacodynamics and pharmacokinetics provide insight into the enhanced safety and efficacy of Remimazolam, as indicated in this meta-analysis, especially in clinical contexts where cardiorespiratory stability and procedural efficiency are critical.

Our meta-analysis provides a more comprehensive and robust evaluation of Remimazolam compared to the work by Zhou et al. Our broad search strategy identified 3,696 initial reports, contrasting their 40 initial reports, allowing us to include more than double the number of trials: 11 RCTs comprising 1,884 patients, compared to their 5 RCTs with 1,080 patients. Methodologically, our analysis incorporated a leave-one-out sensitivity analysis and Baujat plots to test the stability of our findings, a step not reported by Zhou et al. Furthermore, we assessed a wider array of clinically relevant outcomes, including induction time, recovery time, and patient satisfaction, which were not addressed in their study. While our findings were largely concordant, with both analyses concluding that Remimazolam is associated with a reduced incidence of hypotension and respiratory depression, as well as a higher success rate than Midazolam, our more powerful analysis also detected a significant reduction in bradycardia, a finding not observed by Zhou et al. Notably, while their analysis suggested a reduction in hypoxia compared to Propofol, our larger analysis did not find this effect to be statistically significant, indicating that our conclusion is likely the more reliable estimate.[37]

Our findings indicate that Remimazolam may serve as an effective, reliable, and safe sedative for flexible bronchoscopy, providing a clearer understanding of the potential trade-offs associated with selecting a sedative. For instance, Propofol acts rapidly; however, it may increase the likelihood of hypotension and respiratory complications. Conversely, Remimazolam appears to exhibit a superior safety profile, evidenced by a substantial reduction in serious events during the procedure, including a 40% decrease in hypotension and hypoxia, as well as a diminished incidence of bradycardia. This safer profile may be particularly beneficial for elderly individuals or those with additional health concerns.

Compared to Midazolam, Remimazolam demonstrated higher success of sedation, faster induction, and shorter recovery times by approximately 4.5 minutes. In clinical practice, where an average of ten FB procedures is performed daily without transbronchial needle aspiration, each session lasts around 19 minutes and costs USD 289.00.[41,42] Our analysis reveals a total inefficiency of 5.18 minutes per procedure, resulting from a 0.69-minute longer induction and 4.49 minutes of delayed recovery compared to Midazolam. This results in a daily cost impact of roughly USD 788.71. We suggest that Remimazolam could serve as a useful alternative, enhancing patient safety and workflow efficiency. Future large-scale RCTs should establish standardized dosing protocols and evaluate performance in vulnerable populations, such as patients with severe cardiopulmonary disease and morbid obesity. Pharmacoeconomic analyses are paramount for determining whether benefits translate into cost savings, and research on long-term cognitive effects is essential for clarifying its role in procedural sedation.

A major limitation was the high heterogeneity in some outcomes, including hypotension and hypoxia, which our sensitivity analysis and Baujat plot revealed was primarily driven by two methodologically distinct trials: Pastis et al. and Zhou et al. (2024) (Supplemental Fig. 2).[32,37] These studies diverge significantly from the other nine trials in our analysis. Pastis et al. stands out as the only study conducted in a US population, using a bolus-only dosing strategy and Midazolam as the comparator, with a primary endpoint of procedural success. Conversely, Zhou et al. (2024) is unique for its use of Dexmedetomidine as the comparator and the ultra-short-acting opioid Remifentanil as a co-analgesic.[37] The remaining nine trials were more homogenous, essentially comparing Remimazolam infusions with Propofol in East Asian populations while using short-acting synthetic opioids like Fentanyl or Alfentanil. This concentration of heterogeneity within two studies with unique protocols suggests that while our overall pooled estimates are valuable, the clinical effects of Remimazolam are significantly affected by the choice of comparator drug, dosing strategy, patient ethnicity, and the specific opioid used.

Another significant limitation stems from the geographic concentration of most included RCTs. Since most of them were conducted in China, the ethnic diversity of the patients is narrow, which raises clear questions about generalizability. This is a notable consideration for Remimazolam, as it is metabolized by tissue Carboxylesterases (CES). Genetic variations in these enzymes are common within the Chinese population, and these polymorphisms can significantly affect how a person responds to a drug, affecting both its efficacy and potential for toxicity.[43,44] Because these genetic profiles differ across the globe, the specific safety and effectiveness we observed might not be the same for patients in North America or Europe.[45] Therefore, validating our findings in trials with more diverse, multi-ethnic populations is a necessary next step to truly understand Remimazolam's global clinical value. Furthermore, in two of the studies included in this analysis, flumazenil was routinely administered at the end of the procedure to reverse sedation.[23,25] This practice was standard protocol rather than a response to adverse events and could potentially have influenced outcomes such as recovery time and patient satisfaction. However, including these studies did not increase heterogeneity or change the overall significance of the pooled results, including those related to recovery time and satisfaction.

