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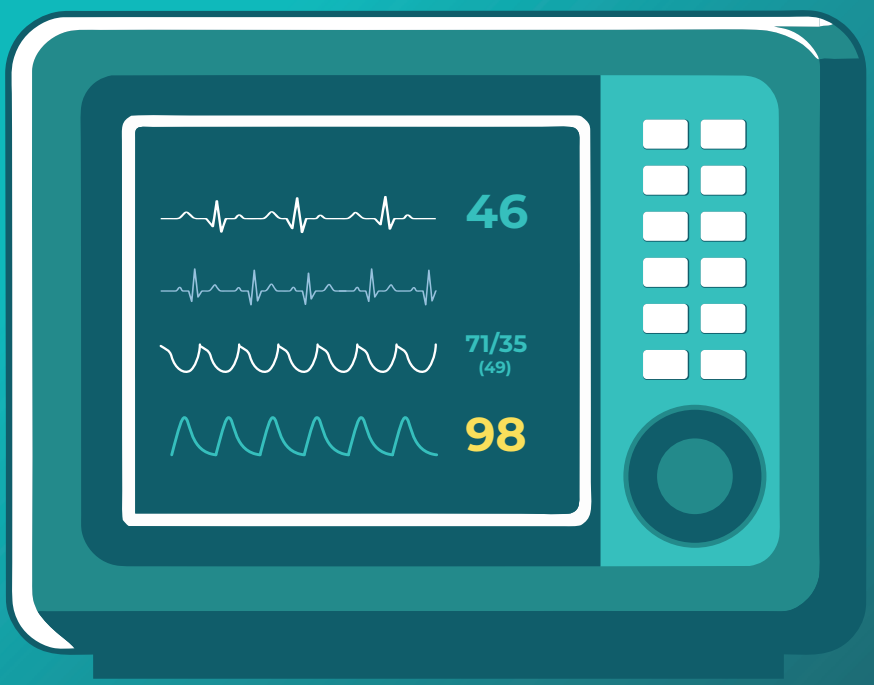
Intraoperative hypotension and organ protection



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EDITORIAL

The hidden cost of hypotension: redefining hemodynamic management to improve patient outcomes



Traditionally, the approach to hemodynamic stability during anesthesia has focused on maintaining an appropriate depth of anesthesia and avoiding extreme fluctuations in blood pressure (BP). Significant but brief BP changes are often managed with rapid administration of vasopressors or vasodilators, without fully considering their impact on patient safety and outcomes. However, growing evidence suggests that even short episodes of intraoperative hypotension, lasting only a few minutes, can negatively affect clinical outcomes.[1–5]

Is this surprising? Suppose a healthy individual suddenly experiences a systolic BP of around 70 mmHg. In that case, he/she will likely seek a place to sit down and wait for symptoms such as dizziness, nausea, or vertigo to subside. The older the person, the more pronounced these symptoms are likely to be. Under anesthesia, patients are unable to express discomfort or alert the surgical team about the feelings of hypotension. Therefore, anesthesiologists should maintain rigorous, continuous BP monitoring and proactively prevent and manage hypotension to ensure patient safety.

Recent European Society of Cardiology guidelines[6] for managing elevated BP and hypertension recognize and address the adverse effects of perioperative hypotension and recommend avoiding large perioperative fluctuations in BP. They also suggest using preoperative ambulatory BP as a baseline. However, implementing these recommendations is challenging.

Perioperative hypotension is influenced by factors such as patient health, anesthesia, and surgery type, with higher risks linked to advanced age, low preoperative BP, and use of antihypertensives. Causes of intraoperative hypotension include depth of anesthesia, vasodilation, and blood loss, while postoperative hypotension may occur due to ischemia, hypovolemia, infections, or other complications.[7]

The primary adverse outcomes associated with intraoperative hypotension are acute kidney injury (AKI), myocardial injury after noncardiac surgery (MINS), delirium, stroke, hospital readmissions, and increased mortality in both cardiac and noncardiac procedures, among others.[8–16] These conditions often lead to further complications, such as the progression to chronic kidney disease in cases of AKI, which can affect life expectancy.[17]

To date, there is no clear definition of perioperative hypotension. Still, most studies define it as a decrease of more than 10% to 20% from baseline values, a systolic pressure < 90 mmHg, or a MAP < 60 mmHg.[18,19] Additionally, the number and duration of hypotensive episodes should be considered. Salmasi et al.[16] found that more than 13 cumulative minutes with MAP < 65 mmHg increased the risk of MINS and AKI, with half of the study patients experiencing episodic drops below this threshold.

In a large retrospective cohort study of 166,091 operations, Schnetz et al.[20] developed a risk model to evaluate intraoperative hypotension by analyzing over 7.3 million intraoperative MAP measurements. They observed that the risk of intraoperative hypotension, defined as MAP < 65 mmHg, increased exponentially as MAP approached this threshold. For instance, MAP values of 70 mmHg were associated with a fourfold higher risk of intraoperative hypotension episodes than 80 mmHg despite both values being within reference ranges. These findings highlight the need for increased vigilance, especially in patients with elevated preoperative risk factors, even when MAP levels are within traditional reference ranges.

Wesselink et al.[21] conducted a systematic review of 42 studies analyzing different MAP thresholds and their impact on outcomes to assess the association between intraoperative hypotension and adverse postoperative outcomes in noncardiac operations. They found that brief exposures to MAP < 70 mmHg slightly increased the risk of organ injury, while prolonged exposures (10 minutes or more) to MAP < 80 mmHg further increased this risk. When MAP remained between 60 and 65 mmHg for 5 minutes or more, the risk of AKI and MINS became significant, and any exposure to

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MAP < 50 and 55 mmHg was associated with a higher risk of stroke and delirium.

Marcucci et al.[22] conducted a randomized study (PeriOperative ISquemic Evaluation (POISE)-3) involving 7,490 patients on long-term antihypertensive therapy undergoing noncardiac surgery. They compared strategies aimed at avoiding hypotension (target MAP ≥ 80 mmHg) vs hypertension (target MAP ≥ 60 mmHg). Both groups showed similar rates of vascular complications, indicating that maintaining a higher MAP target did not reduce complications. However, the hypotension-avoidance group had a lower incidence of clinically significant intraoperative hypotension episodes. Although the groups had significantly different cumulative durations of hypotension (< 60 mmHg), a post-hoc analysis confirmed that the differences in vascular outcomes between the groups were not statistically significant.[23]

Several studies have reported a high incidence of intraoperative hypotension episodes, with rates ranging from around 20% to 30% in cohorts of thousands of patients primarily undergoing noncardiac operations.[3,24–26] Thus, it is clear that maintaining BP levels above intraoperative hypotension thresholds is challenging. Although the oscillometric method is considered the standard for intraoperative BP measurement, it has significant limitations, such as the possibility of “blind spots” between measurements. One potential solution is continuous, noninvasive BP monitoring using pulse wave analysis with finger-cuff technologies.[27] Although studies show mixed results regarding the correlation between finger-cuff measurements and invasive BP readings,[28–32] finger-cuff technologies could eliminate “blind spots” in MAP measurements and provide relevant hemodynamic information to support goal-directed hemodynamic therapy (GDHT). By providing metrics such as stroke volume, stroke volume variation, cardiac output, and vascular resistance, they could help identify the underlying causes of intraoperative hypotension and guide targeted interventions.[33,34] Unfortunately, widespread adoption of this technology is limited by high costs and scientific validation challenges.

Although the current literature compares GDHT with several postoperative outcomes, evidence linking it directly to a reduction in intraoperative hypotension episodes is sparse.[33,35,36] Alternatively, emerging monitoring modalities based on artificial intelligence (AI) and machine learning show potential when integrated with GDHT.[37] One notable example is the Hypotension Prediction Index (HPI), which calculates the probability of an imminent hypotensive event on a scale from 0 to 100. The HPI identifies patterns suggesting a decrease in BP and indicates the underlying causes, allowing precise, targeted interventions. It can be used with both invasive and noninvasive BP monitoring, although its algorithm remains a topic of debate.[30,38–40]

In general, trials involving HPI have shown an effective reduction in the duration of intraoperative hypotension, but they are not yet sufficiently powered to assess complex outcomes, such as major morbidity and mortality.[41] A small observational study[42] demonstrated that the areas under the receiver operating characteristic curve for the HPI (0.89) and concurrent MAP (0.88) were nearly identical in predicting hypotension within 5 minutes. This finding suggests that adjusting MAP alarm thresholds to 72 or 73 mmHg could serve as an alternative to using the HPI. However, research on these technologies faces significant challenges, including a lack of standardized interventions and outcomes. Variations in protocol adherence, especially in multicenter studies, complicate the ability to draw unbiased and consistent conclusions.

Recent evidence supports the use of cerebral monitoring during anesthesia to guide hemodynamic optimization.[43,44] Since the seminal studies on the "triple low" condition, characterized by the concurrent presence of a low bispectral index (< 45), low MAP (< 75 mmHg), and low minimum alveolar concentration (MAC) (< 0.8), and its association with adverse outcomes such as increased mortality, there has been growing recognition of the importance of effectively managing both the depth of anesthesia and hemodynamic disturbances to normalize altered brain wave patterns.[45,46] In many patients, the lower limit of the cerebral blood flow autoregulation curve shifts to the right, a phenomenon that can be identified through cerebral monitoring during anesthesia.[47] This shift is especially relevant when burst suppression (BS) on processed electroencephalography (pEEG) or desaturation on cerebral oximetry is detected, as these abnormalities frequently resolve with MAP increases in both cardiac and noncardiac operations.[48,49]

For instance, a study by Georgii et al.[50] demonstrated that pEEG-guided interventions during anesthesia, which involve adjusting MAP and anesthetic concentrations, significantly reduced the duration and intensity of BS in older patients. In 55% of cases, correcting MAP alone was sufficient to resolve BS episodes, suggesting that hypotension may be an underlying cause. Similarly, Thomsen et al.[51] conducted a study in which patients undergoing vascular surgery were randomized to receive either pEEG-guided general anesthesia or standard anesthesia. Norepinephrine was administered to maintain MAP > 65 mmHg to prevent intraoperative hypotension. The results showed that the pEEG-guided group required about one-third less norepinephrine, likely due to lighter anesthesia reducing the hypotension typically induced by anesthetic agents. Although still showing inconsistent outcome results, intraoperative brain monitoring can help guide hypotension treatment.[52–54] Payne et al.[52] conducted a systematic review and meta-analysis of randomized controlled trials and found that depth-of-anesthesia monitoring may reduce postoperative mortality, although further research is needed to confirm these findings.

Attention should also be given to the entire perioperative period, extending vigilant BP management to the postoperative period. Smischney et al.,[55] in a multicenter retrospective study, analyzed data from 3,185 noncardiac surgery patients who did not experience intraoperative hypotension (defined as MAP ≤ 65 mmHg) and were discharged from the intensive care unit after 48 hours. They found that postoperative hypotension (MAP ≤ 65 mmHg and ≤ 55 mmHg) was associated with an increased risk of critical adverse events within 30 and 90 days. MAP ≤ 65 mmHg raised the likelihood of severe cardiac or cerebrovascular events, while MAP ≤ 55 mmHg further increased this risk and was associated with higher mortality. Additionally, MAP ≤ 55 mmHg was also linked to a higher risk of advanced-stage AKI. These findings are consistent with those by Marcucci et al.,[22] who did not find differences in vascular outcomes when treating intraoperative hypotension. The authors emphasized the importance of further research into postoperative hypotension as a contributor to organ injury.

Therefore, it is evident that maintaining BP stability requires a collaborative perioperative effort, with continuous vigilance. In the real world, is such engagement feasible in current clinical practice? Until the current paradigm shifts, certain efforts may prove valuable. In a study involving postcardiac surgery patients, Desebbe et al.[56] showed that those managed with a closed-loop vasopressor (CLV) system spent only 1.4% of the time in hypotension (MAP $<$ 65 mmHg) compared to 12.5% with manual control. The CLV system maintained MAP within the target range (65-75 mmHg) 95% of the time vs 66% with manual control, with significantly more infusion adjustments, demonstrating its effectiveness. Hence, the use of AI-based predictive algorithms such as the HPI and advanced monitoring techniques could revolutionize perioperative care. Nevertheless, the validation and clinical implementation of these technologies remain challenging.

A novel concept termed "protective hemodynamics" has emerged, focused on minimizing the risks associated with hypotension interventions.[57] The objective of this approach is to reduce harm from excessive vasoconstriction while prioritizing patient outcomes rather than rigidly adhering to BP targets. It involves the implementation of dynamic BP targets that decrease in response to increasing vasopressor dosages. The BP target should be maintained within the reference range, particularly when vasopressor use is minimal or absent. As vasopressor dosage increases, lower BP targets should be accepted. This adaptive strategy aims to reduce iatrogenic harm linked to high doses of vasopressors by minimizing the risk of adverse effects. Elevated mean BP values due to increased doses of catecholamines are associated with increased mortality rates.[58] A recent meta-analysis comparing permissive vs targeted intraoperative MAP targets showed that MAP $\geq$ 60 mm Hg was not always equal to end-organ perfusion, whereas MAP $\leq$ 60 mm Hg was not associated with increased mortality or adverse effects.[59] These findings promoted the development of the C.L.E.A.R. protective hemodynamics approach for organ protection: a) **C**ustomize targets (e.g., reduce and individualize MAP targets and avoid overtreatment), b) **L**imit catecholamines (e.g., minimize the use of catecholamines, consider drugs acting on different receptors, and administer the right vasopressor to the right patient at the right time), c) **E**nhance flow focusing on microcirculation and regional blood flow, d) **A**djust fluid balance guided by echocardiography with optimal cardiac output and microvascular blood flow, and e) **R**esolve underlying conditions (e.g., with the use of steroids, sedation, and temperature control).[57] The impact of this approach needs to be validated in multicenter randomized control trials.

In summary, intraoperative hypotension is a frequent challenge during surgery and is linked to significant adverse outcomes, including an increased risk of mortality. Effective perioperative BP management is essential in modern anesthesia practice. A key area requiring further investigation is the routine application of a uniform low MAP threshold of 65 mmHg for most patients, without accounting for individualized targets tailored to pressure, flow, and oxygen delivery needs. The integration of algorithm-driven hemodynamic monitoring systems, combined with a redefined approach to hemodynamic stability, has the potential to support intraoperative and postoperative teams in optimizing patient outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 2013;119:507–15.
2. D'Amico F, Fominskiy EV, Turi S, et al. Intraoperative hypotension and postoperative outcomes: a meta-analysis of randomised trials. Br J Anaesth. 2023;131:823–31.
3. Gregory A, Stapelfeldt WH, Khanna AK, et al. Intraoperative Hypotension Is Associated With Adverse Clinical Outcomes After Noncardiac Surgery. Anesth Analg. 2021;132:1654–65.
4. Ke JXC, George RB, Beattie WS. Making sense of the impact of intraoperative hypotension: from populations to the individual patient. Br J Anaesth. 2018;121:689–91.
5. Meng L. Heterogeneous impact of hypotension on organ perfusion and outcomes: a narrative review. Br J Anaesth. 2021;127:845–61.
6. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45:3912–4018.
7. Guarracino F, Bertini P. Perioperative hypotension: causes and remedies. J Anesth Analg Crit Care. 2022;2:17.
8. Wachtendorf LJ, Azimaraghi O, Santer P, Linhardt FC, Blank M, Suleiman A, et al. Association Between Intraoperative Arterial Hypotension and Postoperative Delirium After Noncardiac Surgery: A Retrospective Multicenter Cohort Study. Anesth Analg. 2022;134:822–33.
9. Wongtangman K, Wachtendorf LJ, Blank M, et al. Effect of Intraoperative Arterial Hypotension on the Risk of Perioperative Stroke After Noncardiac Surgery: A Retrospective Multicenter Cohort Study. Anesth Analg. 2021;133:1000–8.
10. Jung H, Mohr N, Hulde N, Krannich A, Storm C, von Dossow V. Intraoperative hypotension and its association with acute kidney injury in patients undergoing elective cardiac surgery: a large retrospective cohort study. Euro J Anaesthesiol Int Care. 2024;3:e0048.
11. Cohen B, Rivas E, Yang D, et al. Intraoperative Hypotension and Myocardial Injury After Noncardiac Surgery in Adults With or Without Chronic Hypertension: A Retrospective Cohort Analysis. Anesth Analg. 2022;135:329–40.
12. Hallqvist L, Granath F, Fored M, Bell M. Intraoperative Hypotension and Myocardial Infarction Development Among High-Risk Patients Undergoing Noncardiac Surgery: A Nested Case-Control Study. Anesth Analg. 2021;133:6–15.
13. Hallqvist L, Granath F, Huldt E, Bell M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery: An observational study. Eur J Anaesthesiol. 2018;35:273–9.
14. Hallqvist L, Martensson J, Granath F, Sahlen A, Bell M. Intraoperative hypotension is associated with myocardial damage in noncardiac surgery: An observational study. Eur J Anaesthesiol. 2016;33:450–6.
15. Turan A, Rivas E, Devereaux PJ, et al. Relative contributions of anaemia and hypotension to myocardial infarction and renal injury: Post hoc analysis of the POISE-2 trial. Eur J Anaesthesiol. 2023;40:365–71.
16. Salmasi V, Maheshwari K, Yang D, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. Anesthesiology. 2017;126:47–65.

17. Gumbert SD, Kork F, Jackson ML, et al. Perioperative Acute Kidney Injury. Anesthesiology. 2020;132:180—204.
18. Weinberg L, Li SY, Louis M, et al. Reported definitions of intraoperative hypotension in adults undergoing non-cardiac surgery under general anaesthesia: a review. BMC Anesthesiol. 2022;22:69.
19. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181—247.
20. Schnetz MP, Danks DJ, Mahajan A. Preoperative Identification of Patient-Dependent Blood Pressure Targets Associated With Low Risk of Intraoperative Hypotension During Noncardiac Surgery. Anesth Analg. 2023;136:194—203.
21. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth. 2018;121:706—21.
22. Marcucci M, Painter TW, Conen D, Lomivorotov V, Sessler DI, Chan MTV, et al. Hypotension-Avoidance Versus Hypertension-Avoidance Strategies in Noncardiac Surgery: An International Randomized Controlled Trial. Ann Intern Med. 2023;176:605—14.
23. Fujieda T, Kurokawa T, Tanimoto T. Hypotension-Avoidance Versus Hypertension-Avoidance Strategies in Noncardiac Surgery. Ann Intern Med. 2023;176:eL230323.
24. Jacquet-Lagreze M, Larue A, Guilherme E, et al. Prediction of intraoperative hypotension from the linear extrapolation of mean arterial pressure. Eur J Anaesthesiol. 2022;39:574—81.
25. Hatib F, Jian Z, Buddi S, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. Anesthesiology. 2018;129:663—74.
26. Davies SJ, Vistisen ST, Jian Z, Hatib F, Scheeren TWL. Ability of an Arterial Waveform Analysis-Derived Hypotension Prediction Index to Predict Future Hypotensive Events in Surgical Patients. Anesth Analg. 2020;130:352—9.
27. Saugel B, Hoppe P, Nicklas JY, et al. Continuous noninvasive pulse wave analysis using finger cuff technologies for arterial blood pressure and cardiac output monitoring in perioperative and intensive care medicine: a systematic review and meta-analysis. Br J Anaesth. 2020;125:25—37.
28. Lakhal K, Dauvergne JE, Messet-Charriere H, et al. Risk factors for poor performance in finger cuff non-invasive monitoring of arterial pressure: A prospective multicenter study. Anaesth Crit Care Pain Med. 2024;43:101333.
29. Eley V, Christensen R, Guy L, et al. ClearSight finger cuff versus invasive arterial pressure measurement in patients with body mass index above 45 kg/m^2. BMC Anesthesiol. 2021;21:152.
30. Rellum SR, Kho E, Schenk J, van der Ster BJP, Vlaar APJ, Veelo DP. A comparison between invasive and noninvasive measurement of the Hypotension Prediction Index: A post hoc analysis of a prospective cohort study. Eur J Anaesthesiol. 2024. https://doi.org/10.1097/EJA.0000000000002082. Online ahead of print.
31. Kouz K, Weidemann F, Naebian A, et al. Continuous Finger-cuff versus Intermittent Oscillometric Arterial Pressure Monitoring and Hypotension during Induction of Anesthesia and Noncardiac Surgery: The DETECT Randomized Trial. Anesthesiology. 2023;139:298—308.
32. Eley V, Llewellyn S, Pelecanos A, et al. Finger cuff versus invasive and noninvasive arterial pressure measurement in pregnant patients with obesity. Acta Anaesthesiol Scand. 2024;68:645—54.
33. Jessen MK, Vallentin MF, Holmberg MJ, et al. Goal-directed haemodynamic therapy during general anaesthesia for noncardiac surgery: a systematic review and meta-analysis. Br J Anaesth. 2022;128:416—33.
34. Sun Y, Chai F, Pan C, Romeiser JL, Gan TJ. Effect of perioperative goal-directed hemodynamic therapy on postoperative recovery following major abdominal surgery-a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2017;21:141.
35. Hrdy O, Duba M, Dolezelova A, et al. Effects of goal-directed fluid management guided by a non-invasive device on the incidence of postoperative complications in neurosurgery: a pilot and feasibility randomized controlled trial. Perioper Med (Lond). 2023;12:32.
36. Philteos J, McCluskey SA, Emerson S, Djaiani G, Goldstein D, Soussi S. Impact of goal-directed hemodynamic therapy on perioperative outcomes in head and neck free flap surgery: A before-and-after pilot study. Health Sci Rep. 2024;7:e1943.
37. Mukkamala R, Schnetz MP, Khanna AK, Mahajan A. Intraoperative Hypotension Prediction: Current Methods, Controversies, and Research Outlook. Anesth Analg. 2024. https://doi.org/10.1213/ANE.0000000000007216. Online ahead of print.
38. Wijnberge M, van der Ster BJP, Geerts BF, et al. Clinical performance of a machine-learning algorithm to predict intra-operative hypotension with noninvasive arterial pressure waveforms: A cohort study. Eur J Anaesthesiol. 2021;38:609—15.
39. Vistisen ST, Enevoldsen J. CON: The hypotension prediction index is not a validated predictor of hypotension. Eur J Anaesthesiol. 2024;41:118—21.
40. Longrois D, de Tymowski C. PRO: The hypotension prediction index is clinically relevant: A physiologic/pathophysiologic approach opposed to a purely computational debate. Eur J Anaesthesiol. 2024;41:115—7.
41. Mehta D, Gonzalez XT, Huang G, Abraham J. Machine learning-augmented interventions in perioperative care: a systematic review and meta-analysis. Br J Anaesth. 2024;133:1159—72.
42. Mulder MP, Harmannij-Markusse M, Fresiello L, Donker DW, Potters JW. Hypotension Prediction Index Is Equally Effective in Predicting Intraoperative Hypotension during Noncardiac Surgery Compared to a Mean Arterial Pressure Threshold: A Prospective Observational Study. Anesthesiology. 2024;141:453—62.
43. Jarry S, Halley I, Calderone A, et al. Impact of Processed Electroencephalography in Cardiac Surgery: A Retrospective Analysis. J Cardiothorac Vasc Anesth. 2022;36:3517—25.
44. Dhawan R. EEG in Cardiac Surgery-Moving Past the Obvious. J Cardiothorac Vasc Anesth. 2022;36:3526—8.
45. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg. 2005;100:4—10.
46. Sessler DI, Sigl JC, Kelley SD, et al. Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. Anesthesiology. 2012;116:1195—203.
47. Vu EL, Brown CHt, Brady KM, Hogue CW. Monitoring of cerebral blood flow autoregulation: physiologic basis, measurement, and clinical implications. Br J Anaesth. 2024;132:1260—73.
48. Couture EJ, Deschamps A, Denault AY. Patient management algorithm combining processed electroencephalographic monitoring with cerebral and somatic near-infrared spectroscopy: a case series. Can J Anaesth. 2019;66:532—9.
49. Battaglini D, Pelosi P, Robba C. The Importance of Neuromonitoring in Non Brain Injured Patients. Crit Care. 2022;26:78.
50. Georgii MT, Kreuzer M, Fleischmann A, Schuessler J, Schneider G, Pilge S. Targeted Interventions to Increase Blood Pressure and Decrease Anaesthetic Concentrations Reduce Intraoperative Burst Suppression: A Randomised. Interventional Clinical Trial. Front Syst Neurosci. 2022;16:786816.
51. Thomsen KK, Sessler DI, Krause L, et al. Processed electroencephalography-guided general anesthesia and norepinephrine requirements: A randomized trial in patients having vascular surgery. J Clin Anesth. 2024;95:111459.
52. Payne T, Braithwaite H, McCulloch T, et al. Depth of anaesthesia and mortality after cardiac or noncardiac surgery: a systematic

review and meta-analysis of randomised controlled trials. Br J Anaesth. 2023;130:e317—e29.
53. Lee KH, Egan TD, Johnson KB. Raw and processed electroencephalography in modern anesthesia practice: a brief primer on select clinical applications. Korean J Anesthesiol. 2021;74:465—77.
54. Pawar N, Barreto Chang OL. Burst Suppression During General Anesthesia and Postoperative Outcomes: Mini Review. Front Syst Neurosci. 2021;15:767489.
55. Smischney NJ, Shaw AD, Stapelfeldt WH, et al. Postoperative hypotension in patients discharged to the intensive care unit after non-cardiac surgery is associated with adverse clinical outcomes. Crit Care. 2020;24:682.
56. Desebbe O, Rinehart J, Van der Linden P, et al. Control of Postoperative Hypotension Using a Closed-Loop System for Norepinephrine Infusion in Patients After Cardiac Surgery: A Randomized Trial. Anesth Analg. 2022;134:964—73.
57. D'Amico F, Marmiere M, Monti G, Landoni G. Protective Hemodynamics: C.L.E.A.R.!. J Cardiothorac Vasc Anesth. 2024. https://doi.org/10.1053/j.jvca.2024.10.021. Online ahead of print.
58. Singer M, Matthay MA. Clinical review: Thinking outside the box - an iconoclastic view of current practice. Crit Care. 2011;15:225.
59. D'Amico F, Pruna A, Putowski Z, et al. Low Versus High Blood Pressure Targets in Critically Ill and Surgical Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Crit Care Med. 2024;52:1427—38.

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY



EDITORIAL

Shaping the future of anesthesia research: celebrating progress and embracing new challenges

The Brazilian Journal of Anesthesiology (BJAN), originally founded as the "Revista Brasileira de Anestesiologia" in 1951, has been a cornerstone of scientific advancement in anesthesiology for over seven decades. Initially launched in Portuguese, it transitioned to full English publication to align with global scientific communication standards and enhance its international reach. As one of the oldest continuously published anesthesiology journals, BJAN has embraced open access since its inception, supported by the Brazilian Society of Anesthesiology (SBA). Over time, the journal has evolved through innovations such as adopting modern editorial practices, fostering international collaborations, enhancing peer-review processes, and leveraging digital platforms to broaden its audience. Today, BJAN stands as a relevant platform for the dissemination of high-quality research in Latin America and globally, reflecting its commitment to excellence in medical science and education.

A journal's success relies on the content and quality of its published manuscripts. However, this success is never the work of one individual; rather, it is the collective achievement of a dedicated team. This team includes authors, peer reviewers, editors, board members, and readers. Each one has played a pivotal role in shaping the BJAN's identity and ensuring its relevance and impact in the field. The BJAN team sincerely thanks all its contributors for their indispensable roles in this process.

In particular, the reviewers' contributions are fundamental to maintaining the journal's high standards. The reviewers, often working behind the scenes in a blinded peer-review process, perform the critical task of evaluating manuscripts, providing constructive remarks, and assisting editors in making informed decisions. Their scrutiny not only sharpens the quality of submissions but also ensures that published research is both rigorous and accessible to readers. The BJAN editorial office extends its gratitude to these invaluable collaborators, whose expertise and dedication form the backbone of the journal's scientific integrity.

BJAN has solidified its role as a premier journal in Latin America, serving as a critical platform for researchers from the region and the developing world to publish high-quality studies. Its Open Diamond model ensures free access for both authors and readers, providing an invaluable resource for disseminating scientific knowledge without financial barriers. The journal's commitment to accessibility has made it a basis for scientific advancement in anesthesiology, pain management, intensive care, and perioperative medicine across resource-limited settings. This openness fosters collaboration and ensures that groundbreaking research reaches practitioners and researchers who might otherwise lack access.

Recognizing the evolving needs of its audience, BJAN has embraced a paperless format, reflecting the habits of its readers who increasingly access content in digital formats. This shift has also been facilitated by the strategic partnership with Elsevier and the Editorial Manager platform, which have streamlined the processes of manuscript submission, review, and publication. These platforms enable seamless communication among authors, reviewers, and editors, ensuring efficient and transparent workflows.

Scientific integrity remains a key priority for BJAN and its editorial board. As fraud in science continues to threaten trust in research, the journal is committed to adopting stringent measures to detect and prevent unethical practices. Moving forward, BJAN has implemented enhanced plagiarism detection tools, promoted transparency through pre-registration of clinical trials, and encouraged authors to make raw data available in repositories. Additionally, BJAN has implemented strategies to educate reviewers and authors on best practices in ethical research and reporting, ensuring that publications meet the highest standards of integrity.

The journal recognizes the transformative role of artificial intelligence (AI) in modernizing editorial workflows. AI tools will increasingly assist in manuscript screening, plagiarism detection, and identifying potential conflicts of interest. These advancements will streamline peer-review processes and ensure efficient, high-quality evaluations. Furthermore, AI-driven analytics will provide insights into

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submission trends and help the journal adapt to emerging topics in anesthesiology and perioperative medicine.

BJAN has also developed robust social media strategies to enhance its visibility and impact. The creation of a Scientific Hub has enabled the production of educational content and facilitated discussions on scientific evidence and methodology. By joining platforms such as Instagram, YouTube, and Spotify, BJAN has expanded its reach, connecting with a global audience of researchers, clinicians, and students. These efforts have not only increased the visibility of published articles but also fostered a sense of community among professionals in anesthesiology.

Last year, BJAN adopted a continuous publication format, allowing for the timely dissemination of articles as soon as they are ready while still maintaining the tradition of organizing six curated issues per year. These issues are thoughtfully compiled to highlight the most relevant and impactful papers published in each cycle, with a focus on hot topics in anesthesia and related areas, including the publication of large observational studies,[1-5] randomized clinical trials,[6-9] systematic reviews,[10-12] and practice guidelines adapted to the reality of developing countries.[13-15] Each issue also features editorials crafted by members of the editorial board or invited experts, offering in-depth commentary and insights on key advances and challenges within the field.[16-20] These contributions reflect BJAN's commitment to addressing contemporary issues with scholarly rigor and clinical relevance.

In the upcoming editorial cycle, BJAN intends to implement more comprehensive statistical analyses for all accepted articles. The idea is for a dedicated team of statistical experts to review manuscripts, ensuring methodological robustness and data accuracy. This initiative aims to enhance the credibility and impact of published research. Additionally, to maintain and enhance the quality of its publications, BJAN plans to recruit and train a new generation of peer reviewers. Mentorship programs will be established to help reviewers develop critical evaluation skills, ensuring thorough and constructive feedback. By increasing the number and diversity of reviewers, BJAN will strengthen its peer-review process, reduce evaluation times, and support the publication of impactful research.

As my run comes to an end, it is time to pass the responsibility of editor-in-chief to someone whose skills and creativity are capable of meeting the journal's demands. It is an honor to introduce the next editor-in-chief, Professor Liana Maria Torres de Araújo Azi, an esteemed academic and anesthesiologist from the Federal University of Bahia (UFBA). Professor Liana Azi, the fourth woman in the last six editors of BJAN, symbolizes the growing prominence of female leadership in science. This transition reflects BJAN's and SBA's commitment to inclusivity and the promotion of women as scientific leaders. Her leadership promises to bring renewed vision and energy to the journal, continuing its mission of advancing anesthesiology and perioperative medicine.

The challenges that lie ahead for BJAN are both formidable and invigorating. The journal's future rests on sustaining high-quality publications, fostering ethical practices, embracing technological advancements, and engaging with readers across platforms. All of us look forward to working with the new editor-in-chief to advance the care of our patients and improve the scientific understanding in anesthesiology. I thank the authors, reviewers, readers, and the SBA for allowing me to have a wonderful professional experience as your editor-in-chief these last few years. With an unwavering commitment to excellence, BJAN will undoubtedly remain a reference of scientific integrity and innovation for Latin America and beyond.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Bieze M, Zabida A, Martinelli ES, et al. Intraoperative hypotension during critical phases of liver transplantation and its impact on acute kidney injury: a retrospective cohort study. Braz J Anesthesiol. 2024;74:844566.
2. Stahlschmidt A, Passos SC, Cardoso GR, et al. Postoperative intensive care allocation and mortality in high-risk surgical patients: evidence from a low- and middle-income country cohort. Braz J Anesthesiol. 2024;74:844517.
3. Sari S, Brooker J, Montalvo-Campana M, et al. The association of hemoglobin with postoperative delirium and atrial fibrillation after cardiac surgery: a retrospective sub-study. Braz J Anesthesiol. 2024;74:744424.
4. Bajracharya GR, Esa WAS, Mao G, et al. Regional analgesia and surgical site infections after colorectal surgery: a retrospective cohort analysis. Braz J Anesthesiol. 2023;73:10—5.
5. Almonacid-Cardenas F, Rivas E, Auron M, et al. Association between preoperative anemia optimization and major complications after non-cardiac surgery: a retrospective analysis. Braz J Anesthesiol. 2024;74:744474.
6. Castro GIP, Castro RSAP, Lima RME, Santos BND, Navarro E, Lima LH. Fluid therapy and pulmonary complications in abdominal surgeries: randomized controlled trial. Braz J Anesthesiol. 2024;74:844500.
7. Vale AGG, Govêia CS, Guimarães GMN, Terra LR, Ladeira LCA, Essado GA. Comparison of arterial hypotension incidence during general anesthesia induction - target-controlled infusion vs. bolus injection of propofol: a randomized clinical trial. Braz J Anesthesiol. 2024;74:844503.
8. de Queiroz MN, Mendonça FT, de Matos MV, Lino RS, de Carvalho LSF. Metoprolol for prevention of bucking at orotracheal extubation: a double-blind, placebo-controlled randomised trial. Braz J Anesthesiol. 2024;74:744455.
9. Davolos FJC, Modolo NS, Braz LG, Nascimento Junior PD. Palonosetron versus ondansetron for prophylaxis of postoperative nausea and vomiting in laparoscopic cholecystectomy: a non-inferiority randomized controlled trial. Braz J Anesthesiol. 2024;74:744216.
10. Pereira EMM, Nascimento TSD, da Costa MG, Slawka E, Júnior CG. Comparison of intranasal dexmedetomidine versus oral midazolam for premedication in pediatric patients: an updated meta-analysis with trial-sequential analysis. Braz J Anesthesiol. 2024;74:844520.
11. Amaral S, Lombardi R, Drabovski N, Gadsden J. Infraclavicular versus costoclavicular approaches to ultrasound-guided brachial plexus block: a systematic review and meta-analysis. Braz J Anesthesiol. 2024;74:744465.
12. Assis IC, Govêia CS, Miranda DB, Ferreira RS, Riccio LGC. Analysis of the efficacy of prophylactic tranexamic acid in preventing postpartum bleeding: systematic review with meta-analysis of randomized clinical trials. Braz J Anesthesiol. 2023;73:467—76.

13. de Barros GAM, Pos AM, Sousa ÂM, et al. Cannabinoid products for pain management: recommendations from the São Paulo State Society of Anesthesiology. Braz J Anesthesiol. 2024;74: 844513.
14. Martins MP, Ortenzi AV, Perin D, Quintas GCS, Malito ML, Carvalho VH. Recommendations from the Brazilian Society of Anesthesiology (SBA) for difficult airway management in adults. Braz J Anesthesiol. 2024;74:744477.
15. Lima LC, Cumino DO, Vieira AM, et al. Recommendations from the Brazilian Society of Anesthesiology (SBA) for difficult airway management in pediatric care. Braz J Anesthesiol. 2024;74: 744478.
16. Schmidt AP, Bevilacqua Filho CT. The impact of anesthesia on postoperative outcomes: the effect of regional anesthesia on the incidence of surgical site infections. Braz J Anesthesiol. 2023;73:1—2.
17. Quintão VC, Carlos RV, de Sousa GS, Carmona MJC. Mind the gap between low- and middle-income countries (LMICs) and high-income countries (HICs): fostering pediatric anesthesia globally. Braz J Anesthesiol. 2024;74:844544.
18. Costa LGVD, Papa FV, Hare GMT, Salgado-Filho MF, Lineburger EB, Schmidt AP. Anemia and outcomes in cardiac surgery. Braz J Anesthesiol. 2024;74:844504.
19. Martinelli ES, McCluskey SA, Karkouti K, et al. The debate on antifibrinolytics in liver transplantation: always, never, or sometimes? Braz J Anesthesiol. 2024;74:844562.
20. Cachefo-Pereira A, Souza Neto EP. Greening the operating room. Braz J Anesthesiol. 2024;74:744464.

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ORIGINAL INVESTIGATION

Intraoperative hypotension and postoperative delirium in elderly male patients undergoing laryngectomy: a single-center retrospective cohort study

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KEYWORDS
Hypotension;
Laryngectomy;
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Abstract

Background: Postoperative delirium (POD) is a common, transient postoperative cognitive dysfunction in elderly patients. The relationship between POD and intraoperative hypotension remains unclear. This study aims to determine if intraoperative hypotension predicts POD in elderly male patients undergoing laryngectomy.

Methods: This study included male patients over 65 years old who underwent laryngectomy between April 2018 and January 2022. The Confusion Assessment Method (CAM) was used to diagnose delirium. Intraoperative hypotension was defined as a Mean Arterial Pressure (MAP) during surgery that was less than 30% of the preoperative level for at least 30 minutes. The relationship between intraoperative hypotension and POD incidence was adjusted for patient demographics and surgery-related factors.

Results: Out of 428 male patients, 77 (18.0%) developed POD, and 166 (38.8%) experienced intraoperative hypotension. Surgery duration ≥ 300 minutes (OR = 1.873, 95% CI 1.041–3.241, $p = 0.036$), intraoperative hypotension (OR = 1.739, 95% CI 1.039–2.912, $p = 0.035$), and schooling (OR = 2.655, 95% CI 1.338–5.268) were independent risk factors for POD. The association between intraoperative hypotension and POD was significantly influenced by surgery duration (p for interaction = 0.008), with a stronger association in prolonged surgeries (adjusted OR = 4.902; 95% CI 1.816–13.230).

Conclusions: Intraoperative hypotension and low education level are associated with an increased risk of POD in elderly male patients undergoing laryngectomy, especially with prolonged surgery duration.

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Introduction

As the population ages, the number of elderly individuals requiring surgical treatment is increasing.[1-3] Elderly patients

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often experience more age-related complications due to frailty and physical deterioration.[4,5] Postoperative cognitive impairment is a common complication in elderly patients.[6] Postoperative delirium (POD), characterized by severe fluctuations in cognitive function and attention deficits, is a transient form of this impairment.[7,8] POD can lead to adverse outcomes, including prolonged hospital stays, increased costs, postoperative mortality, poor long-term quality of life, and even long-term cognitive impairment.[9-11]

The causes of POD are multifactorial. Clinical studies have identified several unmodifiable risk factors, including sensory deficits, impaired functional status, cognitive impairment, comorbidities, and frailty.[7,12] Modifiable risk factors, such as medication use, type of anesthesia, and perioperative management strategies, also play a role. Since treatment options for delirium are limited, prevention strategies targeting these modifiable factors are crucial.[13,14]

Intraoperative hypotension is a common side-effect of general anesthesia and is associated with postoperative adverse events like acute kidney injury and myocardial ischemia.[15,16] While the brain can typically respond to ischemia and hypoxia,[17,18] this capacity is diminished in elderly patients due to reduced arterial elasticity and other comorbidities.[19,20] Prolonged intraoperative hypotension can compromise cerebral perfusion, potentially leading to neurological complications.[21,22] While several studies have explored the relationship between intraoperative hypotension and POD, their results have been inconclusive.[2,23,24]

Our study uniquely focuses on elderly patients undergoing laryngectomy, a procedure involving significant physiological stress and extended duration, both of which may influence POD incidence.[25] By examining this specific surgical population, we aim to provide detailed insights into the interaction between intraoperative hypotension and other potential risk factors for POD, such as surgery duration, patient demographics, and dexmedetomidine use.[25]

Therefore, in this retrospective study, we investigated whether intraoperative hypotension would predict the onset of POD in elderly patients undergoing laryngectomy. We also considered other potential risk factors, including education level and preoperative cognitive status, to better understand their roles in the development of POD.

Methods

Data source

This retrospective cohort study was conducted at the Eye and Ear Nose Throat (ENT) Hospital, Fudan University. The study was approved by the hospital's review board, and informed consent was waived. The study adhered to the Declaration of Helsinki and followed STROBE guidelines for observational studies. Data were obtained from 812 patients who underwent laryngectomy at the Eye and ENT Hospital from April 2018 to January 2022. Patients' characteristics and perioperative data were obtained from the hospital information system (apprefms) and the anesthetic system (DoCare V5.0).

Study population

The enrollment criteria were as follows: male patients aged 65 years or older who underwent laryngectomy under general anesthesia. Exclusion criteria included neurodegenerative diseases, history of delirium, history of mental illness, and missing data for potential confounding variables. Female patients were excluded due to the very low prevalence of laryngeal cancer in females (1.3%)[26] and their frequent refusal to participate in the study. This decision was made to ensure a sufficient sample size and homogeneous study population.

Data collection

Detailed information on patient demographics and clinical characteristics was collected: cancer stage, education level (highest degree completed, with high school corresponding to 12 years of schooling), MMSE scores (Mini-Mental State Examination) (Appendix 1), CIRS scores (Cumulative Illness Rating Scale) (Appendix 2), comorbidities (history of cerebral stroke, hypertension [systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg], diabetes mellitus), smoking status (regular tobacco use), drinking status (regular alcohol consumption), family history of dementia, preoperative poor sleep quality (self-reported sleep disturbances in the month prior to surgery), surgery type, surgery duration, amount of fluid infusion, and intraoperative dexmedetomidine use. Intraoperative Mean Arterial Pressure (MAP) data was obtained from the anesthetic system (DoCare V5.0), which documented at a 5-min interval.

Consistent with our previous study,[25] intraoperative hypotension was defined as a MAP decrease of 30% or more below the preoperative baseline, lasting for at least 30 minutes. We redefined intraoperative hypotension as a MAP decrease of 30% or more below the preoperative baseline, lasting for at least 30 minutes. This definition was based on prior studies that have shown significant associations between sustained reductions in MAP and delirium.[27]

Patients with a MMSE score $<$ 27 were considered to have preoperative cognitive impairment.[28] The score of the CIRS was used to assess preoperative comorbidity, patients with a score $\geq$ 8 were considered high comorbidity.[8] Low education level was defined as patients graduated from less than high school (corresponding to 12 years of schooling). Prolonged surgical duration was defined as surgery duration $\geq$ 300 minutes. The amount of rehydration $\geq$ 3000 mL was considered to have excessive fluid replacement.

Outcome

Since symptoms of POD are often worse at night,[29] patients were interviewed daily using the Confusion Assessment Method (CAM) diagnostic algorithm[30] (Appendix 3) between 4 p.m. and 6 p.m. during the first five days after surgery. For patients in ICU, the CAM-ICU was used. Accurate detection of delirium with the CAM requires evaluation of four features: acute onset with a fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Patients meeting the CAM criteria on any assessed day were considered positive for delirium. Prior to the initial study, the investigators conducting the postoperative follow-up and delirium assessment had received specialized training related to psychiatry.

Statistical analysis

Data were analyzed using SPSS 22.0. A p-value < 0.05 (two-sided) was considered statistically significant. Normally distributed data were presented as means with Standard Deviations (SD) and analyzed with two-sample Student's t-tests. Skewed continuous data were presented as medians with Interquartile Ranges (IQR) and evaluated using Wilcoxon signed rank tests. Categorical variables were expressed as numbers (percentage) and tested using χ^2 test, Fisher's exact test, or Cochran-Mantel-Haenszel χ^2 test. Variables associated ($p < 0.2$) with POD in univariate analysis and potential variables (older age, CIR > 8, and no intraoperative dexmedetomidine use) which have been shown as risk factors in previous studies[8,25] were used as candidate risk factors for the stepwise logistic regression multivariate models.

We performed a stratified analysis based on the variables associated ($p < 0.05$) with POD in multivariable logistic regression analysis to further explore whether the association between hypotension and POD might be modified by these factors.

Results

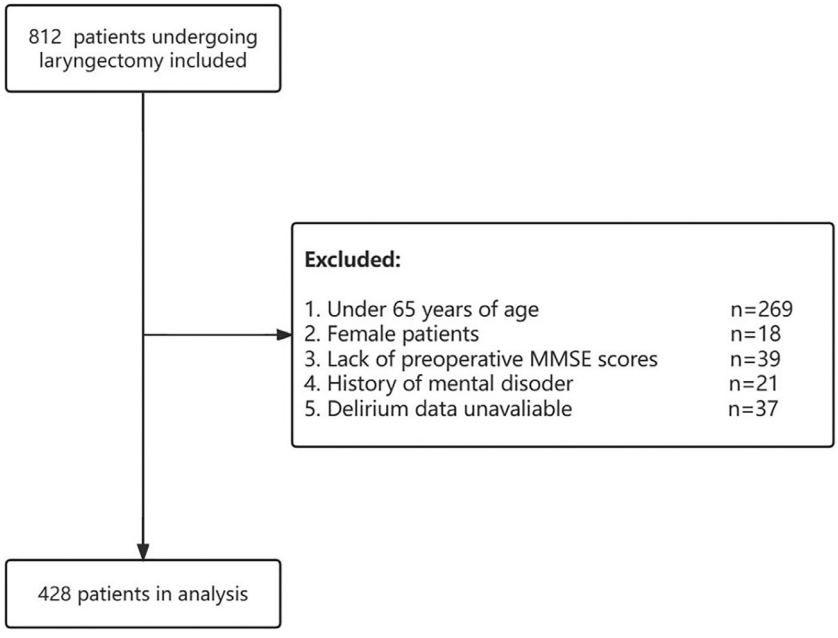
From April 2018 to January 2022, a total of 812 patients undergoing laryngectomy were included in this study. According to inclusion and exclusion criteria, data of 428 patients were finally analyzed (Fig. 1).

The demographic and clinical characteristics of the study population are summarized in Table 1. The mean age of the patients was 69.5 years (SD = 4.4 years). Among the patients, 39.5% had advanced-stage laryngeal cancer (stage III or IV), and 70.8% had low education levels. The mean MMSE score was 23.8 (SD = 6.2). The prevalence of comorbidities included 9.6% with a history of cerebral stroke, 44.6% with hypertension, 14.5% with diabetes mellitus, and 3.7% with a family history of dementia. The mean CIRs score was 5.4 (SD = 2.5). Additionally, 24.5% of patients reported poor sleep quality preoperatively, 88.3% of the patients were smokers, and 63.3% reported regular alcohol consumption. The median surgery duration was 209.6 minutes (IQR: 109—275 min), and 21.3% of the patients underwent surgery lasting 300 minutes or longer. Intraoperative dexmedetomidine was used in 49.3% of cases. A total of 11.7% of patients received more than 3000 mL of fluids intraoperatively, and 38.8% experienced hypotension during the procedure.

The prevalence of POD was 18.0% (77/428) during the first five days postoperatively. Patients with POD were more likely to have low education levels (p = 0.001), lower MMSE scores (p = 0.012), prolonged surgery duration (p = 0.019), and intraoperative hypotension (p = 0.036; Table 1). The incidence of POD was not reduced by intraoperative dexmedetomidine use (p = 0.5).

Multivariate logistic regression model showed that low education level (OR = 2.655; 95% CI 1.338—5.268; p = 0.005), prolonged surgery duration (OR = 1.873; 95% CI 1.041—3.241; p = 0.036) and intraoperative hypotension (OR = 1.739; 95% CI 1.039—2.912; p = 0.035) were independently associated with occurrence of POD. However, preoperative hypertension appeared to be a protective factor for POD (OR = 0.572; 95% CI 0.335—0.975; p = 0.042) (Fig. 2).