Further methodological limitations should also be acknowledged. Data regarding three outcomes, time to recovery of consciousness, induction time, and patient satisfaction, were reported as median and IQR or median and range. Despite applying the validated methods proposed by Luo and Wan, this variability can lead to inaccuracies and imprecision.[28,29] Additionally, the precision of our estimates in certain subgroup analyses was constrained by the limited number of included trials. This scarcity of head-to-head comparisons, combined with the overall clinical heterogeneity, ultimately precluded our ability to perform a meta-regression to investigate the dose-related effects of Remimazolam.

Conclusion

Remimazolam is associated with a significantly lower risk of hypotension, bradycardia, hypoxia, and respiratory depression compared to pooled sedatives. Our findings clarify the clinical trade-offs: it is demonstrably safer than Propofol, while also offering greater sedation success than Midazolam, higher satisfaction, lower hypoxia incidence, shorter induction time and faster recovery than Dexmedetomidine. It presents a reliable balance of safety and efficacy, making it a valuable agent for FB. Nonetheless, these conclusions should be interpreted in light of certain methodological limitations, such as the presence of high heterogeneity in some outcomes, the predominance of single-country data, and the limited number of trials for specific subgroup comparisons. Future trials should focus on standardized dosing, vulnerable populations, and the pharmacoeconomic impact of a broad adoption of Remimazolam.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Abbreviations

ASA, American Society of Anesthesiology; BPM, Beats Per Minute; FB, Flexible Bronchoscopy; $GABA_A$, γ-Aminobutyric Acid A; HR, Heart Rate; IQR, Interquartile Range; MAP, Mean Arterial Pressure; MD, Mean Difference; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROSPERO, Prospective Register of Systematic Reviews; RCT, Randomized Controlled Trial; RR, Risk Ratio; SBP, Systolic Blood Pressure; SD, Standard Deviation; SMD, Standard Mean Difference; USA, United States of America.

Artificial Intelligence (AI) statement

No AI tools were used in this manuscript.

Authors' contributions

Luiz Fábio Silva Ribeiro: Conceptualization; Writing-original draft; Project administration, Lucas Rezende de Freitas: Conceptualization; Methodology; Writing-original draft; Validation; Project administration, Tauãna Terra Cordeiro de Oliveira: Formal analysis; Investigation; Validation, Laiz Gomes Carneiro Novaes: Formal analysis; Investigation; Validation, Rafael Arsky Lombardi: Supervision; Validation; Writing-review & editing.

All authors read and approved the final version of the manuscript.

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Conflicts of interest

The authors certify no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844729.

Editor

Liana Azi

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LETTER TO THE EDITOR

Sex (as recorded) of anesthesia providers and perioperative outcomes: a systematic review and meta-analysis

Dear Editor,

There has been increasing interest in whether clinician sex is associated with patient outcomes in perioperative care. Evidence from surgical fields suggests that provider-level factors, including surgeon sex, may be associated with postoperative outcomes.[1] In contrast, anesthesiology differs from surgery in several structural and clinical aspects that may limit provider-related variability in outcomes. Anesthesia care is commonly delivered within supervised, team-based models and guided by standardized monitoring and protocol-driven practice, which may reduce individual provider-related variability in perioperative outcomes compared with surgical practice.[2,3] Nevertheless, whether anesthesia provider sex is associated with measurable differences in perioperative outcomes remains unclear.

To address this gap, we performed a systematic search of PubMed, Embase, and Scopus from inception to November 2025. A detailed search strategy is available in Table S1. We included studies enrolling adult (≥ 18 years) surgical patients who received any type of anesthesia delivered by female or male anesthesiologists, anesthesiology residents or fellows, or certified registered nurse anesthetists. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[4] (PROSPERO: CRD420251166322). We excluded studies with overlapping populations from the same study centers or cities, retaining the study with the largest population when overlap was identified, and studies that did not compare anesthesia provider sex.

We selected all-cause 30-day mortality as the main outcome because it is a clinically meaningful endpoint commonly reported in perioperative cohorts. Intraoperative hypotension and postoperative renal complications were chosen as additional outcomes because they are commonly reported perioperative quality indicators and were available across the included cohorts.