The incidence of intraoperative hypotension in patients with or without POD was 49.4% (38 patients) and 36.5% (128 patients), respectively (p = 0.036, Table 1). The stratified analysis showed that the effect of intraoperative hypotension on POD varied in different strata of surgical duration (p for interaction = 0.008) rather than preoperative hypertension (p for interaction = 0.288) and education level (p for interaction = 0.198) (Table 2).



Figures 1 Diagram of trial recruitment with inclusion and exclusion criteria.

Table 1 Preoperative Variables Related to the Development of POD.

Factor	Total patients (n = 428)	POD (n = 77)	Non-POD (n = 351)	*p*-value[a]
Age	69.5 (4.4)	69.0 (3.8)	69.6 (4.5)	0.256
Cancer stage				0.293
I	117 (27.3%)	18 (23.4%)	99 (28.2%)	
II	142 (31.2%)	22 (28.6%)	120 (34.2%)	
III	106 (24.8%)	21 (27.3%)	85 (24.2%)	
IV	63 (14.7%)	16 (20.8%)	47 (13.4%)	
Education level				0.001
Low (less than high school)	303 (70.8%)	66 (85.7%)	237 (63.5%)	
High (greater than high school)	125 (29.2%)	11 (14.3%)	114 (32.5%)	
MMSE (< 27)	236 (55.1%)	52 (68.4%)	184 (52.6%)	0.012
CIRS (> 8)	77 (18.0%)	10 (13.0%)	67 (19.1%)	0.203
Previous cerebral stroke	41 (9.6%)	9 (11.7%)	32 (9.1%)	0.487
Hypertension	191 (44.6%)	27 (31.5%)	164 (46.7%)	0.062
Diabetes mellitus	62 (14.5%)	10 (13.0%)	52 (14.8%)	0.680
Smoke	378 (88.3%)	67 (87.0%)	311 (88.6%)	0.694
Drink	271 (63.3%)	47 (61.0%)	224 (64.0%)	0.625
Family history of dementia	16 (3.7%)	3 (3.9%)	13 (3.7%)	0.936
Preoperative poor sleep quality	105 (24.5%)	16 (20.8%)	89 (29.4%)	0.394
Surgery type				0.245
PL	134 (31.3%)	25 (32.5%)	109 (31.1%)	
PL and ND	100 (23.4%)	16 (20.8%)	84 (23.9%)	
TL	79 (18.5%)	9 (11.7%)	70 (19.9%)	
TL and ND	94 (21.9%)	21 (27.3%)	73 (20.4%)	
Total laryngopharyngectomy and ND	21(4.9%)	6 (7.8%)	15 (4.3%)	
Surgery duration ≥ 300 min	91 (21.3%)	24 (31.2%)	67 (19.1%)	0.019
Intraoperative hypotension	166 (38.8%)	38 (49.4%)	128 (36.5%)	0.036
Fluid infusion ≥ 3000 mL	50 (11.7%)	9 (11.7%)	41 (11.7%)	0.999
Intraoperative dexmedetomidine use	211 (49.3%)	36 (46.8%)	175 (51.0%)	0.5

Data are shown as mean (SD), or number (percentage).
MMSE, Mini-Mental State Examination; CIRS, Cumulative Illness Rating Scale; POD, Postoperative Delirium; PL, Partial Laryngectomy; ND, Neck Dissection; TL, Total Laryngectomy.
[a] Comparison between the POD group and the non-POD group.

Discussion

Our study found that the prevalence of POD was 18.0% in elderly male patients after laryngectomy. Three risk factors were identified: intraoperative hypotension, low education level, and surgery duration of 300 minutes or longer. Intraoperative hypotension is clearly associated with an increase in the odds of POD and this association between

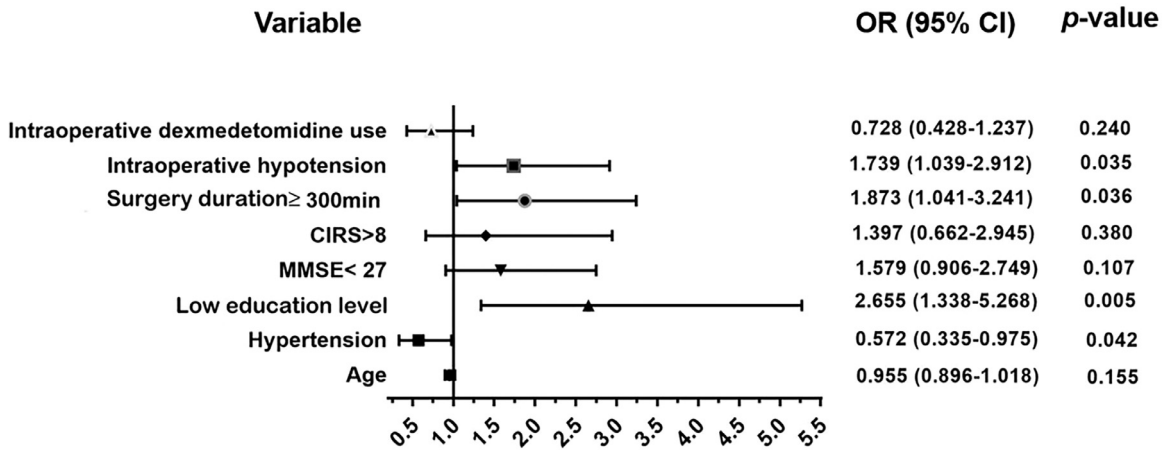


Figure 2 Forest plot of multivariate logistic regression analysis demonstrating factors associated with POD. POD, Postoperative Delirium.

Table 2 Stratified analysis of the effect of intraoperative hypotension on POD.

Factors	Adjusted OR (95% CI)	*p* for interaction
Hypertension		0.288
No history of hypertension	1.424 (0.753–2.698)	
History of hypertension	2.589 (1.116–6.006)	
Education level		0.198
Low education level	1.421 (0.829–2.462)	
High education level	3.642 (1.003–13.224)	
Surgery duration		0.008
< 300 min	1.195 (0.660–2.162)	
≥ 300 min	4.902 (1.816–13.230)	

POD, Postoperative Delirium; OR, Odd Ratio.

intraoperative hypotension and POD was magnified in patients with prolonged surgery duration.

The adverse effect of intraoperative hypotension on the development of POD is not clear due to inconsistent definitions of hypotension and varying populations in previous studies.[31-33] A retrospective study showed intraoperative hypotension (MAP ≤ 65 mmHg) for ≥ 5 min was associated with an increased incidence of POD after thoracic and orthopedic surgery in the elderly.[34] In patients undergoing noncardiac surgery, a MAP < 55 mmHg was a risk factor for POD.[24] Our previous observational study showed that intraoperative hypotension was a risk factor for POD in patients undergoing laryngectomy.[25] In this study, we found that intraoperative hypotension increased the incidence of POD with an OR = 1.739 (95% CI 1.039—2.912). It is well recognized that the capability of cerebral autoregulation may be impaired in older patients.[35,36] Hypotension results in reduction of cerebral perfusion pressure and mean cerebral blood flow velocity, and this effect is especially pronounced in elderly people with higher cardiovascular risk,[37,38] which finally leads to cerebral dysfunction. Our finding supported that POD may be a manifestation of cerebral dysfunction due to temporary intraoperative cerebral under-perfusion[39] and perioperative blood pressure should be strictly controlled in elderly patients.[40]

Previous studies determined that prolonged surgery duration was a risk factor for POD.[7,9] Our analysis indicated that the association between intraoperative hypotension and POD was significantly influenced by surgery duration (*p* for interaction = 0.008). Specifically, the effect of intraoperative hypotension on the incidence of POD was more pronounced in patients who underwent prolonged surgeries (≥ 300 min). Consistent with a previous study,[24] our finding suggests that patients who experience intraoperative hypotension during extended surgical procedures are at a higher risk of developing POD. Clinically, this underscores the importance of meticulous blood pressure management during long surgeries to mitigate the risk of POD. Prolonged surgeries may contribute to a cumulative stress response and increased vulnerability to hypotension-induced cerebral hypoperfusion, thereby elevating the risk of cognitive dysfunction postoperatively.

The underlying association between intraoperative hypotension and POD can be explained by several factors: reduced cerebral perfusion, especially in elderly patients with compromised cerebral autoregulation;[20,21] the inflammatory response induced by surgical procedures;[37] and pre-existing vulnerabilities such as cerebrovascular disease or other comorbidities.[8,12]

Education level and preoperative cognitive dysfunction have been identified as risk factors in POD studies.[25,41,42] Higher education levels are associated with better cognitive reserve, potentially protecting against POD.[43]

A meta-analysis demonstrated a significant association between blood pressure reduction using antihypertensive agents and a reduced risk of incident dementia or cognitive impairment.[43] However, the impact of preoperative hypertension on postoperative cognitive function is not yet fully understood. While some studies have suggested that preoperative hypertension was not associated with postoperative cognitive dysfunction,[44,45] our findings indicated that preoperative hypertension may be a protective factor against POD (OR = 0.572, 95% CI 0.335—0.975). Specifically, we identified preoperative hypertension as a protective factor against POD, while intraoperative hypotension was found to be a risk factor. Chronic hypertension patients may experience reduced cerebral perfusion during intraoperative hypotension, potentially causing neuronal dysfunction. Moreover, these patients often have impaired cerebral autoregulation, making them more vulnerable to blood pressure fluctuations and thereby increasing the risk of POD. It is important to acknowledge the limitations of this retrospective study, such as potential selection bias and incomplete data, which may affect the generalizability of our findings. Further prospective studies are needed to validate these results and explore the underlying mechanisms in more detail.

Our study has several limitations. First, the data were exclusively from male patients, limiting generalizability. Second, POD incidence was recorded within five days postoperatively, without long-term cognitive assessment. Third, missing delirium data for 37 patients may affect robustness. Finally, intraoperative hypotension was recorded as a categorical variable without detailed analysis.

Conclusion

In conclusion, our study demonstrates an association between intraoperative hypotension and POD in elderly male patients undergoing laryngectomy, particularly with prolonged surgery duration. Preventing intraoperative hypotension could be a modifiable risk factor for POD prevention

in this patient population. Additionally, low educational level is also associated with POD. Future studies addressing the limitations mentioned, such as gender selection, time window for POD assessment, and detailed blood pressure analysis, are warranted to provide a more comprehensive understanding of the relationship between intraoperative hypotension and POD.

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.2024.844560.

References

1. Daiello LA, Racine AM, Yun GR, et al. Postoperative Delirium and Postoperative Cognitive Dysfunction: Overlap and Divergence. Anesthesiology. 2019;131:477—91.
2. Hirsch J, DePalma G, Tsai TT, et al. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. Br J Anaesth. 2015;115:418—26.
3. Richards S, Frizelle FA, Geddes JA, et al. Frailty in surgical patients [J] Int J Colorectal Dis. 2018;33:1657—66.
4. Hamel MB, Henderson WG, Khuri SF, et al. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc. 2005;53:424—9.
5. Sunayama T, Matsue Y, Dotare T, et al. Multidomain Frailty as a Therapeutic Target in Elderly Patients with Heart Failure. Int Heart J. 2022;63:1—7.
6. Olotu C. Postoperative neurocognitive disorders. Curr Opin Anaesthesiol. 2020;33:101—8.
7. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2017;34:192—214.
8. Cerejeira J, Nogueira V, Luís P, et al. The Cholinergic System and Inflammation: Common Pathways in Delirium Pathophysiology. J Am Geriatr Soc. 2012;60:669—75.
9. Galyfos GC, Geropapas GE, Sianou A, et al. Risk factors for postoperative delirium in patients undergoing vascular surgery. J Vasc Surg. 2017;66:937—46.
10. Jankowski CJ, Trenerry MR, Cook DJ, et al. Cognitive and Functional Predictors and Sequelae of Postoperative Delirium in Elderly Patients Undergoing Elective Joint Arthroplasty. Anesth Analg. 2011;112:1186—93.
11. Sauër AC, Veldhuijzen DS, Ottens TH, et al. Association between delirium and cognitive change after cardiac surgery. Br J Anaesth. 2017;119:308—15.
12. Inouye SK. Delirium in older persons. N Engl J Med. 2006;354:1157—65.
13. Inouye SK, Bogardus SJ, Baker DI, et al. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital Elder Life Program. J Am Geriatr Soc. 2000;48:1697—706.
14. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev. 2016;3:CD005563.
15. Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. Anesthesiology. 2012;116:658—64.
16. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 2013;119:507—15.
17. Claassen J, Thijssen D, Panerai RB, et al. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021;101. 1487-59.
18. Sforza M, Bianchini E, Alivernini D, et al. The impact of cerebral vasomotor reactivity on cerebrovascular diseases and cognitive impairment. J Neural Transm (Vienna). 2022;129:1321—30.
19. Eames PJ, Blake MJ, Panerai RB, et al. Cerebral autoregulation indices are unimpaired by hypertension in middle aged and older people. Am J Hypertens. 2003;16:746—53.
20. Immink RV, van den Born BJ, van Montfrans GA, et al. Impaired cerebral autoregulation in patients with malignant hypertension. Circulation. 2004;110:2241—5.
21. Investigators N. Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): a prospective cohort study. Lancet. 2019;394:1022—9.
22. Sun LY, Chung AM, Farkouh ME, et al. Defining an Intraoperative Hypotension Threshold in Association with Stroke in Cardiac Surgery. Anesthesiology. 2018;129:440—7.
23. van Zuylen ML, Gribnau A, Admiraal M, et al. The role of intraoperative hypotension on the development of postoperative cognitive dysfunction: a systematic review. J Clin Anesth. 2021;72:110310.
24. Wachtendorf LJ, Azimaraghi O, Santer P, et al. Association Between Intraoperative Arterial Hypotension and Postoperative Delirium After Noncardiac Surgery: A Retrospective Multicenter Cohort Study. Anesth Analg. 2022;134:822—33.
25. Wang Y, Yu H, Qiao H, et al. Risk Factors and Incidence of Postoperative Delirium in Patients Undergoing Laryngectomy. Otolaryngol Head Neck Surg. 2019;161:807—13.
26. Zhang SS, Xia QM, Zheng RS, et al. Laryngeal cancer incidence and mortality in China, 2010. J Cancer Res Ther. 2015;11(Suppl 2):C143—8.
27. Liu W, Wang Y, Chen K, et al. Effect of Intraoperative Dexmedetomidine Use on Postoperative Delirium in the Elderly After Laryngectomy: A Randomized Controlled Clinical Trial. Drug Des Devel Ther. 2023;17:2933—41.
28. Folstein MF, Folstein SE, McHugh PR. Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189—98.
29. Parikh SS, Chung F. Postoperative delirium in the elderly. Anesth Analg. 1995;80:1223—32.
30. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941—8.
31. Aldemir M, Ozen S, Kara IH, et al. Predisposing factors for delirium in the surgical intensive care unit. Crit Care. 2001;5:265—70.
32. Polito A, Eischwald F, Maho A L, et al. Pattern of brain injury in the acute setting of human septic shock. Crit Care. 2013;17:R204.
33. Wijdicks EF, Stevens M. The role of hypotension in septic encephalopathy following surgical procedures. Arch Neurol. 1992;49:653—6.
34. Duan W, Zhou CM, Yang JJ, et al. A long duration of intraoperative hypotension is associated with postoperative delirium occurrence following thoracic and orthopedic surgery in elderly. J Clin Anesth. 2023;88:111125.

35. Guichard JL, Desai RV, Ahmed MI, et al. Isolated diastolic hypotension and incident heart failure in older adults. Hypertension. 2011;58:895—901.
36. Nguyen DN, Huyghens L, Parra J, et al. Hypotension and a positive fluid balance are associated with delirium in patients with shock. PLoS One. 2018;13:e0200495.
37. Chaix I, Manquat E, Liu N, et al. Impact of hypotension on cerebral perfusion during general anesthesia induction: A prospective observational study in adults. Acta Anaesthesiol Scand. 2020;64:592—601.
38. Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced Cerebral Perfusion Pressure during Lung Transplant Surgery Is Associated with Risk, Duration, and Severity of Postoperative Delirium. Ann Am Thorac Soc. 2016;13:180—7.
39. Wesselink EM, Kappen TH, van Klei WA, et al. Intraoperative hypotension and delirium after on-pump cardiac surgery. Br J Anaesth. 2015;115:427—33.
40. Wijnberge M, Geerts BF, Hol L, et al. Effect of a Machine Learning-Derived Early Warning System for Intraoperative Hypotension vs Standard Care on Depth and Duration of Intraoperative Hypotension During Elective Noncardiac Surgery: The HYPE Randomized Clinical Trial. JAMA. 2020;323:1052—60.
41. Jones RN, Yang FM, Zhang Y, et al. Does educational attainment contribute to risk for delirium? A potential role for cognitive reserve. J Gerontol A Biol Sci Med Sci. 2006;61:1307—11.
42. Oliveira FR, Oliveira VH, Oliveira ÍM, et al. Hypertension, mitral valve disease, atrial fibrillation and low education level predict delirium and worst outcome after cardiac surgery in older adults. BMC Anesthesiol. 2018;18:15.
43. Hughes D, Judge C, Murphy R, et al. Association of Blood Pressure Lowering with Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-analysis. JAMA. 2020;323:1934—44.
44. Feinkohl I, Lachmann G, Brockhaus WR, et al. Association of obesity, diabetes and hypertension with cognitive impairment in older age. Clin Epidemiol. 2018;10:853—62.
45. Lachmann G, Feinkohl I, Borchers F, et al. Diabetes, but Not Hypertension and Obesity, Is Associated with Postoperative Cognitive Dysfunction. Dement Geriatr Cogn Disord. 2018;46:193—206.

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ORIGINAL INVESTIGATION

Prevalence and predictors of confirmed infection in patients receiving empiric antimicrobials in the intensive care unit: a retrospective cohort study

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Abstract

Background: Infection diagnosis in Intensive Care Units (ICUs) is a challenge given the spectrum of conditions that present with systemic inflammation, the illness severity and the delay and imprecision of existing diagnostic methods. We hence sought to analyze the prevalence and predictors of confirmed infection after empirical antimicrobials during ICU stay.

Methods: retrospective cohort of prospectively collected ICU data in an academic tertiary hospital in São Paulo, Brazil. We included all adult patients given a new empirical antimicrobial during their ICU stay. We excluded patients using prophylactic or microbiologically guided antimicrobials. Primary outcome was infection status, defined as confirmed, probable, possible, or discarded. In a multivariable analysis, we explored variables associated with confirmed infection.

Results: After screening 1721 patients admitted to the ICU from November 2017 to November 2022, we identified 398 new antimicrobial prescriptions in 341 patients. After exclusions, 243 antimicrobial prescriptions for 206 patients were included. Infection was classified as confirmed in 61 (25.1%) prescriptions, probable in 39 (16.0%), possible in 103 (42.4%), and discarded in 40 (16.5%). The only factor associated with infection was deltaSOFA (OR = 1.18, 95% CI 1.02 to 1.36, p = 0.022).

Conclusion: Suspected infection in the ICU is frequently not confirmed. Clinicians should be aware of the need to avoid premature closure and revise diagnosis after microbiological results. Development and implementation of new tools for faster infection diagnosis and guiding of antimicrobial prescription should be a research priority.

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Introduction

Sepsis and septic shock are common causes of Intensive Care Unit (ICU) admission and account for approximately 11 million deaths worldwide annually.[1] During hospitalization, clinical worsening often raises the suspicion of a new infectious event or a previous infection not properly treated, and due to morbidity and mortality, rapid diagnosis and treatment have become indicative of good medical practice, resulting in a probable reduction in the number of deaths.[2-4]

However, diagnosis of infection in ICUs is a major challenge for the intensive care physician, given the wide spectrum of conditions that present as a systemic inflammatory response, the severity of the patients and the delay and imprecision of existing diagnostic methods.[5] In this context, antimicrobials are administered to approximately 70% of individuals cared for in intensive care units, but approximately half of these prescriptions may be unnecessary.[6,7]

Both undertreatment and unnecessary antimicrobial prescriptions are associated with worse outcomes in patients with suspected sepsis.[8] Excessive use of antimicrobials has been associated with significant increases in the occurrence of multidrug resistant microorganisms beyond the creation of new drugs. In addition, health services are burdened due to the costs of new drugs as well as due to side effects of the therapy.[6]

Previous research in emergency departments or with recently admitted ICU patients has shown that a sizable proportion of patients initially treated with antimicrobials ultimately have no infection or only possible infection.[9,10] However, there are scarce data in the literature regarding prevalence of confirmed infection among patients admitted for other reasons in the ICU that developed signs or symptoms of infection, and received empirical antimicrobials during ICU stay. Considering the complex course of critical illness, with several confounders that may be sepsis mimics, results of previous studies may not apply to these patients. To fulfill this gap in the literature we sought to analyze, in a cohort of critically ill patients, the prevalence of confirmed infection after empirical antimicrobial prescription during ICU stay.

Methods

Study design and ethics

This is a retrospective cohort study taking advantage of a prospectively collected ICU database, reported in accordance with STROBE guidance.[11] We followed all the recommendations of the Helsinki Declaration. The Research Ethics Committee approved the study protocol (number 6.122.265), and informed consent was waived.

Setting

The study was conducted at a mixed/medical ICU of an academic tertiary hospital in São Paulo, Brazil. This ICU currently has 8 beds, however, the number of beds fluctuated from five to 12 during the study period depending on funding for staffing.

In this ICU there is a well-established antimicrobial stewardship program focused on appropriate antimicrobial use. In short, whenever a patient's condition worsens and there is suspicion of infection, there is a great effort to identify the infectious source (through laboratory tests, images, and cultures), as well as to identify diagnostic alternatives. If the patient is stable and without shock, antimicrobials are withheld, and the patient is observed until infection is confirmed or another cause for clinical worsening is identified. In case of deterioration or shock, empirical antimicrobials are started with the narrowest possible coverage (according to site of suspected infection and multidrug resistance pathogen risk factors). When an antimicrobial is started, its maintenance is re-evaluated daily and, facing early clinical improvement (< 12-hours), or late non-improvement (> 72-hours), mainly if cultures were negative and images non-suggestive of infection, the antimicrobial is withdrawn.[2,12]

Participants

We assessed the ICU database, which is hosted in Microsoft Access® by the senior consultants in charge of the ICU, and includes baseline and daily data of all patients, used for administrative and benchmarking purposes. Through this database, we identified all adult patients (> 18-years) from November 2017 to November 2022 who started a new antimicrobial during their ICU stay. We excluded patients receiving antimicrobials in the first 48 hours after ICU admission to keep only patients with suspected nosocomial infections acquired in ICU.

The patients identified in screening had their electronic medical records reviewed to extract relevant data and ascertain infection status. The first step was to confirm that the new antimicrobial was started empirically. We excluded cases with prophylactic antimicrobials or prescription guided by microbiological confirmation (in which cultures were collected and antimicrobials were initially withheld, being started only after infection had been confirmed by cultures). We also excluded patients erroneously identified in the database (patients identified in initial screening that did not receive a new antimicrobial or that were already using an antimicrobial). Given that a patient could receive empirical antimicrobials several times during ICU stay, patients could be included more than once.

Data collection and extraction

We extracted age, gender, SAPS3 (Simplified Acute Physiology Score III, measured in ICU admission), comorbidities (summarized by a modified Charlson comorbidity index, excluding age), immunosuppression status (high dose glucocorticoids, immunosuppressants, AIDS or chemotherapy), admission source (ward, emergency, operation room), antimicrobial use upon admission, initial diagnosis and status performance prior to ICU admission (assessed through ECOG

scale — Eastern Cooperative Oncology Group performance status scale).[13-15]

Moreover, electronic medical records were reviewed and data regarding new antimicrobial start were collected, including time after hospital and ICU admission, Sequential Organ Failure Assessment (SOFA)[16] on antimicrobial start day and variation in the previous 24h (deltaSOFA), mechanical ventilation and vasoactive drug use, vital signs, total leucocyte count, blood glucose levels on antimicrobial start day, and modified Systemic Inflammatory Response Syndrome (SIRS) criterion (see below). We also checked which antimicrobial was prescribed and results of microbiologic tests performed between 2 days before and 2 days after antimicrobial start. Finally, ICU and hospital length-of-stay, and mortality were registered.

Outcomes and predictors

Our primary outcome was the proportion of confirmed infections among critically ill patients that received a new empirical antimicrobial during ICU stay. Since there is no practical gold standard for definition of confirmed infection in ICU, we adopted the definitions used by Hooper et al.,[9] with some modifications to fit our database. Infections were defined as confirmed, probable, possible, or discarded (more details below).

Furthermore, we explored clinical and laboratory variables associated with confirmed infection. Predictors of infection were selected *a priori* based on clinical relevance for higher probability of infection, and included: SOFA on antimicrobial day, deltaSOFA, modified Charlson Comorbidity index, prior antimicrobial use upon admission, immunosuppression, mechanical ventilation or vasoactive drugs on antimicrobial day, maximum heart rate on antimicrobial day, maximum and minimum temperature on antimicrobial day, maximum blood glucose on antimicrobial day, and leucocytes on antimicrobial day.

Definitions

We defined infections as follows: Confirmed: positive cultures of sterile sites (e.g., blood, cerebrospinal fluid) with use of antimicrobials for more than 48 hours. In case of potential contaminants (e.g., coagulase negative Staphylococci) we required growth in more than one sample and indication in medical records that antimicrobials were used to treat the microorganism. Probable: Positive cultures of non-sterile or potentially non-sterile sites (e.g., urine, tracheal aspirates) with use of antimicrobials for more than 48 hours. Possible: Negative cultures, but with a high enough suspicion to keep a full course of antimicrobials (more than 48—72 hours) or death in less than 48 hours of antimicrobial start (without another clear cause than infection). Discarded: None of the above (negative cultures and antimicrobials withdrawn within 48 hours). We considered that in critically ill patients with suspected nosocomial infection, a very short course of antimicrobials would potentially be insufficient for adequate treatment, so that improvement in this context was correlated with a very low probability of infection.

Both probable and possible categories were designed to reflect cases in which suspicion of infection was high enough to justify a full course of antimicrobials (or scenarios in which an infection could not be ruled out), but the main difference between them was that in cases classified as probable there was microbiological evidence of infection, while this was absent in cases assigned as possible infection. Moreover, the probable infection category addresses the intrinsic uncertainty regarding cultures of non-sterile sites (in which distinction between infection and colonization may be difficult). In possible infections, culture results were all negative, however patients were considered to have an infection, even with negative microbiological investigations, considering that in some scenarios culture yield is low. Culture harvesting was performed in accordance with the attending physicians whenever any infection was suspected. In general, at least two blood culture samples were obtained for all patients, with additional samples (e.g., tracheal aspirate, urine, catheter tip) collected according to the suspected source of infection.

To define the presence of SIRS we did not have the vital signs at the exact moment of decision to start an antimicrobial, but only the lower and the higher values in the day. To account for daily variation, we chose to modify some cut-offs to improve specificity. SIRS was defined by at least 2 of 4: leucocytes higher than 12,000 mm^3 or lower than 4,000 mm^3, temperature higher than 38°C or lower than 35°C, respiratory rate higher than 25 breaths per minute and heart rate higher than 110 beats per minute. In case of more than one leucocyte count on the same day we registered the highest.

After investigating the infectious status, we recorded the source of infection based on clinical and laboratory data. In case of an inconclusive source of infection, we assumed the source considered most likely as noted in the medical records. If it was still not possible to define the source, we considered it as unknown. Finally, to describe the microorganisms isolated in culture samples we used the same definition used in the Eurobact-2 cohort.[17]

Statistical analysis

Categorical variables were expressed as numbers and percentages. We checked normality in the distribution of variables using histograms and the Shapiro test. As most variables had a non-normal distribution, quantitative variables are presented as median and 25—75th percentile. Differences between categorical variables were assessed with chi-square or Fisher exact test, while the Kruskal-Wallis test was used for continuous variables. For the descriptive analysis of the primary outcome, binomial 95% Confidence Intervals are presented. Missing data were present in a small number of cases, so a complete case analysis was undertaken.

Given the observational nature of this study, we did not perform an *a priori* sample size estimation. We chose the five-year period for logistical reasons (related to the implementation of specific software for medical records in the hospital).

We assessed variables associated with higher odds of confirmed infection (predictors). In this analysis, infection status was dichotomized as present (confirmed, probable and possible) or absent (discarded). Considering that some patients were included in the study more than once (e.g., if a patient received 2 distinct empirical antimicrobial treatments along ICU stay, they could be included twice in the

study), our observations in those cases were not independent, as some variables (e.g., age, immunosuppression, SAPSIII) were intrinsic to each patient. To overcome this, we used a hierarchical multiple logistic regression model accounting for clustering within patients in this analysis (by adding a term "patient id" in the model). Predictors were defined *a priori* (see above) and selection of variables to be retained in the final model was done with a backward stepwise elimination process using Akaike Information Criterion.

We planned some sensitivity analysis including: 1) Patients assigned "possible infection" because of death within 48h were considered "discarded"; 2) Infection status dichotomized as present (confirmed and probable — culture proven infection) and absent (possible and discarded); 3) An alternative model with numeric predictors dichotomized according to clinical practice (maximum heart rate higher than 120 beats per minute, maximum temperature higher than 38°C, minimum temperature lower than 35°C, leucocytes count higher than 15.000 cell.mm^{-3} and maximum glucose higher than 180 mg.dL^{-1}). We also performed a *post-hoc* exploratory analysis to verify the number of patients with discarded infection who received another empiric antimicrobial course during their ICU stay and how many of them had infection confirmed thereafter. This *post-hoc* analysis was done to increase the certainty regarding absence of infection and ensure that classification done in the main analysis was accurate. All analyses were performed using *R* free source software[18] version 4.1.3 and a p-value < 0.05 was considered for hypothesis testing.

Results

Descriptive analysis

Between November 2017 and November 2022, a total of 1721 patients were admitted to the ICU study and included in the administrative database. After screening, we identified 398 new antimicrobial prescriptions in 341 patients. After exclusions, 243 antimicrobial prescriptions for 206 patients were included. A detailed description is presented in Figure 1. The general characteristics of the study patients are presented in Table 1. In summary, the cohort had high disease severity (median SAPS3 = 68.5) at ICU admission and at empirical antimicrobial initiation (median SOFA = 8), with high ICU (38%) and hospital (56%) mortality and long ICU and hospital stay. Most admissions came from the emergency department due to respiratory and neurological diseases.

Infection was classified as confirmed in 61 (25.1%, 95% CI 20%—31%) prescriptions, probable in 39 (16.0%, 95% CI 12%—21%), possible in 103 (42.4%, 95% CI 36%—49%), and discarded in 40 (16.5%, 95% CI 12%—22%). Table 2

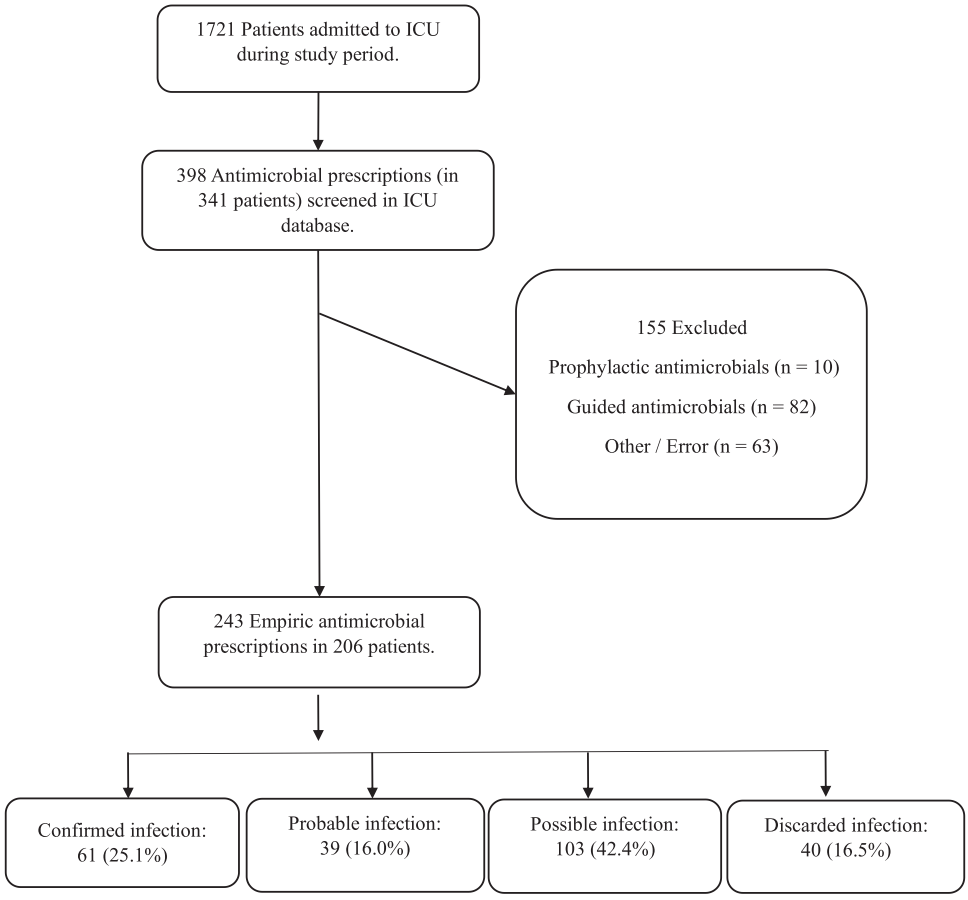

Figure 1 Study flowchart.

Table 1 General characteristics of included patients.

Variables	N (%) or Median [P25, P75]
Age, years	55.00 [42.25, 66.75]
Sex: Male	121 (58.7)
SAPS3	68.50 [57.00, 80.75]
Modified Charlson	1.00 [0.00, 3.00]
Comorbidities	
Hypertension	108 (52.4)
Uncomplicated diabetes	17 (8.3)
Complicated diabetes	40 (19.4)
Heart failure	15 (7.3)
COPD	7 (3.4)
Solid tumor	10 (4.9)
Cirrhosis	4 (1.9)
ECOG	77 (37.4)
0	53 (25.7)
1	36 (17.5)
2	36 (17.5)
3	77 (37.4)
4	4 (1.9)
Antimicrobial use on ICU admission	149 (72.3)
Admission cause	
Respiratory	110 (53.4)
Neurologic	36 (17.5)
Sepsis	18 (8.7)
Trauma	10 (4.9)
Gastrointestinal	8 (3.9)
Post-surgery	8 (3.9)
Cardiovascular	6 (2.9)
Other	10 (4.9)
Admission source	
Emergency department	74 (35.9)
Other ICU	65 (31.6)
Ward	33 (16.0)
Operation room	33 (16.0)
Other	1 (0.5)
Immunosuppression	42 (20.4)
ICU length of stay	17.00 [10.00, 25.00]
Hospital length of stay	26.00 [16.00, 52.75]
ICU mortality	79 (38.3)
Hospital mortality	116 (56.3)

SAPS3, Simplified Acute Physiology Score III; COPD, Chronic Obstructive Pulmonary disease; ECOG, Eastern Cooperative Oncology Group performance status scale; ICU, Intensive Care Unit.

describes clinical variables present on the day of empirical antimicrobial prescription in the overall cohort and stratified by infection status. Data regarding antimicrobials used and pathogen characteristics are detailed in Table 3. There were no missing data regarding the primary outcome or patient characteristics. Regarding vital signs on the day the antimicrobial was initiated, we had very few missing values (one or two for most vital signs, except for SpO2 measurements, with eight missing values). Using a complete case analysis, these missing data led to the exclusion of only four antimicrobial prescriptions from the main model (which was run with 239 new antimicrobial prescriptions).

Association between predictors and infection

From the twelve predictors initially considered by clinical relevance, four variables were retained in the final model: deltaSOFA, antimicrobial use on ICU admission, mechanical ventilation, and total leucocyte count (Table 4). The only predictor with statistically significant association with infection was deltaSOFA (OR = 1.18, 95% CI 1.02 to 1.36, p = 0.0224).

Sensitivity analyses

If prescriptions in which patients died within 48h and cultures results were negative were assigned as discarded infection, 62 (25.5%) patients were considered to have absent infection. When the final model was run using this modified criterion, the association between deltaSOFA and infection was no longer present (Table S1). In another sensitivity analysis we considered that infection was present only if cultures were positive (confirmed and probable — culture proven infection). The hierarchical logistic regression model using this definition retained three variables: antimicrobial on admission, immunosuppression, and maximum serum glucose on antimicrobial day. Only immunosuppression had a statistically significant association with culture proven infection (Table S2). An alternative model with predictors dichotomized according to clinical practice is presented in Table S3.

In a *post-hoc* exploratory analysis we assessed the number of patients with discarded infection that received another empirical antimicrobial course during ICU stay. From 40 prescriptions classified as discarded, ten patients were prescribed another empirical antimicrobial after a median of 6 days after discarded infection (mean of 7.3 days). Among these ten patients, six were classified as possible, one as probable, and three as confirmed.

Discussion

Main findings

In this cohort of critically ill patients who received a new antimicrobial prescription for a suspected nosocomial infection, we observed that in 16.5% of the events an infectious condition was discarded and in more than 40% it was only possible (antimicrobials were maintained, despite negative cultures). Several predictors commonly used in clinical practice (e.g., leucocytes count, fever) failed to discriminate between events of infection present or discarded and the only predictor with a statistically significant association to infection was variation of SOFA score in the 24 hours before antimicrobial initiation.

Relationship with the literature

There are few reports evaluating the incidence of nosocomial infections in patients with empirical antimicrobial use. Our results were similar to a previous observational study that evaluated a cohort of patients admitted to ICU with suspected infection and found that 43% of them had an infection status categorized as discarded or possible.[10] Another more recent cohort including only patients treated in emergency department with suspected sepsis found lower

Table 2 Clinical variables on the day of empiric antimicrobial prescription, stratified by infection status.

Variable	Overall	Confirmed	Probable	Possible	Discarded
Number of prescriptions	243	61	39	103	40
Time after hospital admission, days	12.0 [8.0, 20.5]	13.0 [9.0, 22.0]	11.0 [7.0, 18.0]	12.0 [7.0, 21.0]	11.0 [7.7, 16.0]
Time after ICU admission, days	9.0 [6.0, 15.0]	10.0 [7.0, 15.0]	7.0 [4.5, 13.0]	8.0 [5.0, 14.5]	9.5 [6.0, 13.5]
SOFA score	8.0 [4.0, 13.0]	8.0 [3.0, 14.0]	9.0 [5.0, 13.0]	9.0 [5.0, 13.0]	7.0 [4.0, 11.0]
DeltaSOFA	1.0 [0.0, 4.0]	1.0 [0.0, 4.0]	1.0 [0.0, 3.0]	1.0 [0.0, 4.0]	0.0 [0.0, 2.2]
Mechanical ventilation, n (%)	155 (63.8)	38 (62.3)	30 (76.9)	61 (59.2)	26 (65.0)
Vasopressors, n (%)	105 (43.2)	28 (45.9)	19 (48.7)	45 (43.7)	13 (32.5)
Maximum heart rate, beats per minute	118.0 [104.0, 133.0]	121.0 [105.0, 135.0]	118.0 [107.0, 131.0]	115.5 [103.2, 130.7]	121.0 [99.5, 136.0]
Maximum temperature, °C	37.5 [37.0, 37.9]	37.4 [37.0, 37.8]	37.5 [37.1, 37.8]	37.5 [36.9, 37.9]	37.6 [36.9, 38.0]
Minimum temperature, °C	35.7 [35.1, 36.2]	35.6 [35.1, 36.1]	35.9 [35.5, 36.2]	35.6 [35.0, 36.1]	35.8 [35.2, 36.3]
Minimum oxygen saturation, %	86.0 [84.0, 90.0]	86.0 [82.5, 90.0]	86.0 [83.0, 90.0]	86.0 [85.0, 90.0]	88.0 [84.0, 91.0]
Total leucocytes count, cells.mm^{-3}	18020 [11597.5, 25735.0]	17760 [11310.0, 24670.0]	20850 [15135.0, 26990.0]	18850 [12350.0, 25915.0]	14310 [10747.5, 21702.5]
Maximum blood glucose, mg.dL^{-1}	156.0 [123.0, 220.0]	170.0 [124.7, 234.5]	166.0 [123.5, 261.5]	156.5 [124.2, 197.7]	148.0 [126.0,201.0]
Modified SIRS criteria, n (%)	199 (81.9)	49 (80.3)	33 (84.6)	83 (80.6)	34 (85.0)

ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment; deltaSOFA, Variation in SOFA score in the previous 24h before antimicrobial start; SIRS, Systemic Inflammatory Response Syndrome.

Table 3 Antimicrobials used and pathogen characteristics.

Variable	n (%)
Empiric antimicrobials used[a]	
Vancomycin	147 (60.5)
Levofloxacin	70 (28.8)
Piperacillin + Tazobactam	62 (25.5)
Ciprofloxacin	25 (10.3)
Metronidazole	13 (5.3)
Ceftriaxone	12 (4.9)
Polymyxins	10 (4.1)
Clindamycin	5 (2.0)
Ampicillin	4 (1.6)
Ceftazidime	4 (1.6)
Amikacin	3 (1.2)
Fluconazole	3 (1.2)
Meropenem	2 (0.8)
Sulfamethoxazole + Trimethoprim	2 (0.8)
Other	7 (2.8)
Empiric broad spectrum antimicrobials	170 (69.9)
Infection source	
Respiratory	112 (46.1)
Abdominal	23 (9.5)
BSI	21 (8.6)
Skin / Soft tissue	13 (5.3)
Urinary	8 (3.3)
CNS	7 (2.9)
Endocarditis	1 (0.4)
Unknown	18 (7.4)
None (Infection discarded)	40 (16.5)
Isolated pathogens	171
Gram positive bacteria	82 (48.0)
Staphylococcus aureus / MRSA	46 / 18
Staphylococcus coagulase negative[b] */ MRSE*	21 / 12
Enterococcus spp. / VRE	8 / 0
Other gram positives	7
Gram negative bacteria	80 (46.8)
Pseudomonas spp. / DTR	28 / 1
Klebsiella pneumoniae / DTR	13 / 4
Enterobacter spp. / DTR	8 / 0
E. coli / DTR	6 / 0
Acinetobacter spp. / DTR	4 / 3
Other gram negatives / DTR	21 / 4
Fungi	7 (4.1)
Candida albicans	3
Candida non-albicans spp.	4
Strict Anaerobic bacteria	2 (1.2)

[a] Each prescription could include more than one antimicrobial, so total antimicrobial count is higher than the number of prescription events.

[b] Most coagulase negative staphylococci were considered contaminants.

BSI, Bloodstream Infection; CNS, Central Nervous System; MRSA, Methicillin Resistant Staphylococcus Aureus; MRSE, Coagulase negative Staphylococcus Resistant to Methicillin; VRE, Vancomycin Resistant Enterococcus; DTR, Difficult to Treat Resistance. No pan-drug resistant bacteria were isolated.

incidences, with 9.5% of patients with infection discarded and 9.7% with only a possible infection.[9] Nevertheless, our findings reflect an already restrictive antimicrobial

Table 4 Variables associated with infection (confirmed, probable or possible).

Variables	Odds-Ratio	95% CI	p-value
DeltaSOFA	1.18	1.02 to 1.36	0.0224
ATB use upon ICU admission	1.69	0.79 to 3.57	0.170
Mechanical ventilation	0.56	0.25 to 1.26	0.162
Leucocytes (cells.mm^{-3}/1000)	1.04	0.99 to 1.08	0.0587

CI, Confidence Interval; deltaSOFA, Variation in SOFA score in the previous 24h before antimicrobial start; ATB, Antimicrobial.

prescription culture, in which empiric antimicrobials were started only in cases of shock or very high suspicion of infection. Possibly, false positive rates would be higher in other scenarios where a more liberal antimicrobial prescription policy is present.

Our criteria for defining infection were different from previous trials, which may explain some of the differences in our results. We relied on culture results and time on antimicrobials to define the presence of infection, and although this approach has some limitations, it made our infection status classification process more objective, reducing the risk of measurement bias. Furthermore, objective inclusion and exclusion criteria allowed patient selection before data collection began, reducing the risk of selection bias.

We aimed to evaluate predictors of confirmed infection by a hierarchical logistic regression model. While needed to overcome the clustering of observations between repeated patients, this model had some limitations, including a low number of patients, some imprecision in the estimates and possible non-linear relationships between outcomes and predictors. Despite these limitations, some observations caught our attention: 1) Common markers of infection used in clinical practice (temperature, leucocyte count, heart rate) were not able to discriminate between events of confirmed or discarded infection, reflecting low specificity in a population of critically ill patients with high disease severity and often multiple organ dysfunction; 2) In the main model, deltaSOFA was able to predict infection, but this was no longer true in sensitivity analysis (when we considered only patients with culture proven infection or used a different definition for possible infection assigning patients who died within 48 hours of antimicrobial prescription with negative cultures as discarded). In this scenario, deltaSOFA was possibly a marker of more severe disease (which led to maintenance of antimicrobials) and not a marker of infection itself.

This is not surprising, as the reasons for prescribing or continuing empirical antimicrobials may be related to perceived risks of withholding this therapy, constraints by local protocols or regulatory norms and concerns regarding ethical and legal consequences of undertreatment, and also are influenced by the degree of uncertainty and difficulty in reaching a correct diagnosis.[19] In a previous report, antimicrobials were given even when conviction of an infection was low and it was confirmed only in 54% of the cases.[20] Despite advocacy of most sepsis guidelines for early and aggressive antimicrobial treatment, evidence supporting this strategy is controversial.[3,7,21-23] Both undertreatment and unnecessary antimicrobial use may be harmful and expose patients and health systems to undesirable consequences.[8,24]

Implications for practice and research

Efforts should be made to increase precision and certainty regarding infection diagnosis in critically ill patients. This is a major challenge as there is no gold standard for infection diagnosis, clinical course and presentation is highly heterogenous, and several other conditions present in ICU may be sepsis mimics (e.g., atelectasis, chemical phlebitis, neurologic diseases, pulmonary embolism, drug reactions). Microbiologic cultures are the current reference for infection diagnosis; however, their results take time, may be influenced by sampling techniques and sensitivity may be low depending on the suspected source of infection. Moreover, factors like contamination and previous antimicrobial use may further affect culture accuracy.[5]

In this study, we found that change in SOFA score in the 24 hours prior to antimicrobial initiation was the only independent predictor of confirmed infection. Despite some concerns, this finding is novel and should undergo prospective validation in future trials before widespread use.

New tools such as Multiplex Polymerase Chain Reaction and chromogenetics are not widely available but may have a role in the future, allowing faster identification of an infectious agent and guiding of antimicrobial therapy.[25,26] Machine learning algorithms able to use real time data to predict sepsis and septic shock in critically ill patients have emerged recently with promising results, however those methods still require prospective validation and standardization.[27-29] Further research and implementation of more precise diagnostic tools for infection in critically ill patients should be a priority. Meanwhile, clinicians should be aware that a considerable number of patients exposed to empirical antimicrobials may not have an infection. Daily reassessment of infection status, including clinical course and microbiologic findings, is critical to identify situations in which antimicrobials can be safely withdrawn.

Limitations

This study has several limitations. It was conducted in a single ICU in an academic hospital of a middle-income country, with selective antimicrobial practices, which reduces generalizability of the findings to other ICU settings. However, our results were in line with previous publications performed in North America and Europe. We excluded patients with suspected nosocomial infections acquired outside the ICU (e.g., in the ward) that led to admission to the intensive care unit and focused only on the patients that worsened during their ICU stay. We did not have granular data before ICU admission and it is important to consider that nosocomial infections acquired in the ICU may have a different clinical course

compared to infections developed in the ward/emergency room, which would have introduced heterogeneity to our results. Confirmed and probable infections were defined based on positive cultures, which may be biased by several factors such as prior antibiotic use, presence of fastidious organisms, localized infections, presence of low-level bacteremia, or specific infections where culture yield is low. Moreover, we did not analyze detailed clinical or laboratory data to adjudicate the presence of infection. Our criterion for discarded infection was arbitrary and based on withdrawing of antimicrobials within 48 hours with clinical improvement. We believe that a very short antimicrobial course would be inappropriate for most ICU-acquired infections (specially in our cohort with high disease severity), but for some patients this short course could have been sufficient for improvement. The sample size was not large, but we had at least 50 events/non-events to perform analysis, enough for inclusion of at least 4 or 5 strong predictors. Nevertheless, only deltaSOFA was statistically associated with the primary outcome.