Effect estimates were extracted from adjusted models and aligned to a common comparator (male vs female anesthesia provider). For the purpose of quantitative synthesis, we attempted to harmonize outcome definitions across studies. Hypotension was considered present when reported as either an episode requiring vasopressor treatment or a mean arterial pressure < 65 mmHg. Postoperative renal complications were defined as any reported impairment in renal function, and mortality as all-cause death within 30 days after surgery. When multiple definitions were available, the outcome most closely matching this definition was extracted. Detailed outcome definitions for each study were provided in Table S2.

Adjusted effect estimates were extracted from multivariable models in each study. The covariate sets differed across studies, typically including combinations of patient characteristics, procedural variables, and provider-related factors. These differences in model specification may affect the comparability of adjusted estimates and should be considered when interpreting pooled results. Detailed adjustment variables for each study are provided in Table S3.

Two authors (TT and BF) independently screened studies and extracted data, while two others (VT and FM) independently assessed risk of bias using ROBINS-I tool (Fig. S1).[5] Statistical analyses were conducted using Review Manager 5.4.1 software (Nordic Cochrane Centre, The Cochrane Collaboration, 2014; Copenhagen, Denmark). Adjusted estimates were log transformed with corresponding standard errors and pooled as Odds Ratios (OR) with 95% Confidence Intervals using a random-effects model ($p < 0.05$).

We included four studies,[6-9] comprising 1,632,086 patients in total, of whom 537,681 (32.9%) received care from female anesthesia providers. Table 1 and Figure S2 present the key characteristics of the included studies and the corresponding study selection process, respectively. Across included studies, anesthesia provider sex was recorded as a binary variable (female vs. male), obtained either from administrative databases or self-reported at credentialing or employment. Gender identity was not collected in the included datasets. These differences in data sources should be considered when interpreting sex-based comparisons across studies.

Anesthesia provider sex was not associated with statistically significant differences in all-cause 30-day mortality (OR = 1.04 [95% CI 0.97–1.11]; $p = 0.32$, $I^2 = 84\%$, n = 1,624,394; Fig. 1A), intraoperative hypotension (OR = 1.02 [95% CI 1.00–1.04]; $p = 0.10$, $I^2 = 52\%$, n = 458,683; Fig. 1B), or postoperative renal complications (OR=1.00 [95% CI 0.98 –1.02]; $p = 0.98$, $I^2 = 0\%$, n = 101,946; Fig. 1C). Sample sizes

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Table 1 Baseline characteristics of the included studies.

Author, year	Country	Female / Male providers (%)	Patients cared by a female / male provider (n)	ASA status	Type of anesthesia provider	Anesthesia provider sex	Type of surgery	Duration of surgery [min] Mean ± SD
Chui, 2025	Canada	NA	1,275 / 6,417	I = 131 II = 1,377 III = 4,563 IV = 1,593 ND = 20	Attending anesthesiologist; Trainee (resident, fellow); Neuroanesthesia fellowship-trained anesthesiologist; Canadian-certified anesthesiologist	Sex was recorded as a binary variable and was extracted from the institutional administrative database, although authors use the term gender in the supplementary material.	Instrumentation and fusion; Lumbar discectomy and/or laminectomy; Spinal tumor; Kyphosis or scoliosis correction	145.0 ± 90.0
Jerath, 2024	Canada	31.5% / 68.5%	311,822 / 853,889	NA	Attending anesthesiologist (specialty-trained physician); Trainee (resident, fellow)	Anesthesia provider sex was self-reported at the time of credentialing and obtained from the Corporate Provider Database. Sex was recorded as a binary variable (female vs. male), while provider gender was not collected.	Cardiovascular; General Surgery; Neurosurgery; Obstetrics and gynecology; Otolaryngology; Orthopedic; Plastic; Thoracic; Urology; Vascular	Female 124.9 ± 99.6 Male 122.4 ± 105.8
von Wedel, 2024	USA	43.2% / 56.8%	185,170 / 179,259	I = 46,135 II = 179,632 III = 117,887	Trainee (resident, fellow); CRNA; Attending anesthesiologist	Anesthesia provider sex was self-reported upon employment and obtained from the employee database. Sex was recorded as a binary variable (female vs. male), while the provider's gender was not collected.	Cardiac surgery; Cardiology; Colorectal; Ear, nose, throat Gastrointestinal; General surgery; Gynecology and obstetrics Neurosurgery; Ophthalmology; Orthopedic surgery; Plastic surgery; Podiatry; Surgical oncology; Thoracic; Trauma; Transplant; Urology; Vascular	Female 113.7 ± 85.2 Male 126.6 ± 80.8

Table 1 *(Continued)*

Author, year	Country	Female / Male providers (%)	Patients cared by a female / male provider (n)	ASA status	Type of anesthesia provider	Anesthesia provider sex	Type of surgery	Duration of surgery [min] Mean ± SD
IV = 20,775								
Zeiner, 2024	Austria	41.8% / 58.2%	39,414 / 54,840	I = 24,732 II = 36,779 III = 27,676 IV = 4,338 V = 725	Anesthesiologists (physicians)	Anesthesia provider sex was self-reported biological sex, extracted from institutional provider databases. Sex was recorded as a binary variable (female vs. male), and provider gender was not collected.	Cardiothoracic; Dermatological; Ear, nose and throat; General surgery; Gynecology; Maxillofacial; Neurosurgery; Non-operating-room anesthesia; Obstetric; Orthopedic; Robotic; Trauma; Urology; Vascular	Female 138.0 ± 102.0 Male 144.0 ± 102.0

ASA, American Society of Anesthesiologists; CRNA, Certified Registered Nurse Anesthetist; NA, Not Available; ND, Not Documented/unclear.

differed across outcomes because not all studies contributed data to each synthesis. For all-cause 30-day mortality, Chui et al.[6] was excluded due to likely population overlap with Jerath et al.,[7] and the larger cohort (Jerath et al.) was retained. The overall risk of bias was moderate (Fig. S1), mainly due to residual confounding inherent to the observational design.

Few studies have examined provider sex in anesthesia, and this meta-analysis did not demonstrate statistically significant differences in all-cause 30-day mortality, intraoperative hypotension, or postoperative renal complications based on anesthesia provider sex. To our knowledge, this is the first meta-analysis assessing whether anesthesia provider sex is associated with perioperative outcomes, a question of increasing relevance amid ongoing scrutiny of gender equity in perioperative care. Women remain underrepresented in perioperative roles and continue to face disparities in income, leadership opportunities, and career advancement.[10] Understanding whether such structural inequities translate into differences in clinical practice or patient outcomes carries both scientific and policy relevance.

In contrast to evidence from surgery, where a recent meta-analysis reported lower postoperative mortality among patients treated by female surgeons[1] we found no statistically significant differences in all-cause 30-day mortality, intraoperative hypotension, or postoperative renal complications based on anesthesia provider sex. Differences in surgical and anesthetic practice structures may partly explain these discrepant findings. The team-based organization of anesthesia care may attenuate individual provider effects on outcomes, as prior evidence shows similar perioperative outcomes across anesthesia care team models.[3]

Despite the high degree of standardization of anesthetic protocols, substantial heterogeneity was observed across most analyses, particularly for mortality (Fig. 1A) and intraoperative hypotension (Fig. 1B), limiting the interpretability of a single pooled estimate and highlighting the need to move beyond average effects. This heterogeneity should also be interpreted considering differences in covariate adjustment across studies. Because only four studies were included, subgroup analyses or meta-regression were not performed. As these outcomes are associated with multiple patient-, procedure-, and system-level factors, a precise pooled average may obscure clinically relevant, context-specific variations related to case-mix, institutional practices, and residual confounding. Additionally, international differences in the organization of anesthesia care, such as varying levels of autonomy among trainees, could have contributed to the heterogeneity observed across studies. In contrast, no statistical heterogeneity was observed for postoperative renal complications (Fig. 1C), which may reflect more consistent outcome definitions and protocol-driven kidney protection strategies; however, this finding should be interpreted cautiously given the limited number of contributing studies.