It is worth mentioning that the COVID-19 pandemic occurred in the middle of our study period and around 40% of included patients were admitted to the ICU with infection by SARS-CoV-2 as the primary diagnosis. Although our practices regarding antibiotic prescriptions did not change during the pandemic, we had more patients under mechanical ventilation, deep sedation and paralysis, which may expose patients to nosocomial infections. Furthermore, COVID-19 can cause inflammatory signs even weeks after the onset of infection, which may also raise suspicion of a secondary infection. Altogether, there is a chance that our results may have been influenced by the COVID-19 pandemic.

Conclusions

Our data suggest that even in an ICU with a restrictive antimicrobial program, in a noteworthy part of antimicrobial prescriptions an infection was not confirmed. Clinicians should be aware of the need to avoid premature closure and revise diagnosis after microbiological results. Development and implementation of new tools for faster infection diagnosis and guiding of antimicrobial prescription should be a research priority.

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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.2024.844567.

References

1. World Health Organization. WHO. https://www.who.int/news-room/fact-sheets/detail/sepsis. 2020. Sepsis.
2. da Fonseca Pestana Ribeiro JM, Park M. Less empiric broad-spectrum antibiotics is more in the ICU. Intensive Care Med. 2020;46:783–6.
3. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov 2;47 (11):1181–247.
4. Westphal GA, Pereira AB, Fachin SM, et al. Characteristics and outcomes of patients with community-acquired and hospital-acquired sepsis. Rev Bras Ter Intensiva. 2019;31(1).
5. Denny KJ, De Wale J, Laupland KB, Harris PNA, Lipman J. When not to start antibiotics: avoiding antibiotic overuse in the intensive care unit. Clinical Microbiology and Infection. 2020 Jan;26 (1):35–40.
6. Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect Dis. 2018 Dec;18 (12):e368–78.
7. Kalil AC, Timsit JF. Less is more: critically ill status is not a carte blanche for unlimited antibiotic use. Intensive Care Med. 2020;46:2075–8.
8. Rhee C, Kadri SS, Dekker JP, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated with Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Netw Open. 2020;3:e202899.
9. Hooper GA, Klippel CJ, McLean SR, et al. Concordance Between Initial Presumptive and Final Adjudicated Diagnoses of Infection Among Patients Meeting Sepsis-3 Criteria in the Emergency Department. Clinical Infectious Diseases. 2023;76:2047–55.
10. Klein Klouwenberg PMC, Cremer OL, van Vught LA, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care. 2015;19:319.
11. von Elm E, DG Altman, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007 Oct 20;335 (7624):806–8.
12. Giovanetti JN, Libera PH Della, da Silva MLF, et al. Eleven years impact of a stepwise educational program on healthcare associated infections and antibiotics consumption in an intensive care unit of a tertiary hospital in Brazil. J Crit Care. 2024;82:154783.
13. Moreno RP, Metnitz PGH, Almeida E, et al. SAPS 3 – From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med. 2005;31:1345–55.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40:373–83.
15. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.
16. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–10.
17. Tabah A, Buetti N, Staiquly Q, et al. Epidemiology and outcomes of hospital-acquired bloodstream infections in intensive care unit patients: the EUROBACT-2 international cohort study. Intensive Care Med. 2023;49:178–90.
18. R Foundation for Statistical Computing. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, Vienna, Austria; 2022. p. 2022.

19. Pandolfo AM, Horne R, Jani Y, et al. Understanding decisions about antibiotic prescribing in ICU: an application of the Necessity Concerns Framework. BMJ Qual Saf. 2022;31:199—210.
20. Levin PD, Idrees S, Sprung CL, et al. Antimicrobial use in the ICU: Indications and accuracy – an observational trial. J Hosp Med. 2012;7:672—8.
21. Klompas M, Rhee C, Singer M. The Importance of Shifting Sepsis Quality Measures from Processes to Outcomes. JAMA. 2023;329:535.
22. Kalil AC, Gilbert DN, Winslow DL, Masur H, Klompas M. Infectious Diseases Society of America (IDSA) POSITION STATEMENT: Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines. Clinical Infectious Diseases. 2018;66:1631—5.
23. Bassi E, Tomazini BM, Carneiro BV, et al. Impact of withholding early antibiotic therapy in nonseptic surgical patients with suspected nosocomial infection: a retrospective cohort analysis. Braz J Anesthesiol. 2024;74:744431.
24. Le Terrier C, Vinetti M, Bonjean P, et al. Impact of a restrictive antibiotic policy on the acquisition of extended-spectrum beta-lactamase-producing Enterobacteriaceae in an endemic region: a before-and-after, propensity-matched cohort study in a Caribbean intensive care unit. Crit Care. 2021;25:261.
25. Razazi K, Delamaire F, Fihman V, Boujelben MA, Mongardon N, Gendreau S, et al. Potential of Multiplex Polymerase Chain Reaction Performed on Protected Telescope Catheter Samples for Early Adaptation of Antimicrobial Therapy in ARDS Patients. J Clin Med. 2022;11:4366.
26. Mokrani D, Chommeloux J, Pineton de Chambrun M, Hékimian G, Luyt CE. Antibiotic stewardship in the ICU: time to shift into overdrive. Ann Intensive Care. 2023;13:39.
27. Wang D, Li J, Sun Y, et al. A Machine Learning Model for Accurate Prediction of Sepsis in ICU Patients. Front Public Health. 2021;9:754348.
28. Mao Q, Jay M, Hoffman JL, et al. Multicentre validation of a sepsis prediction algorithm using only vital sign data in the emergency department, general ward and ICU. BMJ Open. 2018;8: e017833.
29. Kim T, Tae Y, Yeo HJ, et al. Development and Validation of Deep-Learning-Based Sepsis and Septic Shock Early Prediction System (DeepSEPS) Using Real-World ICU Data. J Clin Med. 2023;12:7156.

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ORIGINAL INVESTIGATION

Oscillatory ventilation enhances oxygenation and reduces inflammation in an animal model of acute respiratory distress syndrome: an experimental study

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KEYWORDS
Acute respiratory distress syndrome;
Mechanical ventilation;
Positive-pressure respiration

Abstract

Background: This study aims to compare the use of variable mechanical ventilation with conventional mechanical ventilation in a porcine model of ARDS induced by oleic acid.

Methods: The animals were divided into two groups (n = 6), Conventional Ventilation (CO) and variable ventilation with Bi-Oscillatory PEEP (BiPEEP). ARDS was induced using intravenous oleic acid (0.15 $mL.kg^{-1}$). After, the animals were evaluated during 180 minutes and, measurements were taken every 30 minutes until the end of the observation period. The animals in the CO group were then ventilated under controlled pressure (Tidal Volume target at 6 $mL.kg^{-1}$) and 5 cm H_2O PEEP. Variable ventilation was characterized by the oscillation of PEEP from 5 to 10 cm H_2O every 4 respiratory cycles. Ventilatory, hemodynamic parameters, oxidative stress, antioxidant enzymes, Interleukin 8 (IL8) and 17-a (IL17a) were evaluated. Histological samples were collected from the upper and the lower portion of the left lungs and analyzed separately.

Results: BiPEEP improved lung compliance and PaO_2 in comparison to control ($p < 0.05$). The levels of oxidative stress and antioxidant enzymes showed no significant difference. There was no difference in IL17a between groups. IL8 was significantly increased in the lung base of CO group in relation to BiPEEP group and it was reduced in the apex of BiPEEP group in comparsion to CO group. The BiPEEP group showed less changes in histopathological patterns.

The work was performed at Hospital de Clinicas de Porto Alegre — HCPA.

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Conclusion: Variable ventilation with bi-oscillatory level of PEEP demonstrated a potential ventilatory strategy for lung protection in an experimental model of ARDS.
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Introduction

Acute Respiratory Distress Syndrome (ARDS) is characterized by acute hypoxemia (PaO_2/FiO_2 < 300 mmHg) and the presence of bilateral infiltrates on chest X-Ray, not explained by the presence of left atrial hypertension, and may be associated with severe hypoxemia.[1]

In the literature, there is great diversity regarding how to ventilate patients with ARDS, but the most used approaches are based on either the ARDS Network or the Open Lung Approach (OLA).[2,3] However, if there is a down adjustment of the values of Positive end Expiratory Pressure (PEEP), this may result in alveolar derecruitment, and similarly high levels of PEEP may be associated with stress and over-distension of the pulmonary parenchyma.[4]

Different ventilatory alternatives have been proposed in patients with ARDS to protect the lungs, improve oxygenation and eventually reach better outcomes.[5,6] Nonetheless, most of these ventilatory strategies differ from spontaneous ventilation because they have a pre-stablished ventilatory pattern, characterized by the maintenance of the respiratory rate, tidal volume and a fixed pressure ventilation.[7] In this setting, variable ventilation has been suggested to improve lung function in experimental models of ARDS and could be a very interesting and effective way to ventilate injured lungs.[8] Different approaches with satisfactory results have been proposed for the use of variable ventilation such as changes in respiratory rate, tidal volume and pressure support.[9-12] Therefore, in variable ventilation one of the ventilatory variables is not fixed or constant. Conventional mechanical ventilation is considered monotonous because the variables are predominantly fixed and constant. Unfortunately, during the pursuit for the ideal ventilatory strategy we face the dilemma between collapse and overdistention. One has to choose an adequate PEEP to prevent collapse during expiration, but at the same time, it has to be low enough to prevent overdistension of previously aerated lung regions. In this study we hypothesized that oscillatory PEEP (BiPEEP) in an experimental model of ARDS is capable of improving gas exchange and reducing inflammatory response when compared to monotonous ventilation.

Methods

The study complies with the regulations of the Brazilian Code of Practice for the care and use of animals for scientific purposes and was approved by the Animal Ethics Committee of the Hospital de Clínicas de Porto Alegre (Protocol 11-432). The present study was carried out in accordance with ARRIVE Guidelines (https://www.equator-network.org/reporting-guidelines/).

Preparation of animals, anesthesia and ventilation

In this study we used 12 male pigs (Large White), weighing on average (SD) 25 ± 13 kg in a protocol of lung injury induced by oleic acid. The allocation of animals to groups was carried out through the website www.randomization.com. The animals were divided into two groups (n = 6), ARDS group with monotonous ventilation (Control) and an oscillatory PEEP group (BiPEEP). Following intramuscular sedation (ketamine 10 $mg.kg^{-1}$ and midazolam 1 $mg.kg^{-1}$) anesthesia was maintained with propofol, morphine, and ketamine as previously described.[12]

The pigs were mechanically ventilated (Inter 7 Plus, Intermed Equipamentos Médicos Hospitalares Ltda, São Paulo, Brasil) via a size 8 mm ID (Internal Diameter) endotracheal tube using the following settings: pressure control, FiO_2 1.0, inspiration to expiration ratio = 1:2, target tidal volume 6 $mL.kg^{-1}$ with the initial respiratory rate adjusted to maintain an end tidal CO_2 tension of 35 to 45 mmHg. The ventilatory parameters were adjusted to maintain a plateau pressure limit of 35 cm H_2O. With the exception of PEEP, the ventilation settings were not changed during the entire protocol. The PEEP setting was 5 cm H_2O in the control group. In the oscillatory bi-level PEEP group, the animals were ventilated with the same ventilatory pattern with the exception of PEEP, which was automatically increased to 10 cm H_20 every 4 breaths.

ARDS injury

After a set of baseline measurements, ARDS was performed by injection of 0.15 $mL.Kg^{-1}$ oleic acid (Sigma-Aldrich®, Steinheim, Germany) in 15 mL of saline administered over 10 minutes through the proximal end of the pulmonary artery catheter[13] until a P/F ratio of 200 to 300 mmHg. Intravenous noradrenaline was used to maintain a MAP ≥ 70 mmHg during the infusion of oleic acid. Intravenous fluid administration was limited to 1 $mL.kg^{-1}.h^{-1}$, after an initial 500 mL over a 30-minute bolus of succinylated gelatin.

Experimental protocol

All 12 pigs received oleic acid. Analysis of respiratory mechanics, ventilatory parameters and arterial blood gases were performed after stabilization of the animals (post-induction). After, the animals were evaluated for 180 minutes and during this period measurements were made every 30 minutes until the end of the observation period. At the end of the experiment, the animals were sacrificed by exsanguination, and we collected tissue samples from the upper and lower portion of the left lungs.

Respiratory mechanics and lung volumes

For the evaluation of mechanical properties of the respiratory system and measures of airflow we used a flow transducer, located in the proximal portion of the endotracheal tube, the Monitor Graph Ventilation – Tracer 5® (Intermed Ltda – São Paulo, Brazil) on the computer which recorded

Pressure curves (P), flow (V ') and Volume (V) versus time (t); curve pressure × volume curve (compliance) and × flow volume curve, through specific software.

Arterial oxygen tension (PaO_2), oxygen saturation, and carbon dioxide tension were measured with a blood gas analyzer immediately after withdrawal (Rapidlab 1200, Siemens, Leverkusen, Germany). PaO_2 over fractional inspiratory oxygen concentration (P/F ratio) was calculated.

Hemodynamic parameters

Mean Arterial blood Pressure (MAP) was measured at the femoral artery. Throughout the study the animals remained in supine position. All hemodynamic pressures were zeroed at the mid axillary line at the level of the sternum and measured during end-expiration.

Oxidative stress — assessment of lipid peroxidation

The Thiobarbituric Acid Reactive Substances (TBARS) technique consists of heating the homogenate with thiobarbituric acid to produce a colored product that is subsequently measured at 535 nm using a spectrophotometer. The TBARS concentration was expressed in $nmoL.mg^{-1}$ of protein.[14]

Antioxidant enzymes — determination of superoxide dismutase (SOD)

The technique used to measure SOD was based on the level of inhibition caused by the reaction of the enzyme with O^{-2}. The enzymatic activity was expressed in SOD/mg of protein units.

Interleukin analysis

After the samples were thawed, a 96-well plate was coated with monoclonal antibodies against IL-8 and IL-17a. The IL-8 and IL-17a concentrations in the homogenized lung samples were calculated based on the results of a standard curve.

Histological analysis

The lung tissue specimens were fixed in formalin and dehydrated, cleared, and embedded in paraffin. The specimens were cut into 5-μm serial sections and stained with hematoxylin-eosin. The same regions were sampled in all groups. A pathologist blinded to the experimental protocol and the region of sampling performed quantitative analysis by light microscopy. Each sample was examined under both low- and high-power fields. At least four sections were obtained from each block, and 20 fields were randomly selected and analyzed for each section. The severity of histological lesions was assessed using a histologic score[15] based on six parameters: intraalveolar edema, hyaline membrane formation, hemorrhage, recruitment of granulocytes into the air spaces, focal alveolar collapse or consolidation, and epithelial desquamation or necrosis of the airways or alveoli. Each parameter was evaluated semi quantitatively using the following scale: 0, absent; 1, mild; 2, moderate; and 3, prominent. In addition, the percentage of the involved area of each histological specimen was estimated (0- = -100%) to quantify the histological changes.[16]

Statistics

The sample size calculation with a confidence interval of 95% for the experimental groups was performed. Normal distributions of means tests were performed for statistical tests. The groups were compared using analysis of variance (ANOVA) followed by a post hoc Tukey test performed using SPSS® version 19.0 (Statistical Package for Social Science). In the case of unequal variances or an abnormal distribution, a nonparametric Kruskal Wallis test was performed, followed by Mann-Whitney *U*-tests for intergroup comparisons. The results are represented as means ± standard deviation. The statistical significance level was set at $p < 0.05$.

Results

There were no significant differences between the groups in terms of mechanical ventilation, with exception for airway resistance from Baseline to 30 minutes in the Control group (Table 1). The groups were not different at baseline, and similar changes in heart rate, PAP and end tidal CO_2 increased in both groups after OA infusion (Table 2).

There was a significant difference in arterial oxygen pressure (PaO_2) at baseline in the control group when compared to post-induction control. The same results were observed at baseline in the BiPEEP group when compared to post-induction BiPEEP ($p < 0.05$). The PaO_2 significantly dropped after induction and remained at low levels in both groups. The fall in PaO_2 was significantly greater in the control group (Fig. 1A).

The blood pressure of carbon dioxide ($PaCO_2$) was significantly lower at baseline in the control group when compared to post-induction control ($p < 0.05$). The same finding was observed in the BiPEEP group. In the control group at 90 ($p < 0.05$) and 120 ($p < 0.01$) minutes, $PaCO_2$ was significantly higher compared to the BiPEEP group. At times 90 ($p < 0.001$), 120 ($p < 0.01$), 150 and 180 minutes ($p < 0.05$) BiPEEP significantly reduced $PaCO_2$ values when compared to post-induction BiPEEP (Fig. 1B).

There were no significant differences between groups and lung regions as to the number of lipid peroxidation products (Fig. 2A). The activity of superoxide dismutase did not change significantly between both groups (Fig. 2B).

Interleukin-17a (IL-17a) showed no significant difference between the control and BiPEEP groups. There was a significant difference ($p < 0.01$) between the apex and the base of lung samples of each group (Fig. 3A). Interleukin-8 (Fig. 3B) demonstrated a significant increase in the samples of lung base from the control group when compared to the BiPEEP group ($p < 0.001$). The apex of the lung in the BiPEEP group presented a significant reduction in IL8 in comparison to control ($p < 0.01$). In both groups there was a significant difference in IL-8 concentration in the apex when compared to the base of the lungs ($p < 0.01$).

The histopathological analysis (Fig. 4) of the control group showed changes in lung morphology characterized by cellular infiltrates, thickening of the alveolar septae and atelectasis, which were attenuated in the BiPEEP group ($p < 0.05$), whereas both groups presented greater histological alterations in the lung bases ($p < 0.01$). However, the BiPEEP group presented less morphological alterations then the control group ($p < 0.05$).

Table 1 Comparison between groups in relation to ventilatory variables.

	Baseline		Post-induction		30 minutes		60 minutes		90 minutes		120 minutes		150 minutes		180 minutes	
	Control	BIPEEP	Control	BIPEEP	Control	BIPEEP	Control	BIPEEP	Control	BIPEEP	Control	BIPEEP	Control	BIPEEP	Control	BIPEEP
Ppico	17 (15–17.2)	17 (17–18.2)	24 (19.2–24.7)	17 (17–23.7)	25 (19.2–27)	21 (19–25.5)	26 (19.2–27.5)	24 (20.7–30)	25 (19.2–27.7)	27 (23–31)	26 (18.5–27.5)	23 (19.5–26)	26 (18–27.7)	24 (23–26)	26 (18.5–27.7)	25 (23–27.2)
Pplatô	15 (13.5–15.2)	17 (14–15.5)	20 (15.2–21.2)	14 (14–20)	22 (15.5–22)	16 (14–20.2)	21 (15.5–22.5)	20 (17.5–22.5)	22 (15.5–23)	21 (19–26.5)	22 (14.7–23)	22 (16.7–27.2)	22 (14.7–22.5	20(17.5–25)	22(14.7–22.5)	20 (19–24.2)
VACe	272 (231–399)	225 (212–373)	210 (188–254)	206 (185–258)	222 (205–227)	212 (184–256)	210 (185–238)	270 (194–403)	198 (155–214)	270 (191–416)	197 (157–221)	290 (184–471)	194 (184–223)	270 (190–483)	199 (192–231)	265 (195–481)
Resist	19.9±9.6	25.9±3.6	26.3±11	30.6±5.7	35.8±6.4	33.5±8	30.1±3.7	31.8±7.0	30.8±3.7	32.8±4.9	30.8±4.3	26.2±5.2	29.8±3.3	30.1±2.3	29.9±3.3	29.1±24
Cest	29.4±8.5	23.8±7.1	13.9±3.1	15.9±8.4	12.9±2.8	14.1±6.7	13.7±3.5	16.1+8.3	12.9±3.4	18.6±11.5	26±3.5	26.2±5.2	12.2±3.2	17.6±10.4	12.6±3.1	19.5±93
Cdin	25.3±4.5	24.3±6.3	10.9±3.1	11.4±4.8	9.8±2.1	10.8±5.1	10±1.9	11.5±5.1	10.2±2.8	14.3±9.2	10±2.9	14.2±9.3	9.7±2.5	14.7±8.1	9.8±2.4	15.8±86

Mechanical ventilation parameters: PPeak, Peak Pressure; Plateau, Plateau pressure; VT, Tidal Volume; Resist, Airway Resistance; Cest, Static Compliance; Cdin, Dynamic Compliance. Make the difference between Baseline Control Resist with 30-minutes Control Resist. Results were expressed in median and interquartile range our mean and standard deviation.

Table 2 Comparison between groups in relation to hemodynamic variables.

	Baseline		After induction		30 minutes		60 minutes		90 minutes		120 minutes		150 minutes		180 minutes	
	PEEP	BIPEEP	PEEP	BIPEEP	PEEP	BIPEEP	PEEP	BIPEEP	PEEP	BIPEEP	PEEP	BIPEEP	PEEP	BIPEEP	PEEP	BIPEEP
HR	79±18	83.2±20.3	92±21.9	99±31.4	95.6±21.3	88.6±18.3	88.6±18.3	103.6±34	87.8±18.4	108.4±30.3	95.6±21.1	111±34.9	91.6± 13	108.6± 35.1	103±5.8	103.8±22.4
PAM	105.2±20.9	86.8±5.2	93.2±16.8	99±5.6	87.6±12.2	98±8.9	92.2±11.5	92.4±12.3	93.7±8.7	94.6±10.5	87.5±12.4	95.6±14.5	95.2± 15.4	91.8± 8.5	91.5±19.3	93.7±8.5
PAP	29.4±10.9	25.6±4.1	41±11.3	40±7.8	33±10.8	35±9.7	35±10.8	33.2±12.2	39.8±12.4	33±15.4	35.8±12.2	36.6±14.6	35.8± 10.2	35± 15.5	35.8±10.5	36.5±14.6
PCP	17.2±8.3	13.2±2.3	15±5.3	15.2±4.6	14.5±2.3	13.6±3	15±2.6	14±1.2	15±2.9	13.8±1.3	15±2.5	11.2±2.9	11.3± 9.8	11.4± 2.2	15±2.6	11.4±2.2
$ETCO_2$	37±10.3	38.2±9.6	47±4.7	52.4±12.3	52.2±4.8	51.3±13.1	48±7.4	50.7±10.3	51.8± 5.9	52.1±9.6	49.8±4.9	51.9±7.4	51.6± 5.8	49.8+9.8	52.2±5.6	51.1±7.8

HR, Heart Rate; MAP, Mean Arterial Pressure; PAP, Pulmonary Arterial Pressure; PCP, Pulmonary Capillary Pressure.

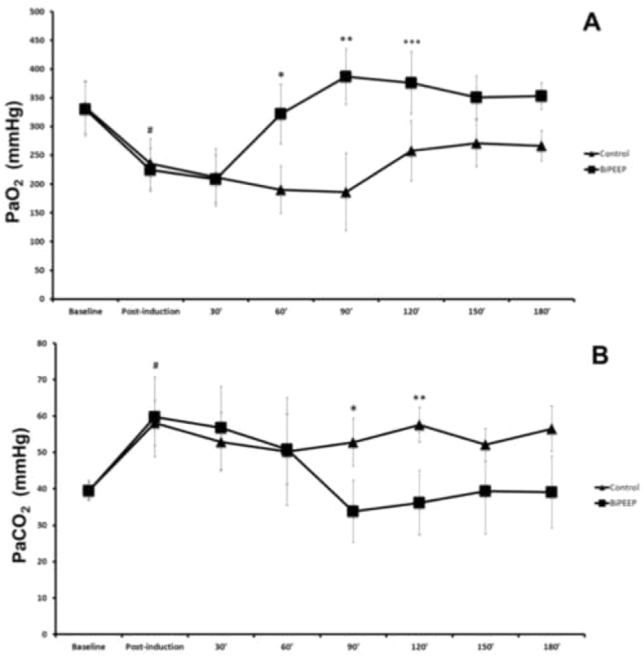

Figure 1 Arterial pressure of Oxigen (PaO_2) in Blood gas analyses (A). Demonstrate significantly difference between Baseline groups with Post-induction groups (# $p < 0.05$), 60' Control with 60' BiPEEP (* $p < 0.001$), 90' Control with 90' BiPEEP (** $p < 0.001$) and 90' Control with 90' BiPEEP (*** $p < 0.01$). Arterial pressure of Dioxide Carbon ($PaCO_2$) in Blood gas analyses (B). Make the difference between Baseline groups with Post-induction groups (# $p < 0.05$), 90' Control with 90' BiPEEP (* $p < 0.05$) and 120' Control with 120' BiPEEP (** $p < 0.01$). Six animals per group.