Although the included studies classified providers by sex, gender inequities represent broader structural and social dynamics, which are not captured by binary sex variables. The absence of measurable differences in clinical outcomes does not indicate that gender inequities in anesthesiology are inconsequential. Persistent gaps in representation, remuneration, and career progression remain well documented.[10] Our

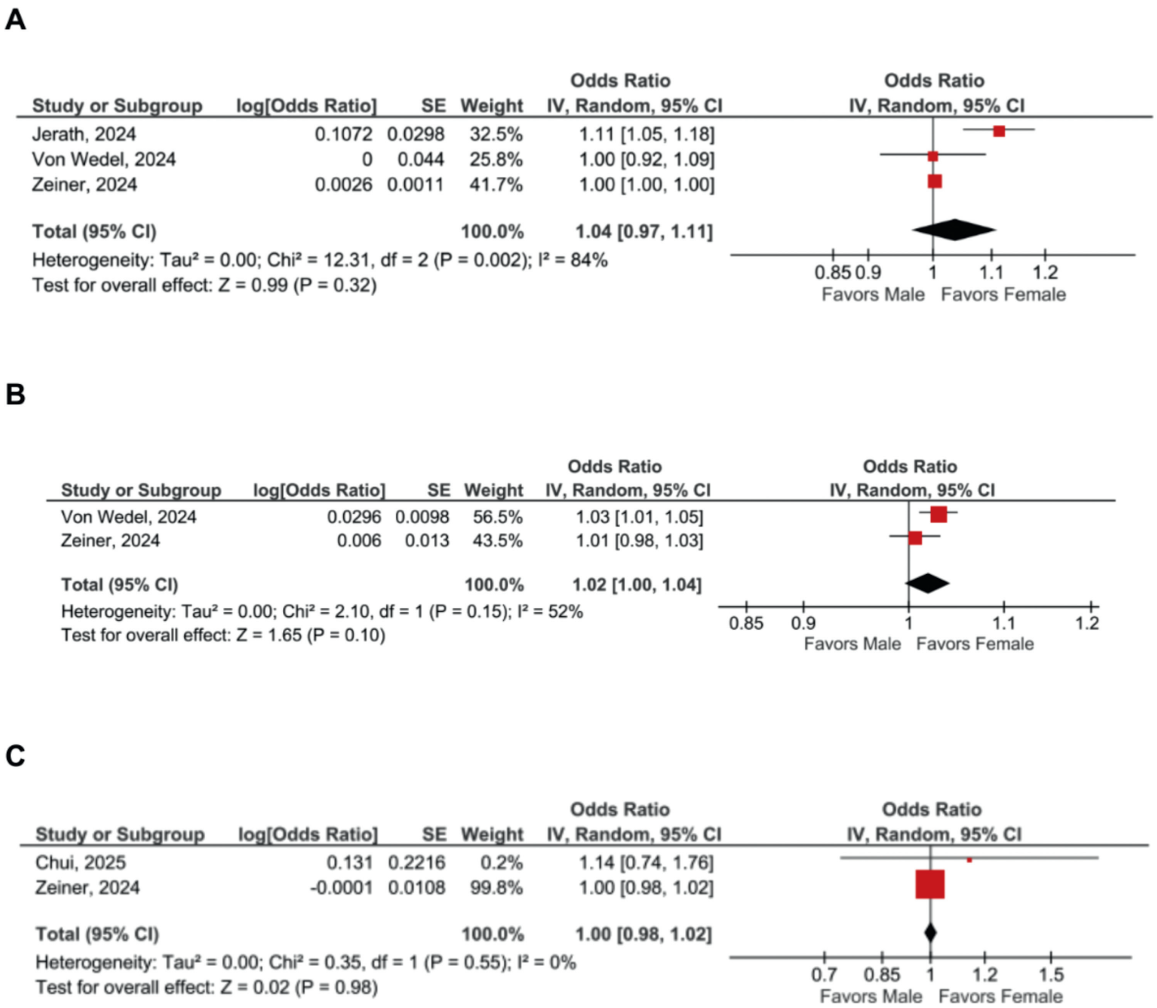

Figure 1 Forest plots of the effect of anesthesia provider sex on (A) All-cause 30-day mortality, (B) Intraoperative hypotension, and (C) Postoperative renal complications. The plot displays odds ratios with 95% Confidence Intervals for each included study and the pooled random-effects estimate. CI, Confidence Interval; SE, Standard Error.

findings suggest these disparities are unlikely to reflect differences in clinical performance, highlighting the need to address structural, cultural, and institutional factors within the specialty.

Our analysis offers an important first step toward understanding the interface between provider sex dynamics and perioperative care quality. As interest in the association between clinician sex and patient outcomes continues to grow, better-designed, adequately powered studies will be essential to refine these estimates and explore potential sex- or gender-related differences in more nuanced domains of anesthetic care.

This meta-analysis has several limitations. First, the evidence base comprised only four observational studies, limiting the robustness of pooled estimates and increasing the risk of publication bias. In the absence of randomized trials, residual confounding remains likely despite adjustment for patient-, provider-, and procedure-level variables. Second, we assessed a binary sex variable that does not capture the complexity of gender identity or gendered experiences, which reflect broader structural and social dynamics and may be associated with differences in communication, decision-making, and team interactions. Third, substantial heterogeneity across studies may reflect differences in healthcare systems, provider qualifications, and perioperative workflows, limiting generalizability. Finally, variations in outcome definitions and measurement methods may have contributed to between-study variability in pooled estimates.

Our findings suggest that within highly protocol-driven anesthesia practice, provider sex does not appear to be associated with clinically meaningful differences in short-term perioperative outcomes at the population level. Future studies with more comprehensive demographic data, broader clinical settings, and more nuanced outcomes will be essential to clarify whether sex and gender are associated with differences in the delivery of perioperative care.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

All authors (1) Read and approved the final version, (2) Met the ICMJE criteria for authorship, (3) Believe the paper represents honest work, and (4) Are able to verify the validity of the results reported.

Disclosures

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Authors' contributions

Conception and design of the study: TT, SA, SS.

Data acquisition and analysis: TT, VT, BF, FM.

Data interpretation: All authors.

Drafting the manuscript or revising it critically for important intellectual content: All authors.

Final approval of the version to be submitted: All authors.

Agreement to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved: All authors.

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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.2026.844745.

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LETTER TO THE EDITOR

Preoperative anxiety in children: bridging the gap between perception and observation

Dear Editor Liana Azi,

Preoperative anxiety is a frequent and clinically relevant emotional response, particularly among pediatric patients and their caregivers.[1] Despite its high prevalence, preoperative anxiety often goes unnoticed or is inadequately quantified in clinical practice. Observable behavioral signs and subjective perceptions do not always align, leading to an underestimation of children's emotional distress before surgery. Understanding this mismatch between what is seen and what is felt – between *observation* and *perception* – is crucial for improving perioperative care.

A cross-sectional study was carried out from August 2022 to October 2023 in the pediatric surgical ward of a tertiary university hospital in São Paulo, Brazil. The study included 50 children aged 4–17 years undergoing elective surgery. Anxiety was evaluated using two validated instruments: the Modified Yale Preoperative Anxiety Scale (mYPAS),[2] to assess behavioral manifestations, and the Visual Analogue Scale (VAS),[3,4] which captures the subjective perception of anxiety reported by children aged ≥ 7 years. Data collection was carried out through convenience sampling by the same researcher in the inpatient unit on the day preceding surgery, in the presence of caregivers, and prior to the administration of any anxiolytic medication.

A total of 50 patients were interviewed, of whom 32/50 (64%) were male. No eligible patient declined to participate in the study. Among the patients, 28/50 (56%) had undergone at least one previous surgical procedure. Over 45/50 (90%) of patients reported no history of previous surgical or anesthetic complications. ROC analysis was used to assess the ability of patient-reported VAS to discriminate high anxiety defined by mYPAS ≥ 30. The analysis included 36 children aged ≥ 7 years with complete data. AUC and its 95% Confidence Interval were calculated using the DeLong method, and the optimal cut-off was identified using the Youden index.

Regarding preoperative anxiety assessed by the VAS in 36 patients, 8/36 (22%; 95% CI 11%–38%) reported the maximum score (10/10), representing the extreme upper bound of the scale. Overall, VAS scores showed a median of 5.0 (IQR 2.75–9.0), with a mean of 5.3 (SD = 3.5), indicating moderate anxiety levels in the cohort.

According to mYPAS assessed in 50 patients, the lowest score recorded was 23.4, observed in 12 patients, while the highest score was 83.4, observed in 1 patient. Using the established cut-off score of 30 to indicate anxiety, 29/50 (58%; 95% CI 43%–72%) patients were classified as anxious. In 36 children, patient-reported VAS showed limited discriminative performance, with an AUC of 0.51 (95% CI 0.32–0.71). The optimal cut-off identified by the Youden index was VAS = 6, yielding a sensitivity of 47% and a specificity of 59% (Fig. 1). Given the AUC close to 0.5 and the wide confidence interval, the ROC results indicate no evidence of meaningful discrimination between VAS and mYPAS in this small sample and should be interpreted as exploratory.