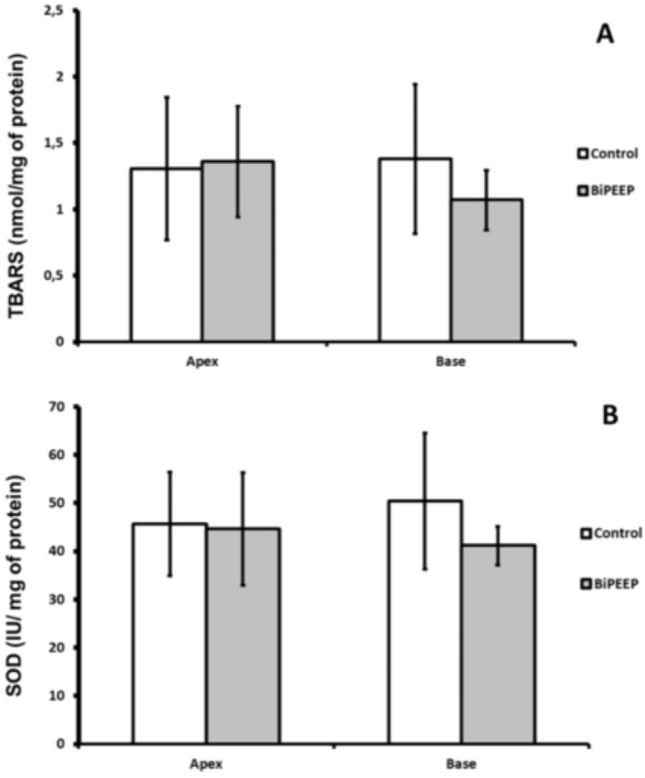

Figure 2 Oxidative Stress and antioxidant enzymes. There was not significant difference between groups at the quantity of lipid peroxidation products (A). There was no difference shown in the SOD activity among the groups (B). Six animals per group.

Discussion

When comparing monotonous ventilation with BiPEEP, the main findings of the study were: 1) A ventilatory strategy with two levels of PEEP resulted in improved gas exchange; 2) The oscillating PEEP showed reduced inflammatory response assessed by IL8; 3) Less structural histological abnormalities when using two levels of PEEP. This study, comparing the two levels of PEEP with conventional ventilation, is the first report in the literature using this ventilatory strategy in an experimental model of ARDS induced by oleic acid.

Variable mechanical Ventilation (VV) attempts to incorporate the physiological basis of spontaneous ventilation during MV and is defined as a ventilatory mode characterized by the oscillation of one or more respiratory parameters. It aims to mimic the variability observed in physiological ventilation and the natural breathing pattern, which changes from cycle to cycle. Several experimental studies reported the beneficial effects of distinct variable ventilation strategies on lung function using different models of lung injury and healthy lungs. Variable ventilation seems to be a viable strategy for improving gas exchange and respiratory mechanics and preventing lung injury associated with mechanical ventilation. However, further clinical studies are necessary to assess the potential of variable ventilation strategies for the clinical improvement of patients undergoing mechanical ventilation.[17]

In this study, the ARDS induced by oleic acid resulted in the reduction of the PaO_2/FiO_2 ratio in both groups, as reported by Schuster.[18] Variable mechanical Ventilation (VV) has been evaluated in experimental studies showing beneficial effects in respiratory mechanics, gas exchange and pulmonary function in animal models with or without lung injury.[17] However, there are only three clinical studies that have evaluated this approach, and the objectives as well as the outcomes are different in each of these studies.[19–21]

When analyzing the respiratory mechanic parameters, we observed a significant increase in airway resistance at 30 minutes after induction in the control group, and no change in the BiPEEP group. Several studies have demonstrated improvement in respiratory mechanics in experimental models of ARDS using VV. A possible explanation may be the use of different changes in PEEP levels during ventilation.[17] Boker et al.[22] compared conventional ventilation to VV during 5 hours in a porcine model of ARDS, with VT and RR as non-fixed variables, and demonstrated improvement in respiratory mechanics, gas exchange and reduction of the shunt fraction. This finding may be associated with the VT variability used by the authors, which was generated randomly, thus reaching the critical pressure of alveolar opening, culminating in the opening of non-ventilated lung regions. We demonstrated the presence of hemodynamic changes (HR, PAP and $ETCO_2$) only after induction with AO, and this finding was evident in a similar way described by Boker et al.,[22] who demonstrated a significant increase in

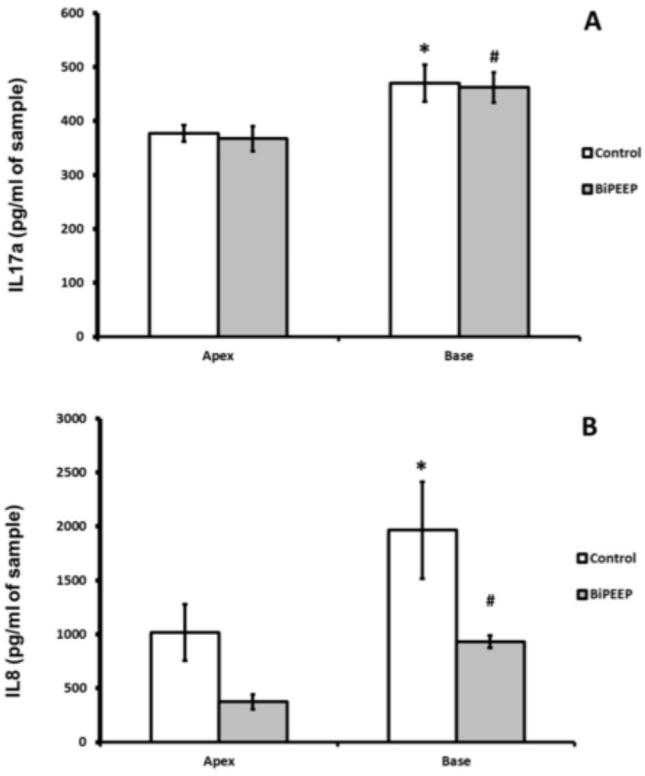

Figure 3 The Interleukin 17a (IL17a) expression (A) demonstrates a significantly difference between apex and base of each group (* $p < 0.01$ and # $p < 0.01$). Interleukin 8 (IL8) expression (B) increased in the both groups between apex in relation to the base ($p < 0.01$). The difference was observed to the Control base in relation to BiPEEP base (* $p < 0.001$) and apex intergroups (# $p < 0.01$). Six animals per group.

hemodynamic variables immediately after induction of lung injury, remaining at high levels during the experiment.

We demonstrated that ventilation using two levels of PEEP improves oxygenation as well as reduces $PaCO_2$. These findings corroborate with several experimental studies in ARDS that demonstrated improvement in gas exchange with VV.[11,22–28] The beneficial effects of variable mechanical ventilation reported in this study are similar to those previously described by Lefevre et al. and Mutch et al. However, in these studies, the respiratory rate was randomly varied at a given value and VT was adjusted to keep minute ventilation constant during oleic acid-induced lung injury or unilateral lung collapse model. In both cases, a single level of variability in mechanical ventilation was applied and resulted in a significant increase in lung compliance and PaO_2 in comparison with conventional ventilation. Nam et al. demonstrated that variable ventilation had no beneficial effects over conventional ventilation. This observation suggests that factors other than variability *per se* can be important for conferring beneficial effects on lung physiology in this setting.

A possible factor responsible for the effectiveness of BiPEEP regarding gas exchange is the effect related to alveolar recruitment and derecruitment. This is evident in the study by Ma et al. whose hypothesis was tested in a computational pulmonary model. The model also showed that recruitment/derecruitment dynamics contributed to a relative efficacy of variable ventilation, providing lung units open faster than close, since the critical opening or closing pressure threshold has been crossed. We conclude that the dynamics of recruitment and derecruitment in the lung may be important factors responsible for the benefits of VV compared to CV.

In our study, we observed a significant reduction in IL-8 levels in the BiPEEP group. Unfortunately, the same finding was

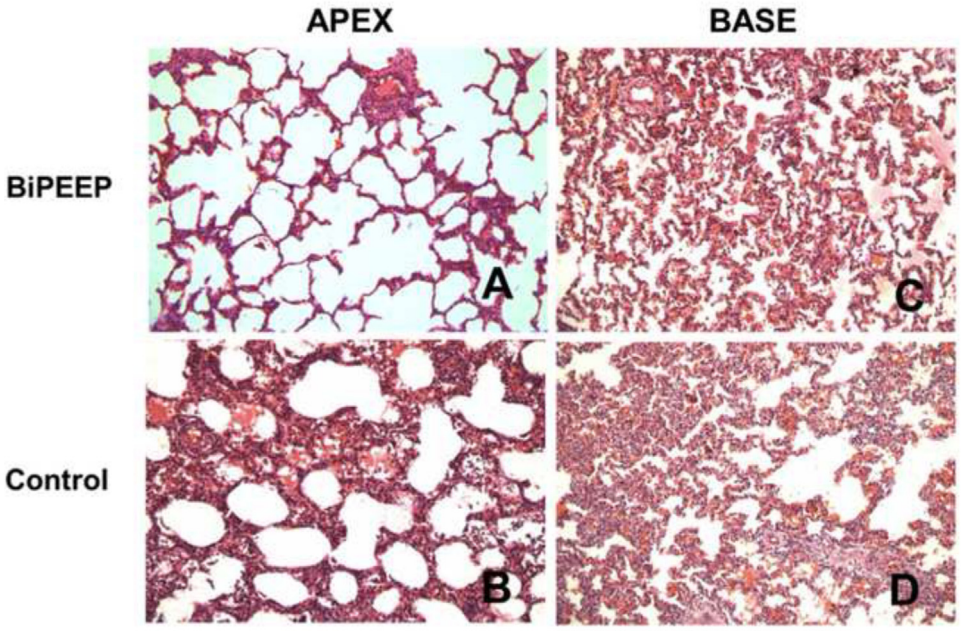

Figure 4 Histopathological analysis (magnification 200 ×) showed cellular infiltrates, thickening of the alveolar septae and atelectasis in the Control group. Both groups presented greater alteration in relation to the base ($p < 0.01$). However, the BiPEEP group presented less morphological alteration in relation to the control group ($p < 0.05$). (A) Apex BiPEEP group; (B) Apex Control group; (C) Base BiPEEP group; (D) Base Control group.

not observed regarding IL-17a. Aberrant IL-17 signaling can lead to an exacerbate inflammation, which can result in a harmful cellular damage. Acute Respiratory Distress Syndrome (ARDS) can develop following traumatic injury and/or a major inflammatory episode, such as sepsis, and is characterized by severe lung dysfunction, fluid accumulation (edema), hypoxia, and excessive neutrophil infiltration/activation.[22] Boker et al. observed that the concentration of interleukin-8 (IL-8) in the tracheal aspirate after 5 hours of VV was lower compared to conventional mechanical ventilation, although with similar findings in pulmonary edema.[22] Corroborating these observations, Arold et al.[11] demonstrated that, after 3 hours of VV in guinea pigs without lung injury, there was a reduction in the concentrations of IL-6 and Tumor Necrosis Factor alpha (TNF-α) in bronchoalveolar lavage.

Thammanomai et al.[4] investigated the physiological consequences of variable mechanical ventilation in a mouse model of ALI and showed to be superior to conventional ventilation in f lung mechanics and injury biomarkers. The possible explanation for the beneficial effects of VV lies in the use of a non-linear system, which is similar to the biological variability of the respiratory system. These models may increase VT based on the nonlinear characteristics of collapsed[8] and normal[9] alveoli. Thus, there are two main reasons for improvement of pulmonary function during VV, recruitment and stabilization of lung regions, enhancing gas exchange, and improvement in ventilation-perfusion ratio.

This study is the first in the use of PEEP as a variable to be modified during VV. However, it presents limitations such as the fact that it is an experimental study which cannot be directly transposed to clinical practice, where the use of variable PEEP could not titrated and this tool is not implemented in all commercially available ventilators. We decided to use PEEP 5 cm H_2O based on clinical observation, where in many centers this is the initial setting PEEP during ventilation, and we aimed to double this value in order to maintain aeration and avoid hyperdistension.

Our study showed that mechanical ventilation with bi-oscillatory levels (BiPEEP) improved ventilatory mechanics and gas exchange, in addition to reducing inflammatory markers and protecting the lungs, resulting in less histological damage.

Conflicts of interest

The remaining authors have disclosed that they do not have any conflicts of interest.

Acknowledgments

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References

1. Acute Respiratory Distress Syndrome: The Berlin Definition. The ARDS Definition Task Force. JAMA. 2012;307:2526–33.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
3. Lachmann B. Open up the lung and keep the lung open. Intensive Care Med. 1992;18:319–21.
4. Thammanomai A, Hueser LE, Majumdar A, Bartolak-Suki E, Suki B. Design of a new variable-ventilation method optimized for lung recruitment in mice. J Appl Physiol. 2008;104:1329–40.
5. Villagrá A, Ochagavía A, Vatua S, et al. Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. Am. J. Respir. Crit. Care Med. 2002;65:165–70.
6. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl Med. 1998;338:347–54.
7. Tobin MJ, Mador MJ, Guenther SM, Lodato RF, Sackner MA. Variability of resting respiratory drive and timing in healthy subjects. J Appl Physiol. 1988;65:309–17.
8. Suki B, Alencar AM, Sujeer MK, et al. Life-support system benefits from noise. Nature. 1998;393:127–8.
9. Gama de Abreu M, Spieth PM, Pelosi P, et al. Noisy pressure support ventilation: A pilot study on a new assisted ventilation mode in experimental lung injury. Crit Care Med. 2008;36:818–27.
10. Lefevre GR, Kowalski SE, Girling LC, Thiessen DB, Mutch AC. Improved arterial oxygenation after oleic acid lung injury in the pig using a computer-controlelled mechanical ventilation. Am J Respir Crit Care Med. 1996;154:1567–72.
11. Arold SP, Mora R, Lutchen KR, Ingenito EP, Suki B. Variable tidal volume ventilation improves lung mechanics and gas exchange in a rodent model of acute lung injury. Am J Respir Crit Care Med. 2002;165:366–71.
12. Regli A, Hockings LE, Musk GC, et al. Commonly applied positive end-expiratory pressures do not prevent functional residual capacity decline in the setting of intra- abdominal hypertension: a pig model. Crit Care. 2010;14:R128.
13. Julien M, Hoeffel JM, Flick MR. Oleic acid lung injury in sheep. J Appl Physiol. 1986;60:433–40.
14. Buege JA, Aust SD. Microsomal lipid peroxidation. Methods Enzymol. 1978;52:302–10.
15. Reiss LK, Uhlig U, Uhlig S. Models and mechanisms of acute lung injury caused by direct insults. Eur J Cell Biol. 2012;91:590–601.
16. Araujo LFL, Holand ARR, Paludo AO, Silva EF, Forgiarini LA, Forgiarini LF. Effect of the systemic administration of methylprednisolone on the lungs of brain-dead donor rats undergoing pulmonary transplantation. Clinics. 2014;69:128–33.
17. Fontela PC, Prestes RB, Forgiarini Jr LA, Friedman G. Variable mechanical ventilation. Rev Bras Ter Intensiva. 2017;29:77–86.
18. Schuster DP. ARDS: clinical lessons from the oleic acid model of acute lung injury. Am J Respir Crit Care Med. 1994;149:245–60.
19. Boker A, Haberman CJ, Girling L, et al. Variable ventilation improves perioperative lung function in patients undergoing abdominal aortic aneurysmectomy. Anesthesiology. 2004;100:608–16.
20. Spieth PM, Güldner A, Huhle R, et al. Short- term effects of noisy pressure support ventilation in patients with acute hypoxemic respiratory failure. Crit Care. 2013;17:R261.
21. Wang R, Chen J, Wu G. Variable lung protective mechanical ventilation decreases incidence of postoperative delirium and cognitive dysfunction during open abdominal surgery. Int J Clin Exp Med. 2015;8:21208–14.
22. Boker A, Graham MR, Walley KR, et al. Improved arterial oxygenation with biologically variable or fractal ventilation using low tidal volumes in a porcine model of acute respiratory distress syndrome. Am J Respir Crit Care Med. 2002;165:456–62.
23. Samary CS, Moraes L, Santos CL, et al. Lung Functional and Biologic Responses to Variable Ventilation in Experimental Pulmonary and Extrapulmonary Acute Respiratory Distress Syndrome. Crit Care Med. 2016;44:e553–62.
24. Lefevre GR, Kowalski SE, Girling LG, Thiessen DB, Mutch WA. Improved arterial oxygenation after oleic acid lung injury in the

pig using a computer-controlled mechanical ventilator. Am J Respir Crit Care Med. 1996;154:1567—72.
25. Mutch WA, Harms S, RuthGraham M, Kowalski SE, Girling LG, Lefevre GR. Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung. Am J Respir Crit Care Med. 2000;162:319—23.
26. Nam AJ, Brower RG, Fessler HE, Simon BA. Biologic variability in mechanical ventilation rate and tidal volume does not improve oxygenation or lung mechanics in canine oleic acid lung injury. Am J Respir Crit Care Med. 2000;161:1797—804.
27. Ma B, Suki B, Bates JH. Effects of recruitment/derecruitment dynamics on the efficacy of variable ventilation. J Appl Physiol. 2011;110:1319—26.
28. Arold SP, Suki B, Alencar AM, Lutchen KR, Ingenito EP. Variable ventilation induces endogenous surfactant release in normal guinea pigs. Am J Physiol Lung Cell Mol Physiol. 2003;285:L370—5.

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ORIGINAL INVESTIGATION

Efficacy of dexamethasone or clonidine as adjuvants in interscalene brachial plexus block for preventing rebound pain after shoulder surgery: a randomized clinical trial

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KEYWORDS
Brachial plexus block;
Clonidine;
Dexamethasone;
Pain

Abstract

Background: Rebound pain is believed to involve both nociceptive pain due to insufficient analgesia and hyperalgesia induced by regional anesthesia. Adjuvant's addition could prevent rebound pain. This study aimed to determine if the addition of dexamethasone or clonidine to local anesthetic when performing interscalene block could prevent rebound pain.

Methods: This was a multicenter, prospective, parallel grouping, randomized clinical trial conducted with patients receiving a single injection of bupivacaine 0.375% in interscalene block ultrasound guided and general anesthesia for shoulder surgery were randomly assigned to either no additives (control), clonidine (30 mcg), or dexamethasone (4 mg). The primary outcome was rebound pain, defined as sudden onset of pain, moderate to severe intensity (VAS ≥7) without improvement with oral medication, followed by VAS pain at rest, required rescue analgesia, the occurrence of adverse events or complications, and satisfaction survey assessments between groups. Rebound pain and pain at rest were assessed 2, 4, 6, 12, 24, and 48 hours after the procedure.

Results: The incidence of rebound pain was not statistically different between groups (p-value = 0.22), with an observed incidence of 41.2% (95% CI 25.9–57.9), 28.6% (95% CI

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16.7–43.3), and 23.3% (95% CI 12.6–37.6) in the control, dexamethasone, and clonidine groups, respectively. Additionally, there were no significant differences between the groups in time, from anesthetic blockade to first complaint of pain or the severity of postoperative pain.
Conclusion: The administration of dexamethasone or clonidine as perineural adjuncts to local anesthesia in single-injection interscalene blocks did not significantly reduce the incidence of rebound pain.
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Introduction

Interscalene block placed before surgery is widely used for pain management after shoulder procedures.[1] Peripheral nerve blocks can be associated with many advantages, including early mobilization, shorter hospital stay, adequate pain control, lower incidence of postoperative nausea and vomiting, increased patient satisfaction, and opioid sparing.[2,3]

However, studies have reported that patients who receive an interscalene block may perceive a more abrupt and disturbing pain trajectory once a block wears off suddenly, often at home, when compared to patients that had no block at all and were managed by conventional analgesics, including high-dose opioids.[4] This phenomenon, described as rebound pain, may entail a separate manifestation of hyperalgesia above and beyond the block simply 'wearing off', culminating in a sudden increase in postoperative pain (as measured by a Visual Analog Scale — VAS) at the end of the blockade duration (onset 12 to 48 hours after surgical intervention).

There is a paucity of current strategies to prevent or attenuate rebound pain. Studies have suggested perineural dexamethasone to prevent rebound pain,[5,6] but this practice may not be risk-free, as long-term safety has not been evaluated.[7] Prolonging the duration of interscalene blockade can improve patient recovery and comfort. This can be achieved with adjuvants, such as buprenorphine, clonidine, dexamethasone, dexmedetomidine, and magnesium[8-10] or carefully selected adjuvant combinations based on prior in vitro[11] and in vivo[12] studies.

Some authors suggest that the mechanism of rebound pain may involve sudden exposure to nociceptive pain due to insufficient preemptive multimodal analgesia, as well as hyperalgesia induced by regional anesthesia and surgical trauma.[13] Regional anesthesia/local anesthetic-induced hyperalgesia may mechanistically be mediated by heat fibers.[14] Younger age, female sex, higher preoperative pain score, and bone surgery have also been suggested as risk factors.[15,16]

It is hypothesized that the occurrence of rebound pain and the consumption of rescue analgesics during the postoperative period of shoulder surgeries can be reduced by combining adjuvants with local anesthetic solutions used to perform brachial plexus blocks.

Our primary aim is to assess whether the addition of adjuvant medications (dexamethasone or clonidine) to local anesthetics while performing a single-injection interscalene block prevents subsequent rebound pain in patients undergoing elective shoulder surgery.

Methods

Study design and participants

This was a multicenter, prospective, parallel grouping, randomized clinical trial. Adult patients (aged 18 years or older) with an American Society of Anesthesiologists (ASA) physical status classification of I or II, who underwent shoulder surgery at three tertiary Brazilian hospitals (Hospital Universitário Cajuru — Grupo Marista da Pontifícia Universidade Católica do Paraná, Curitiba, Paraná; Hospital de Urgências de Goiânia, Goiás; and Hospital São Domingos, São Luís, Maranhão) were eligible.

The non-inclusion criteria were the presence of neuropsychiatric diseases, cognitive impairment, or mental status changes; Monoamine Oxidase Inhibitor (MAOI) or anticonvulsant therapy; other fractures, injuries, or previous surgery on the same limb; paresis or paresthesia of the upper limb not attributable to the main diagnosis; and refusal to participate in the study.

Randomization

Patients were randomly assigned to undergo interscalene block with a single injection of 20 mL bupivacaine 0.375% without vasoconstrictor, without dexamethasone or clonidine (control group); with 30 mcg clonidine (clonidine group); or with 4 mg dexamethasone (dexamethasone group).

An online randomization service generated a random group allocation sequence (Sealed Envelope, London, England). Opaque-sealed envelopes were used to ensure concealment.

Patients, surgeons, anesthesiologists, nurses, data collectors, and outcome assessors were unaware of group allocation.

Outcomes

The primary outcome of this study was the incidence difference between groups of rebound pain, defined as sudden onset of pain, moderate to severe intensity (VAS $\geq$7) without improvement with oral medication at any of the evaluated moments.

The secondary outcomes were VAS pain at rest, required rescue analgesia, the occurrence of adverse events or complications, and satisfaction survey (would you undergo interscalene block again?: yes/no).

Anesthesia

Patients were monitored according to standard ASA recommendations. All received an ultrasound-guided, single-injection interscalene block administered by an experienced anesthesiologist. Patients were sedated with intravenous midazolam and fentanyl and titrated according to their level of anxiety (1—5 mg midazolam and 100 mcg fentanyl).

Each Patient was placed in the supine position with the head turned away from the side to be blocked. A high-frequency linear array transducer (6–13 MHz) was placed over the interscalene region to identify the brachial plexus in the short-axis view.

Following the brachial plexus block, anesthetic induction was performed with propofol 2 $mg.kg^{-1}$, fentanyl 4 $\mu g.kg^{-1}$, and cisatracurium 0.15 $mg.kg^{-1}$ (or atracurium 0.5 $mg.kg^{-1}$, or rocuronium 0.6 $mg.kg^{-1}$). Sevoflurane was used for maintenance, with the MAC adjusted to maintain the desired plane of anesthesia. Intraoperatively, 4 mg of ondansetron, 2g of dipyrone, 100 mg of ketoprofen, or 30 mg of ketorolac were administered.