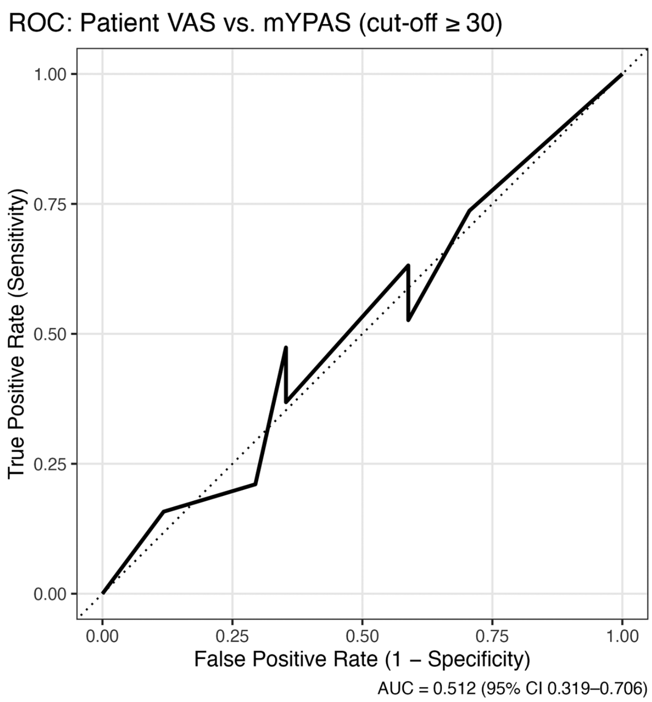

Figure 1 The discriminative validity of the patient's self-reported anxiety (VAS 0–10) was tested using ROC analysis against the mYPAS cut-off (≥ 30). The area under the curve (AUC = 0.512; 95% CI 0.319–0.706) indicated no discriminative ability, suggesting that the self-perceived anxiety level did not correspond to the observational anxiety classification obtained with the mYPAS.

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The main limitations of this study include the use of convenience sampling, the relatively small sample size, the heterogeneity of surgical procedures, and age-related limitations in the application of the VAS. The VAS lacks clearly defined anxiety cutoff points, and children's responses may be influenced by parental presence and individual personality traits.

In conclusion, preoperative anxiety in pediatric surgical patients remains highly prevalent and multifaceted. In this exploratory study, discrepancies were identified between perceived and observed anxiety, indicating that neither instrument alone fully captures the construct.

Conflicts of interest

The authors declare no conflicts of interest.

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Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI assistance disclosure

AI-based language model was used exclusively to assist with language editing and clarity

Authors' contributions

Barbara Monique Calsolari Oliveira: Data collection or management; data analysis; manuscript writing/editing.

Daniela Cristina Ikeda: Data analysis; manuscript writing/editing.

Paulo Cesar Kock Nogueira: Data analysis; manuscript writing/editing.

Mila Torii Corrêa Leite: Protocol/project development; data collection or management; data analysis; manuscript writing/editing.

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LETTER TO THE EDITOR

Patient-centered outcomes and interaction effects in a factorial trial of pneumoperitoneum pressure and neuromuscular blockade depth

Dear Editor,

We read with great interest the randomized, double-blind factorial study by Meletti et al., recently published in Brazilian Journal of Anesthesiology, examining the combined influence of pneumoperitoneum pressure and neuromuscular blockade depth on postoperative recovery after laparoscopic cholecystectomy.[1] By deliberately placing postoperative quality of recovery at the center of their analysis through the use of the validated Quality of Recovery (QoR)-40 questionnaire, the authors move beyond a purely technical intraoperative focus toward outcomes that are directly meaningful to patients. This perspective is particularly relevant in contemporary perioperative practice. At the same time, several methodological and interpretative aspects deserve closer examination, as they may influence how the reported neutral findings should be understood.

In trials using a factorial design, interpretation relies heavily on whether potential interactions between interventions are formally evaluated. In the present study, pneumoperitoneum pressure and neuromuscular blockade depth are intentionally combined within a 2 × 2 framework; however, the results are primarily presented as group-wise comparisons, without explicit assessment of a pressure-neuromuscular blockade interaction. This aspect of the study design is methodologically relevant. Several observations suggest that the effect of neuromuscular blockade depth may vary according to pneumoperitoneum pressure rather than acting uniformly across conditions. Notably, deep neuromuscular blockade under standard pneumoperitoneum pressure was associated with improved surgical field conditions but also with longer post-anesthesia care unit stay, higher resting pain scores at 24 hours, and increased use of rescue antiemetics. In the absence of formal interaction testing, it is difficult to determine whether these findings reflect independent effects, context-dependent interactions, or random variation. Specifically, the published report does not present an interaction term, a p-value for interaction, or model-based factorial estimates assessing whether the effect of neuromuscular blockade depth differs across pneumoperitoneum pressure levels. Outcomes are instead reported as group-wise comparisons across the four study arms. When factorial designs are used to evaluate combined intraoperative strategies, failure to explore interaction effects may weaken conclusions regarding the absence of benefit. At a minimum, reporting a pressure × neuromuscular blockade interaction term with its corresponding p-interaction, or providing model-based estimates stratified by pressure level, would allow readers to distinguish between independent and context-dependent effects.

The contrast between surgeon-rated and patient-reported outcomes is particularly striking. The improvement in surgical field quality observed with deep neuromuscular blockade is consistent with prior randomized trials and meta-analyses demonstrating superior laparoscopic working conditions under deep blockade compared with moderate blockade.[2] Current European guidelines similarly endorse the use of deep neuromuscular blockade to optimize surgical exposure when visualization is limited.[3] However, the present findings also illustrate that technical optimization does not automatically translate into improved patient experience. Despite better intraoperative conditions, patients receiving deep neuromuscular blockade under standard pneumoperitoneum pressure experienced less favorable postoperative outcomes. In procedures such as laparoscopic cholecystectomy, where hospital stay is short and recovery expectations are high, even modest increases in pain, nausea, or recovery time may influence patient satisfaction and the perceived value of care. These observations therefore merit consideration rather than being readily dismissed as clinically insignificant. These secondary outcome differences should be interpreted as hypothesis-generating, particularly in the context of multiple comparisons and the absence of adjustment for multiplicity.

Interpretation of the neutral QoR-40 results also deserves a more nuanced approach. The study was powered to detect a 10-point difference in QoR-40 scores, whereas the most widely accepted evidence-based estimate for the minimum clinically important difference of this instrument remains approximately 6.3 points, derived using anchor- and distribution-based

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methods in perioperative populations.[4] Although this approach was established prior to 2020, it continues to be widely used as a benchmark for interpreting clinical relevance in QoR-40 — based studies and has not undergone major revision in subsequent validation work. It should be acknowledged that estimates of the minimum clinically important difference may vary according to surgical setting, patient population, and timing of assessment. More recent research on postoperative recovery has increasingly focused on abbreviated instruments such as the QoR-15, largely because of their psychometric strength and feasibility in contemporary cohorts.[5] This shift in the literature highlights a key methodological issue: powering a study to detect an effect size substantially larger than the accepted clinically meaningful threshold increases the likelihood of concluding equivalence when smaller, yet patient-relevant, differences in global recovery may exist. From this perspective, the absence of statistically significant differences in QoR-40 scores should be viewed as evidence against a large early effect, rather than as definitive proof that pneumoperitoneum pressure or neuromuscular blockade depth has no meaningful influence on postoperative recovery.

In the published trial, eight of 132 randomized patients (approximately 6%) were excluded after randomization, with analyses conducted per protocol. While modest in magnitude, such post-randomization loss may still influence the interpretation of patient-reported outcomes, particularly when intention-to-treat analyses are not applied. Beyond these design considerations, the role of pharmacological reversal also warrants attention. In this trial, the deep Neuromuscular Block (NMB) group received 4 $mg{\cdot}kg^{-1}$ sugammadex, whereas the moderate NMB group was reversed with neostigmine and atropine. Given the faster and more predictable recovery profile of sugammadex, as well as its distinct side-effect profile compared with acetylcholinesterase inhibitors, differences in post-anesthesia care unit stay and postoperative symptoms such as nausea and resting pain may be confounded by the choice of reversal agent rather than reflecting the isolated effect of neuromuscular blockade depth.

Overall, the trial by Meletti et al. offers important insight into the complex relationship between pneumoperitoneum pressure, neuromuscular blockade depth, and early postoperative recovery. Nevertheless, careful interpretation of its neutral results requires attention to factorial design principles, clinically meaningful effect thresholds, and the potential trade-offs between technical optimization and patient-centered outcomes. Moving forward, intraoperative management strategies must be evaluated not just by technical success, but by their ability to harmonize surgical optimization with the quality of the patient's early functional recovery.

Institutional Review Board (IRB) approval

Not applicable.

This correspondence does not report original patient data and is based on the critical appraisal of a previously published study.

Study registration

Not applicable.

No new clinical study was conducted as part of this correspondence.

Authors' contributions

Conceptualization: Eylem Yasar, Melike Korkmaz Toker.

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Final approval of the manuscript: All authors.

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Declaration of competing interest

The authors declare no conflicts of interest.

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