Measurement and treatment of postoperative pain

In the first hours after surgery, in the anesthesia recovery room, the following supplemental postoperative analgesia protocol was used: intravenous morphine 4 mg every four hours if the pain was above 3 on the VAS.

Before discharge from anesthesia, still in the post-anesthesia recovery room, all patients were instructed on the use of oral medications during the postoperative period, which was started immediately after discharge from the anesthesia recovery room. The following supplemental postoperative analgesia protocol was used: dipyrone 1g, orally, every six hours, ketoprofen 150 mg, orally, every twelve hours and tramadol 50 mg, orally, every eight hours if pain was above 3 on the VAS.

Assessment of patient's characteristics and perioperative data

The characteristics and perioperative clinical data, including mean age, BMI (Body Mass Index), preoperative pain score, and duration of surgery, were collected from medical records or documented by a team member. Also, VAS, ranging from 0 (no pain) to 10 (worst possible pain) were collected on baseline (pre-block), 30 minutes after block and 30 minutes in PACU (Post-Anesthesia Care Unit).

Assessment of postoperative pain

Upon PACU discharge and 2, 4, 6, 12 and 24 after PACU discharge, VAS, ranging from 0 (no pain) to 10 (worst possible pain), was quantified and the cumulative dose of rescue opioids was registered and the patient was asked about rebound pain occurrence.

After 48 hours after PACU discharge, the patients were contacted by telephone and asked to report the use of postoperative medications prescribed, their VAS pain at rest, and the occurrence of rebound pain (and, if so, its duration) during the first 48 hours after the procedure. Patients were also asked whether they required rescue analgesia, whether any adverse events or complications occurred, and the satisfaction regarding the anesthetic technique, evaluated through a dichotomous question: "Would you undergo interscalene block again?" (yes/no).

Sample size

The sample size was calculated based on the results obtained by Woo et al.[6] To compare the mean difference (increase) in pain score before and after interscalene block resolution as assessed by an NRS, considering a mean (standard deviation) score of 4.5±2.4 in the dexamethasone group and 6.9±2.2 in the control group, the minimum sample size was estimated as 25 cases per group. Considering the incidence of rebound pain identified in the aforementioned study (82.9% in the control group and 37.1% in the dexamethasone group), the sample size for this purpose was 29 cases in each of the two groups. The effect size of dexamethasone in relation to control was extrapolated to clonidine; therefore, the same sample size was established for this third group, but as the present study carried out a comparison among three groups, the final sample size of each group was expanded by 15% to correct for this difference. Thus, the sample size was set at 34 cases in each group to allow for a three-group comparison, considering a two-tailed significance level of 5% and a statistical power of 95%. The sample was increased by 15% to account for possible losses.

Ethics statement

This study was approved by the Pontifical Catholic University of Paraná Institutional Review Board (CAAE: 33686720.8.1001.0020) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at https://ensaiosclinicos.gov.br/rg/ (RBR-48gkx3m), Principal investigator: Layana Vieira Nobre, Date of registration: February 25th, 2022). Patient enrollment occurred between March 1st, 2022 and December 31th, 2022.

Statistical analysis

The data were compared among the three groups (Control, Dexamethasone, and Clonidine) using IBM SPSS Version 26.0. The Kolmogorov-Smirnov test was used to verify the assumption of normality. Categorical variables were compared using the chi-squared test, and numerical variables were compared using One-way Analysis of Variance (ANOVA) (parametric data) or Kruskal-Wallis test (nonparametric data), with post hoc analysis using the Bonferroni test; p-values < 0.05 were taken to indicate statistical significance.

Results

A total of 119 patients were included for analysis: 34 in the control group, 42 in the dexamethasone group, and 43 in the clonidine group (Fig. 1).

Patients were similar in terms of sociodemographic data (Table 1).

The incidence of rebound pain was 41.2% (95% CI 25.9–57.9), 28.6% (95% CI 16.7–43.3), and 23.3% (95% CI

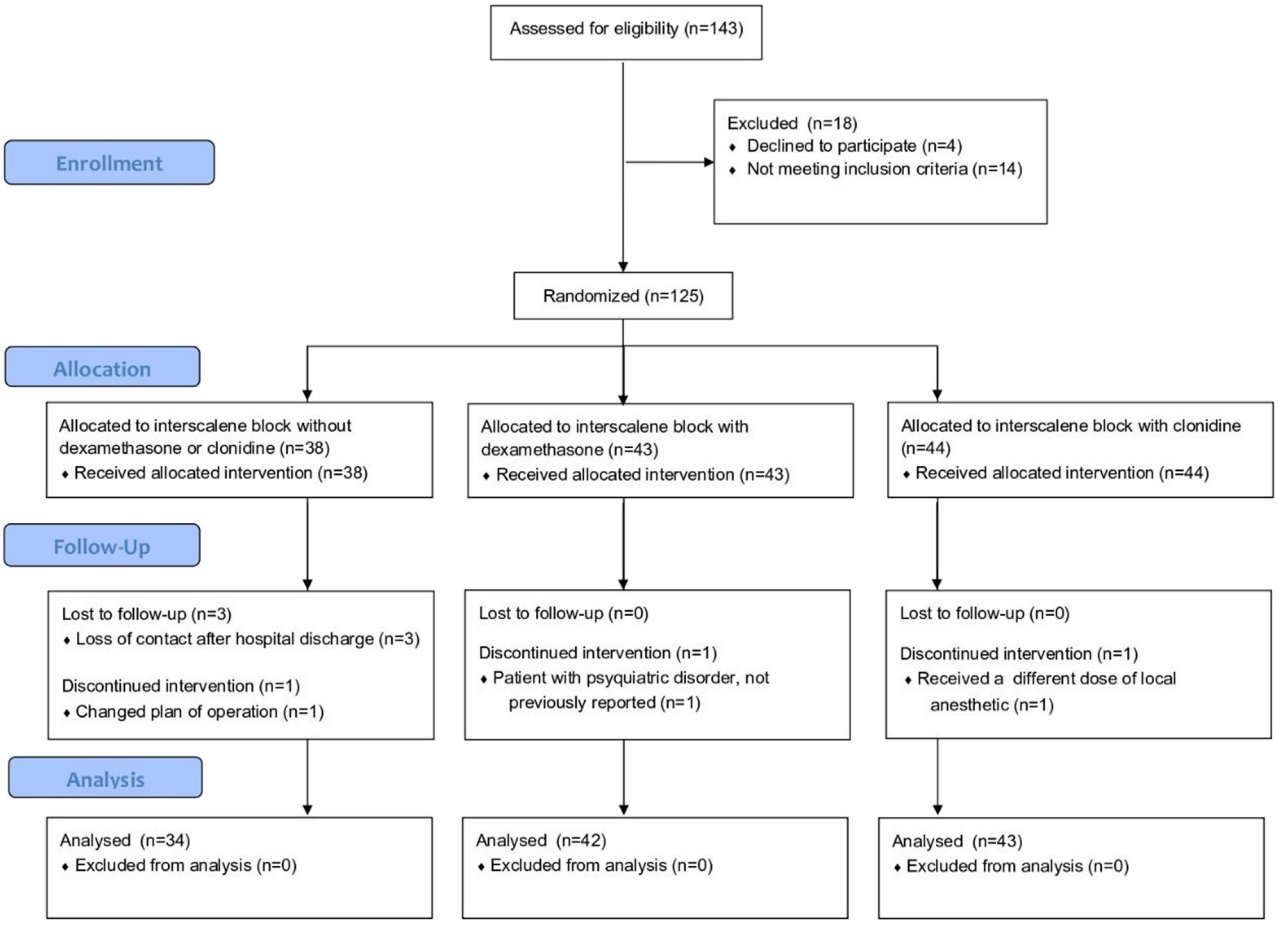

Figure 1 Consort flowchart.

Table 1 Sociodemographic data and surgical characteristics.

Variables	Control	Dexamethasone	Clonidine
Sample size, n	34	42	43
Sociodemography			
Age (years), Mean ± SD	50 ± 17	53 ± 15	51 ± 14
Gender, n (%)			
Male	22 (64.7)	28 (66.7)	28 (65.1)
Female	12 (35.3)	14 (33.3)	15 (34.9)
Anthropometry			
BMI ($Kg.m^{-2}$), Mean ± SD	27 ± 4	28.3 ± 4.3	28.2 ± 4.5
Pre-surgical data			
Comorbidities, n (%)	17 (50.0)	24 (57.1)	22 (51.2)
ASA classification, n (%)			
I	17 (50.0)	18 (42.9)	21 (48.8)
II	17 (50.0)	24 (57.1)	22 (51.2)
Diagnosis, n (%)			
Fracture	11 (32.4)	15 (36.6)	15 (34.9)
AD	6 (17.6)	6 (14.6)	8 (18.6)
Rotator cuff tear	13 (38.2)	14 (34.1)	17 (39.5)
Others	4 (11.8)	6 (14.6)	3 (7.0)
Type of surgery, n (%)			
Open repair	19 (55.9)	23 (54.8)	19 (44.2)
Arthroscopy	15 (44.1)	19 (45.2)	24 (55.8)

ASA, American Society of Anesthesiologist; AD, Acromioclavicular Dislocation.

Table 2 Outcomes of interest across the three groups.

Variables	Control	Dexamethasone	Clonidine	p-value
Sample size, n	34	42	43	
Duration of surgery (min), Mean ± SD	165 ± 73	159 ± 73	149 ± 58	0.55[a]
Rebound pain, n (%)[e]	14 (41.2)	12 (28.6)	10 (23.3)	0.26[b]
Duration of rebound pain (hours), Median ($Q_1 - Q_3$)	2 (1 − 3)	3 (2 − 4)	3 (2 − 5)	0.08[c]
Complaint of pain after block, n (%)	27 (79.4)	36 (85.7)	32 (74.4)	0.42[b]
First complaint (hours) of pain after block, Median ($Q_1 - Q_3$)	12 (8 − 24)	12 (6 − 25)	12 (8 − 22)	0.78[c]
Satisfied, n (%)	33 (97.1)	40 (97.6)	43 (100.0)	–[d]
Postoperative non-opioid analgesics, n (%)	24 (70.6)	32 (76.2)	37 (86.0)	0.10[b]
Metamizole/Ketoprofen	13 (38.2)	15 (35.7)	26 (60.5)	
Metamizole	7 (20.6)	15 (35.7)	10 (23.3)	
Ketoprofen	4 (11.8)	2 (4.8)	1 (2.3)	
Rescue medications, n (%)	18 (52.9)	25 (59.5)	18 (41.9)	0.25[b]
Intraoperative complications, n (%)	0 (0.0)	1 (2.4)	0 (0.0)	–[d]
Postoperative complications, n (%)	0 (0.0)	0 (0.0)	1 (2.3)	–[d]

[a] One-way analysis of variance (ANOVA) parametric test.
[b] Chi-square test.
[c] Kruskal-Wallis nonparametric test. Median (Min–Max): Median (Minimum–Maximum).
[d] Conditions not met for the Chi-Square test; Satisfied: would you undergo interscalene block again?: yes/no. Postoperative non-opioid analgesics: number of patients who required each non-opioid analgesic. Rescue medications: number of patients who required tramadol or morphine even though they were taking non-opioid medications. SD, Standard Deviation.
[e] Simultaneously Sudden-onset rebound pain, VAS ≥ 7 and without improvement with oral medication; Q_1: first quartile – Q_2: third quartile.

12.6–37.6) in the control, dexamethasone, and clonidine groups, respectively. There were no differences in the incidence of rebound pain among groups. There was no significant difference among the groups regarding the proportion of patients who reported pain after block resolution, and among the patients who reported such pain, there was no significant difference among the groups regarding the time (in hours) elapsed from block administration until the onset of pain. There was no significant difference among the groups regarding (i) The proportion of patients who received each analgesic regimen, (ii) The proportion of those who required rescue medication adverse events or complications, being observed in the clonidine group one case of bradycardia in the post-anesthesia recovery room (reversed with atropine) and another in the dexamethasone group, hypotension at the end of surgery (reversed with ephedrine), (iii) Or in the duration of rebound pain in hours (Table 2).

Comparison of the VAS-measured intensity of postoperative pain among the three groups also failed to show any significant difference at any time points evaluated and any significant difference in pain from baseline to each post-block time point (Table 3).

Discussion

In the present study, we did not find a reduction in rebound pain with either clonidine or dexamethasone. Our incidence of rebound pain (29.4%) was distinctly lower than previously reported in the literature (rates of up to 60%).[2,7] Furthermore, there was no statistically significant between-group difference in postoperative analgesia with the current sample size.

This possibly occurred due to the study's conservative criteria of rebound pain. The strict definition of rebound pain used in this study, which considers only episodes of moderate to severe intensity (VAS ≥7), was intentionally adopted to ensure that only the most significant and impactful cases for the patient experience were included in the analysis. This choice aimed to provide a more precise assessment of relevant rebound pain in the clinical context, avoiding dilution of the results with less severe episodes that may not reflect the true burden of postoperative pain. Also, the discrepancy could be attributed to the postoperative analgesic regimen (metamizole and ketoprofen) used in the protocol. Conversely, many studies on rebound pain have not incorporated perioperative systemic analgesia, and outpatients generally receive less analgesia before discharge.[3] Although there is no direct evidence that a consistent multimodal analgesic regimen reduces rebound pain, some studies recommend adequate perioperative analgesia associated with patient education on the duration of analgesia and on the use of oral analgesics before blockade resolution as a way to prevent rebound pain.[3,17-22] Therefore, the formulation of a perioperative care plan that includes around-the-clock analgesic coverage in the first 24 hours appears to be crucial.[19]

This discrepancy in the incidence of rebound pain with the literature can also be explained by the lack of consensus on how this phenomenon should be described or quantified. There is still no widely accepted method to quantify rebound pain, as researchers believe the exact timing of block resolution is challenging to pinpoint.[23] In this study, we defined rebound pain concerning pain intensity and ancillary criteria described in several previous studies.[2,12,16,24]

It is important to emphasize that "rebound pain" and "postoperative pain" are distinct phenomena that require clear definitions. Rebound pain refers to a sudden increase in pain intensity, often associated with the end of an analgesic blockade, whereas postoperative pain refers to pain that may occur during the recovery period, regardless of the

Table 3 Comparison of the three groups regarding pain outcomes scored at different time points (VAS) and the difference in pain from baseline to each post-block time point.

Outcome — Pain intensity (VAS)	Control	Dexamethasone	Clonidine	p-value[a]
Sample size, n	34	42	43	
Pain at rest, Median (Q_1 – Q_2)				
Baseline (pre-block)	6 (3 | 8)	5 (4 | 7)	5 (2 | 7)	0.37
30-minutes after block	0 (0 | 0)	0 (0 | 1)	0 (0 | 0)	0.31
30-minutes in PACU	0 (0 | 0)	0 (0 | 0)	0 (0 | 0)	0.64
upon discharge from PACU	0 (0 | 0)	0 (0 | 1)	0 (0 | 0)	0.51
2 hours after discharge from PACU	0 (0 | 0)	0 (0 | 1)	0 (0 | 1)	0.32
4 hours after discharge from PACU	0 (0 | 0)	0 (0 | 3)	0 (0 | 2)	0.48
6 hours after discharge from PACU	0 (0 | 2)	0 (0 | 3)	0 (0 | 2)	0.53
12 hours after discharge from PACU	2 (0 | 5)	2 (0 | 3)	1 (0 | 5)	0.69
24 hours after discharge from PACU	2 (0 | 4)	3 (0 | 4)	2 (0 | 4)	0.47
48 hours after discharge from PACU	2 (0 | 3)	2 (0 | 3)	2 (0 | 3)	0.62
Difference in pain in each moment compared to baseline (pre-block) Median (Q_1 – Q_2)				
30-minutes after blockade	-5 ([-8 | -3)	-4 (-7 | -3)	-4 (-7 | 0)	0.40
30-minutes in PACU	0 (0 | 0)	0 (0 | 0)	0 (0 | 0)	0.33
At discharge from PACU	0 (0 | 0)	0 (0 | 1)	0 (0 | 0)	0.46
2 hours after discharge from PACU	0 (0 | 0)	0 (0 | 0)	0 (0 | 0)	0.30
4 hours after discharge from PACU	0 (0 | 0)	0 (0 | 0)	0 (0 | 0)	0.13
6 hours after discharge from PACU	0 (0 | 0)	0 (0 | 0)	0 (0 | 0)	0.22
12 hours after discharge from PACU	0 (0 | 3)	0 (0 | 2)	0 (0 | 2)	0.27
24 hours after discharge from PACU	0 (|1 | 0)	0 (0 | 2)	0 (|2 | 1)	0.48
48 hours after discharge from PACU	0 (0 | 0)	0 (|1 | 0)	0 (|1 | 0)	0.98

PACU, Post-Anesthesia Care Unit; Q_1, First quartile; Q_2, Third quartile.
[a] Kruskal-Wallis nonparametric test.

anesthetic technique used. This distinction is crucial for the interpretation of results and clinical application since management strategies and expectations regarding each type of pain can differ substantially.

The combination of peripheral blockade with a local anesthetic and adjuvants is recommended by several authors.[16,20] In these studies, adjuvants were associated with reductions in the incidence of rebound pain and postoperative pain scores. However, in the present study, two separately studied single adjuvants, at least at the doses administered, did not significantly impact the incidence of rebound pain or postoperative pain. Other studies have also failed to find significant results, which shows a lack of consensus on a potential dose-effect relationship.[25-27] These discrepancies may be associated with the broad variation in doses used across different studies, as there is also no consensus on the optimal dose of adjuvants, and also by the volume and concentration of local anesthetics. In another study, neither intravenous nor perineural dexamethasone at a dose of 4 mg prolonged the duration of ulnar nerve blockade.[28] Moreover, another study demonstrated that only intravenous dexamethasone at a dose of 10 mg increased the duration of postoperative analgesia after sciatic nerve block compared to lower doses (2.5 mg or 5 mg) or no adjuvant. Furthermore, higher doses of perineural dexamethasone (4 mg vs. 2 mg) were associated with higher rebound pain scores.[28,29]

However, a meta-analysis with twenty-five studies showed significantly longer analgesic effects compared to the control group and, consequently, better postoperative pain scores with the use of perineural adjuvants (dexmedetomidine and dexamethasone).[10] As mentioned before, methodological differences in the definition of rebound pain may explain this divergence from the present study's findings. The type of local anesthetic, doses, and concentrations were also different from those used in our study, which may have further impacted results.

Further studies are needed to elucidate the optimal dose of dexamethasone and other adjuvants that will be beneficial in reducing and possibly preventing rebound pain.

Our study makes a significant contribution to the understanding of rebound pain. One of the main strengths of our work is introducing a new definition of rebound pain, which enriches the understanding of this phenomenon. Furthermore, unlike previous studies, a multicenter study was carried out, which increases the generalization of the results. Finally, a multimodal postoperative pain control protocol was developed to reproduce in future studies.

The present study had limitations. We administered only one dose of local anesthetic, dexamethasone, and clonidine, and lacked a parallel control between different doses; the optimal dose has yet to be determined and established in the literature. Therefore, we cannot state conclusively that the lack of positive results was due to the choice of anesthetic and adjuvants, as these variables can play a determining role in the results.

Furthermore, the dose/concentration of local anesthetic used in the study is likely hyperalgesic.[14] An idea for future studies, with the association of interscalene plexus block with general anesthesia, would be a lower concentration of local anesthetic such as 0.20%–0.25% and letting the adjuvants possibly show their effects.

Added to this, a lower percentage of rebound pain was observed in the groups evaluated concerning that predicted in the sample calculation. This may have occurred due to the innovative classification used and the postoperative analgesic regimen. Therefore, new clinical trials that can evaluate possible factors that interfere with the occurrence of rebound pain and its prevention methods are essential.

However, the limitations mentioned above, such as the low incidence of rebound pain in the sample, may have compromised the study's statistical power since the calculations were based on high prevalence. New studies with larger sample sizes, meta-analyses incorporating underpowered studies, or using this study as an a priori probability for Bayesian analysis in a new trial may be potential solutions to address this problem.

We conclude that, at the doses used herein, administration of dexamethasone or clonidine as perineural adjuncts to local anesthesia in single-injection interscalene block did not significantly reduce the incidence of rebound pain compared to local anesthesia alone in patients undergoing shoulder surgery. Furthermore, there was no statistically significant between-group difference in postoperative analgesia.

Clinical trial

This study was approved by the Pontifical Catholic University of Paraná Institutional Review Board (CAAE: 33686720.8.1001.0020) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at https://ensaiosclinicos.gov.br/rg/ (RBR-48gkx3m), Principal investigator: Layana Vieira Nobre, Date of registration: February 25th, 2022). The patient enrollment occurred between the March 1st, 2022 and December 31th, 2022.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Abdallah FW, Halpern SH, Aoyama K, Brull R. Will the Real Benefits of Single-Shot Interscalene Block Please Stand Up? A Systematic Review and Meta-Analysis. Anesth Analg. 2015;120:1114–29.
2. Lavand'homme P. Rebound pain after regional anesthesia in the ambulatory Patient. Curr Opin Anaesthesiol. 2018;31:679–84.
3. Muñoz-Leyva F, Cubillos J, Chin KJ. Managing rebound pain after regional anesthesia. Korean J Anesthesiol. 2020;73:372–83.
4. Sunderland S, Yarnold CH, Head SJ, et al. Regional Versus General Anesthesia and the Incidence of Unplanned Health Care Resource Utilization for Postoperative Pain After Wrist Fracture Surgery: Results From a Retrospective Quality Improvement Project. Reg Anesth Pain Med. 2016;41:22–7.
5. Lee HJ, Woo JH, Chae JS, Kim YJ, Shin SJ. Intravenous Versus Perineural Dexamethasone for Reducing Rebound Pain After Interscalene Brachial Plexus Block: A Randomized Controlled Trial. J Korean Med Sci. 2023;38:e183.
6. Woo JH, Lee HJ, Oh HW, Lee JW, Baik HJ, Kim YJ. Perineural dexamethasone reduces rebound pain after ropivacaine single injection interscalene block for arthroscopic shoulder surgery: a randomized controlled trial. Reg Anesth Pain Med. 2021;46:965–70.
7. Duma A, Urbanek B, Sitzwohl C, Kreiger A, Zimpfer M, Kapral S. Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: a randomized, controlled study. Br J Anaesth. 2005;94:112–6.
8. Knight JB, Schott NJ, Kentor ML, Williams BA. Neurotoxicity of common peripheral nerve block adjuvants. Curr Opin Anaesthesiol. 2015;28:598–604.
9. Luan H, Hao C, Li H, Zhang X, Zhao Z, Zhu P. Effect of interscalene brachial plexus block with dexmedetomidine and ropivacaine on postoperative analgesia in patients undergoing arthroscopic shoulder surgery: a randomized controlled clinical trial. Trials. 2023;24:392.
10. Wei XM, Liu Z, Lv LC, et al. Comparison of dexmedetomidine and dexamethasone as adjuvants to the ultrasound-guided interscalene nerve block in arthroscopic shoulder surgery: a systematic review and Bayesian network meta-analysis of randomized controlled trials. Front Med (Lausanne). 2023;10:1159216.
11. Williams BA, Hough KA, Tsui BYK, Ibinson JW, Gold MS, Gebhart GF. Neurotoxicity of adjuvants used in perineural anesthesia and analgesia in comparison with ropivacaine. Reg Anesth Pain Med. 2011;36(3):225–30.
12. Williams BA, Butt MT, Zeller JR, Coffee S, Pippi MA. Multimodal perineural analgesia with combined bupivacaine-clonidine-buprenorphine-dexamethasone: safe in vivo and chemically compatible in solution. Pain Med. 2015;16:186–98.
13. Zhou Q, Yu L, Yin C, et al. Effect of Transauricular Vagus Nerve Stimulation on Rebound Pain After Ropivacaine Single Injection Femoral Nerve Block for Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. J Pain Res. 2022;15:1949–58.
14. Kolarczyk LM, Williams BA. Transient heat hyperalgesia during resolution of ropivacaine sciatic nerve block in the rat. Reg Anesth Pain Med. 2011;36:220–4.
15. Barry GS, Bailey JG, Sardinha J, Brousseau P, Uppal V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. Br J Anaesth. 2021;126:862–71.
16. Touil N, Pavlopoulou A, Barbier O, Libouton X, Lavand'homme P. Evaluation of intraoperative ketamine on the prevention of severe rebound pain upon cessation of peripheral nerve block: a prospective randomized, double-blind, placebo-controlled study. Br J Anaesth. 2022;128:734–41.
17. Admassie BM, Tegegne BA, Alemu WM, Getahun AB. Magnitude and severity of rebound pain after resolution of peripheral nerve block and associated factors among patients undergoes surgery at university of gondar comprehensive specialized hospital northwest, Ethiopia, 2022. Longitudinal cross-sectional study. Ann Med Surg (Lond). 2022;84:104915.
18. Dada O, Gonzalez Zacarias A, Ongaigui C, et al. Does Rebound Pain after Peripheral Nerve Block for Orthopedic Surgery Impact Postoperative Analgesia and Opioid Consumption? A Narrative Review. Int J Environ Res Public Health. 2019;16:3257.
19. Bhatia P, Metta R. Rebound pain: Undesired, yet unexplored. J Anaesthesiol Clin Pharmacol. 2022;38:527–8.
20. Luebbert E, Rosenblatt MA. Postoperative Rebound Pain: Our Current Understanding About the Role of Regional Anesthesia and Multimodal Approaches in Prevention and Treatment. Curr Pain Headache Rep. 2023;27:449–54.

21. Hinther A, Nakoneshny SC, Chandarana SP, et al. Efficacy of Multimodal Analgesia for Postoperative Pain Management in Head and Neck Cancer Patients. Cancers (Basel). 2021;13:1266.
22. Zhu T, Gao Y, Xu X, Fu S, Lin W, Sun J. Effect of Ketamine Added to Ropivacaine in Nerve Block for Postoperative Pain Management in Patients Undergoing Anterior Cruciate Ligament Reconstruction: A Randomized Trial. Clin Ther. 2020;42:882—91.
23. Williams BA, Bottegal MT, Kentor ML, Irrgang JJ, Williams JP. Rebound pain scores as a function of femoral nerve block duration after anterior cruciate ligament reconstruction: retrospective analysis of a prospective, randomized clinical trial. Reg Anesth Pain Med. 2007;32:186—92.
24. Henningsen MJ, Sort R, Møller AM, Herling SF. Peripheral nerve block in ankle fracture surgery: a qualitative study of patients' experiences. Anaesthesia. 2018;73:49—58.
25. Faria-Silva R, Rezende DC de, Ribeiro JM, et al. Associação de clonidina e ropivacaína no bloqueio de plexo braquial para artroscopia de ombro. Rev Bras Anestesiol. 2016;66:335—40.
26. Seering MS, Bayman EO, Wong CA, Ranganath YS, Marian AA. Comparison of the effect of three different adjuvants on the analgesic duration of single injection interscalene brachial plexus block: a prospective, randomized, triple blinded clinical trial. Reg Anesth Pain Med. 2019. rapm-2018-100201.
27. Esteves S, Sá P, Figueiredo D, Pèrez Souto A. Duration and quality of postoperative analgesia after brachial plexus block for shoulder surgery: ropivacaine 0.5% versus ropivacaine 0.5% plus clonidine. Rev Esp Anestesiol Reanim. 2002;49:302—5.
28. Marhofer P, Columb M, Hopkins PM, et al. Dexamethasone as an adjuvant for peripheral nerve blockade: a randomized, triple-blinded crossover study in volunteers. Br J Anaesth. 2019;122:525—31.
29. Kim BG, Lee W, Song JH, Yang C, Heo GA, Kim H. Effect of intravenous dexamethasone on the duration of postoperative analgesia for popliteal sciatic nerve block: a randomized, double-blind, placebo-controlled study. Korean J Anesthesiol. 2021;74:317—24.

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REVIEW ARTICLE

Comparison of the recovery profile of sufentanil and remifentanil in total intravenous anesthesia: a systematic review and meta-analysis of randomized controlled trials☆

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Opioid Analgesics;
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Propofol;
Intravenous anesthesia;
Anesthesia recovery period

Abstract

Introduction: Remifentanil is a short-acting opioid and can be administered during surgery without the risk of delayed postoperative recovery but concerns about hyperalgesia and the shortages of remifentanil lead anesthetists to consider long-acting opioids for Total Intravenous Anesthesia (TIVA). Sufentanil is a more potent opioid with a longer context-sensitive half-life but can promote good postoperative analgesia due to its residual effect. This meta-analysis aimed to compare the recovery profile of remifentanil and sufentanil for TIVA.

Methods: The search strategy was performed in PubMed, CENTRAL, and Web of Science for RCTs comparing sufentanil and remifentanil as part of TIVA in adults undergoing noncardiac surgery. Risk of bias and the quality of evidence were performed using RoB2 and GRADEpro, respectively. The primary outcome was time to tracheal extubation. Secondary analyses included postoperative analgesia, respiratory depression, and Postoperative Nausea and Vomiting (PONV).

Results: Sufentanil increases the time to extubate, MD = 4.29 min; 95% CI: 2.33 to 6.26; $p = 0.001$. It also reduces the need for postoperative rescue analgesia, logOR = -1.07; 95% CI: -1.62 to -0.52; $p = 0.005$. There were no significant differences between both opioids for PONV, logOR = 0.50; 95% CI: -0.10 to 1.10; $p = 0.10$ and respiratory depression, logOR = 1.21; 95% CI: -0.42 to 2.84; $p = 0.15$.

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Conclusion: Sufentanil delays the time to tracheal extubation compared with remifentanil but is associated with a reduced need for postoperative rescue analgesia. No significant differences were observed between the two opioids in terms of postoperative respiratory depression or PONV.
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Introduction

Remifentanil is the most used opioid in the practice of Total Intravenous Anesthesia (TIVA).[1] In addition to its strong synergy with propofol, remifentanil is characterized by a rapid onset and offset of action, facilitating titration, and allowing for long infusion times without delaying patient recovery.[2] However, concerns regarding opioid-induced hyperalgesia and the limited availability of this opioid in certain regions have led anesthetists to explore alternative options to remifentanil. Sufentanil is currently considered the opioid with the highest potency, which is due to its pronounced affinity for μ-receptors.[3] Compared to alfentanil, sufentanil has a shorter context-sensitive half-time for infusions of less than 8 hours.[4] In addition, its residual effects may contribute to satisfactory postoperative analgesia, an aspect that does not occur with the use of remifentanil. In 2018, Wang et al published a meta-analysis comparing the efficacy and safety of sufentanil and remifentanil, particularly in patients undergoing craniotomy.[5] While this study provided valuable insights, it was limited to a single type of surgical procedure. Therefore, we performed this meta-analysis to compare the recovery profile of TIVA with remifentanil and sufentanil in terms of time to tracheal extubation, postoperative pain, postoperative nausea and vomiting, and respiratory depression, considering a broader range of non-cardiac surgical procedures.

Methods

The study was conducted by the recommended process of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).[6] The protocol for this study was registered at PROSPERO under registration number CRD42022366691.

The research question was formulated using the PICOS (Population, Intervention, Comparator, Outcome Study) strategy: Does sufentanil delay tracheal extubation in adults undergoing non-cardiac surgery with TIVA compared to remifentanil? To address this, a systematic search was conducted in September 2022. For the PubMed and CENTRAL databases, a combination of MeSH terms and keywords including "remifentanil" and "sufentanil" were used, both as keywords ([All]) and as MeSH terms. In addition, "propofol" or "total intravenous anesthesia" were also searched for, again using keywords and MeSH terms. The strategy included terms related to randomized trials, using keywords such as "randomized" or "randomised" and the MeSH term "random". The filters applied aimed to combine the anesthetics with randomized trials, resulting in the final search string reflecting the combination of all terms. For the Web of Science, the search strategy was carried out using text terms with the operator "All=", which enables a broad search for any term in all fields of the article data. The terms used were "remifentanil", "sufentanil", "propofol" or "total intravenous anesthesia" as well as words related to randomization, such as "randomized" or "randomised". The search was configured to identify studies that contained all the specified terms simultaneously using the final search string.

The results of the queries in the databases were imported into the Rayyan software [7] (https://www.rayyan.ai/) so that two authors (I.S.C. and R.P.N.) could search for titles and abstracts independently and in a blinded manner. Eligible studies for our review included indexed, published full articles of Randomized Clinical Trials (RCTs) that focused on adult patients undergoing non-cardiac surgery in which propofol-based anesthesia was used and in which the timing of extubation was compared between remifentanil and sufentanil. We specifically excluded studies that involved neuraxial blocks, intravenous adjuncts, inhalational anesthetics, or administration of sufentanil as an intermittent bolus. In addition, letters, editorials, and observational studies were excluded from our analysis. Data for this meta-analysis were extracted solely from peer-reviewed published articles. Data were collected using a standardized form. Information extracted included: author; age and sex of participants; number of members; type of procedure; duration of anesthesia; dose of sufentanil and remifentanil.

All analyses were carried out using STATA software (version 17). In some studies, outcome data were reported as median and interquartile range; therefore, we converted these data to mean and standard deviation using certain equations[8,9] to summarize the effect estimate for all included studies. The random effects and fixed effects models were used when heterogeneity was present and absent, respectively. Heterogeneity was measured by the I^2 statistic ($> 50\%$) and the corresponding p-value (< 0.05). For continuous outcome variables (i.e., extubation time), the Mean Difference (MD) and the corresponding 95% Confidence Interval (95% CI) were pooled using the restricted maximum likelihood or inverse variance method if heterogeneity was present or absent, respectively. For dichotomous outcome variables (i.e., postoperative nausea/vomiting, postoperative rescue analgesia), the Mantel-Haenszel method was used to pool the log Odds Ratio (logOR) and the corresponding 95% CI across studies. If significant heterogeneity occurred in any of the analyses conducted, a leave-one-out sensitivity analysis was performed to determine whether the reported effect estimate would change after excluding one study at a time. Due to the small number of studies included (less than ten studies), an assessment of publication bias was not possible.

The Risk of Bias Tool[10] developed by the Cochrane Collaboration was used to assess the methodological quality of each randomized trial. Two authors (R.P.N. and R.B.D.)

independently reviewed and rated the elements of each trial using this tool. Data relevant to the analyses were extracted using this method. In case of discrepancies in the scoring or extraction of data, these were resolved by a third author (I.S.C.) through discussion. Finally, the quality of evidence for each outcome was evaluated by the same authors following the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system[11] using the GRADEpro Guideline Development Tool (https://www.gradepro.org/) to assess the certainty of the evidence and prepare the summary of findings.

Results

Of the 350 studies identified in our literature search, seven met the inclusion criteria, involving a total of 403 patients (Fig. 1).[12-18] The Cochrane Collaboration's Risk of Bias tool showed that most studies had a moderate risk of bias (Fig. 2). The type of surgery included craniotomy (three studies), intracranial surgery (one study), thyroid surgery (one study), colorectal surgery (one study) and non-gynecological surgery (one study). The absolute dose and administration approach of each procedure, as well as the baseline characteristics of the included trials, are summarized in Table 1.

Tracheal extubation time was reported in the six trials.[12-14,16-18] Overall, compared with remifentanil, patients who received sufentanil had a significant increase in the meantime to extubate (MD = 4.29 mins; 95% CI: 2.33–6.26; $p = 0.001$) (Fig. 3A). However, we found significant statistical heterogeneity ($I^2 = 78.73\%$). Nevertheless, sensitivity analysis (leave-one-out) did not reveal any significant change in the reported effect estimate after excluding one

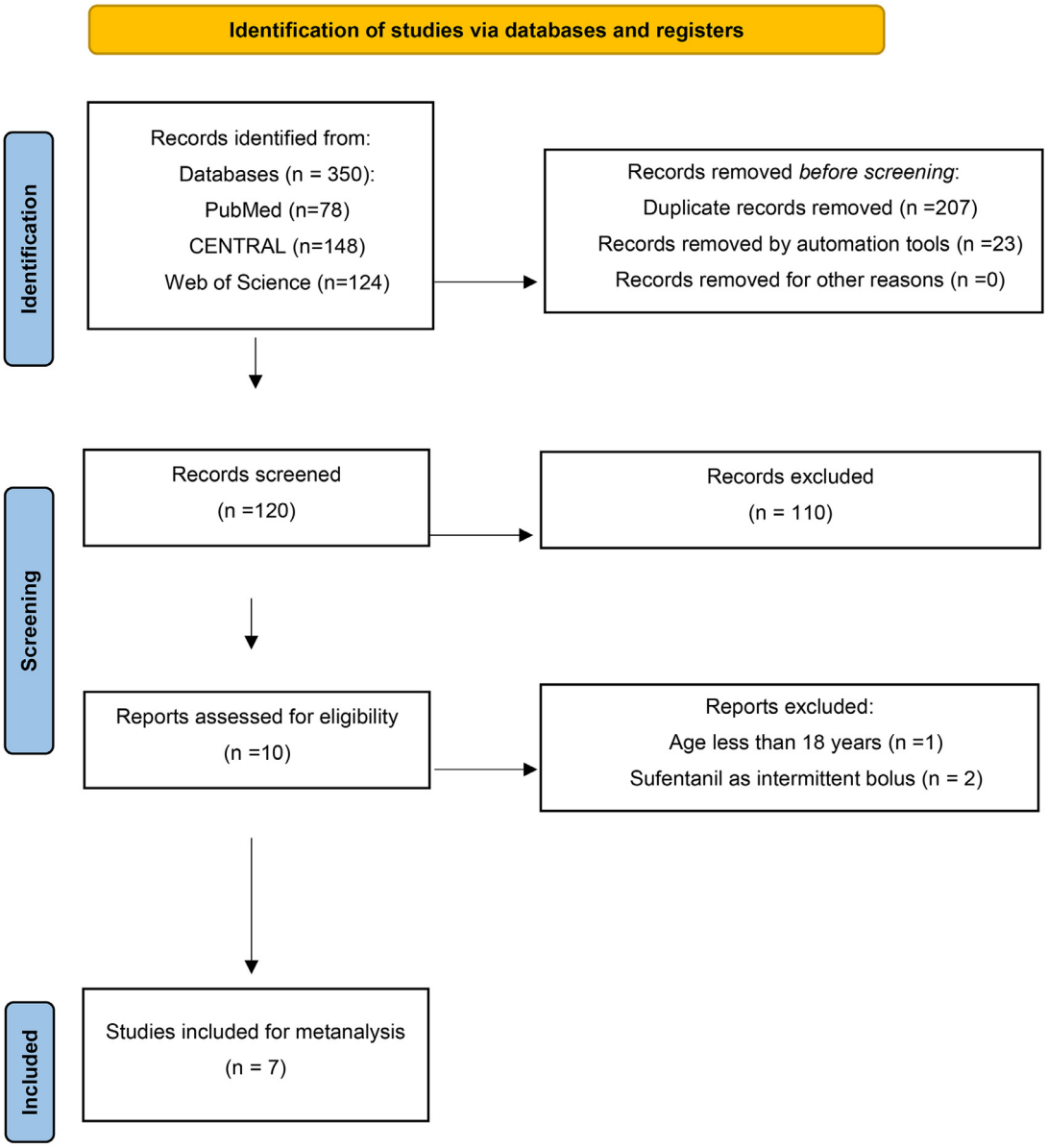

Figure 1 PRISMA flow diagram illustrating literature retrieved, included and excluded results from this review.

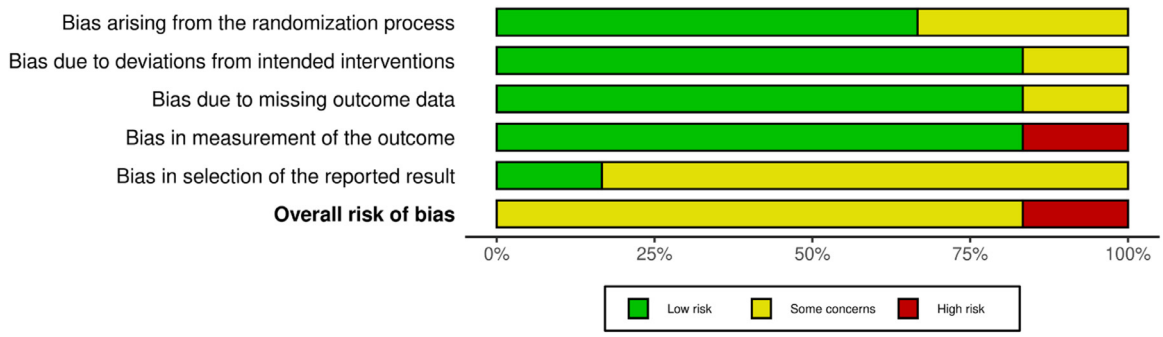

Figure 2 Risk of bias summary of the authors' assessments for each domain, expressed as percentages across all included studies.

study at a time. The subgroup analysis revealed that the duration of anesthesia was a contributor to heterogeneity (Fig. 4). For instance, the heterogeneity was resolved in patients receiving anesthesia for > 200 min (I^2 = 34.94%, p = 0.24). Meanwhile, in those receiving < 200 min of anesthesia, heterogeneity remained substantial (I^2 = 87.17%, p = 0.001). According to the GRADE system (Table 2), the evidence supporting our primary outcome was classified as low.

Postoperative rescue analgesia was assessed in five studies.[12,13,15-17] Moderate evidence indicates sufentanil was associated with a significant reduction in the postoperative rescue analgesia as compared to remifentanil (logOR = -1.07; 95% CI -1.62–-0.52; p = 0.005; I^2 = 26.81%) (Fig. 3B). A total of six studies were conducted to examine the occurrence of PONV in patients.[12-17] Overall, no statistical differences for PONV were observed in patients that had received sufentanil compared to those who received remifentanil (logOR = 0.50; 95% CI: -0.10–1.10; p = 0.10; I^2 = 0%; low-certainty evidence) (Fig. 3C). Pooling data from three studies[14,15,17] showed that there was no difference in the incidence of respiratory depression between sufentanil and remifentanil as part of propofol-based anesthesia (logOR = 1.21; 95% CI -0.42–2.84; p = 0.15; I^2 = 0%; low-certainty evidence) (Fig. 3D). For all the secondary outcomes, a subgroup analysis based on the assessment time-point was not feasible due to the lack of relevant subgroups in at least two studies.

Discussion

Our meta-analysis revealed a statistically significant increase in extubation time of approximately 4.29 minutes when using sufentanil compared to remifentanil for Total Intravenous Anesthesia (TIVA). Although the difference is statistically significant, its clinical relevance needs to be carefully assessed and contextualized, especially in major surgery. Postoperative pain management is critical in such procedures, and the potent analgesic effect of sufentanil may be beneficial. This meta-analysis indicates that using sufentanil is associated with substantial reduction in the need for postoperative rescue analgesia compared with remifentanil. This implies that the administration of remifentanil during surgery could potentially lead to higher postoperative opioid consumption, suggesting the possible development of Opioid-Induced Hyperalgesia (OIH).[1] In situations where pain management is paramount, the advantages of sufentanil may outweigh the disadvantages of prolonged extubation. When choosing between the two drugs, the desired analgesia and the efficiency of extubation should be weighed.

Another important consideration is the risk of respiratory depression due to the accumulation of sufentanil after continued infusion. According to our review, although this finding is not significant, it can be attributed to the small sample sizes of the studies and can be considered relevant, although remifentanil requires the administration of long-acting opioid doses to ensure opioid analgesia, which is not free of complications such as respiratory depression.[19] Given the accumulation of sufentanil with continuous infusion, perhaps the most appropriate approach to sufentanil-based anesthesia is to use its residual effect as the opioid element of a multimodal analgesic strategy. By avoiding combination with other long-acting opioids such as morphine, the aim is to achieve greater safety in terms of potential adverse effects. Even if sufentanil is discontinued before the end of the surgery, its effects may persist and affect respiratory dynamics. Clinicians should monitor respiratory parameters and be prepared to manage potential respiratory problems associated with prolonged sufentanil infusion.

The incidence of Postoperative Nausea and Vomiting (PONV) is remarkably high after surgical procedures. Studies have reported an incidence of 30% that can increase to as high as 80% in patients who are considered high-risk.[20] Opioid analgesics remain the basis for the administration of general anesthesia, especially for TIVA, as propofol has no analgesic properties and the infusion of an opioid is necessary to ensure an adequate anesthetic level. In this review, we found that the incidence of PONV is similar with both opioids.

Interestingly, with the notable exception of postoperative respiratory depression, which was at higher risk with sufentanil, our results closely matched those reported by Wang in the context of craniotomy.[5] The similarity of most of our results to Wang's study confirms the earlier findings in a broader surgical context and supports the generalizability of these results so that clinicians can extrapolate the data from craniotomy cases to other surgical scenarios, albeit with caution regarding respiratory side effects.

It is important to acknowledge that this review has several limitations. Among them is the lack of standardization

Table 1 Characteristics of included studies.

Study	Surgical Procedure	Age (Mean ± SD)		Gender (Male)		Opioid Dose Regimen		Duration of anesthesia (min)	
		Sufentanil (n)	Remifentanil (n)	Sufentanil n (Total)	Remifentanil n (Total)	Sufentanil	Remifentanil	Sufentanil	Remifentanil
Billota et al.	Supratentorial craniotomy	54 ± 11	55 ± 14	14 (29)	13 (30)	Induced at 0.5 $\mu g.kg^{-1}$ and then titrated to lower doses to maintain MAP within 10% of baseline	Induced at 0.5 $\mu g.kg^{-1}.min^{-1}$ and then titrated to lower doses to maintain MAP within 10% of baseline	273 (±58)	259 (±60)
Djian et al.	Nonemergency intracranial surgery	55.3 ± 9	45.7 ± 12	12 (31)	11 (29)	Induced at 0.25 $\mu g.kg^{-1}$ and maintained at 0.0025 $\mu g.kg^{-1}.min^{-1}$	Induced at 1 $\mu g.kg^{-1}$ and maintained at 0.25 $\mu g.kg^{-1}.min^{-1}$	251 (±92)	237 (±74)
Lentschener et al.	Thyroid surgery	48 ± 13	50 ± 15	3 (25)	8 (25)	An initial dose of 0.2 $\mu g.kg^{-1}$ of sufentanil was given followed by a maintenance dose of 0.2 $\mu g.\ kg^{-1}.h^{-1}$	An initial dose of 1.5 $\mu g.kg^{-1}$ was administered followed by a maintenance dose of 0.2 $\mu g.\ kg^{-1}.min^{-1}$	121 (±35)	110 (±26)
Liu et al.	Supratentorial craniotomy	44 ± 10	47 ± 13	15 (23)	12 (22)	TCI started with a Ce of 0.4 ng.mL^{-1} and then titrated according to hemodynamic changes between 0.2 and 0.4 ng.mL^{-1}	For induction, TCI with a Ce of 5 ng.mL^{-1} and then titrated between 3 and 8 ng.mL^{-1} to maintain stable hemodynamics	277 (±27)	332.85 (±24.87)
Martorano et al.	Supratentorial craniotomy	52.8 ± 13	56 ± 13	15 (31)	20 (38)	Continuous infusion; dosage: 0.01–0.04 $\mu g.kg^{-1}.min^{-1}$, reduced to 0.005–0.020 $\mu g.kg^{-1}.min^{-1}$ after dura mater opening	Continuous infusion: dosage 0.2–2 $\mu g.kg^{-1}.min^{-1}$, reduced to 0.1–1 $\mu g.kg^{-1}.min^{-1}$ after opening the dura mater	280 (±17)	302 (±15)
Simoni et al.	Non-gynecological video laparoscopy	46 ± 12	42 ± 12	15 (30)	7 (30)	Induction consisted of a bolus of 0.5 $\mu g.kg^{-1}$ followed by 0.5 $\mu g.kg^{-1}.h^{-1}$. If MAP increase, a 50 μg bolus was	Induction at 0.5 $\mu g.kg^{-1}.min^{-1}$ for 2 minutes and then 0.3 $\mu g.kg^{-1}.min^{-1}$ for maintenance. If the MAP > 15% of	105 (±26)	95 (±9)

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Table 1 (*Continued*)

Study	Surgical Procedure	Age (Mean ± SD)		Gender (Male)		Opioid Dose Regimen		Duration of anesthesia (min)	
		Sufentanil (n)	Remifentanil (n)	Sufentanil n (Total)	Remifentanil n (Total)	Sufentanil	Remifentanil	Sufentanil	Remifentanil
						given. If MAP < 15% of baseline, the CI was turned off	baseline, it was increased by 0.1 $\mu g.kg^{-1}.min^{-1}$		
Vasian et al.	Colorectal surgery	61.4 ± 12	60.4 ± 11	20 (30)	19 (30)	TCI with initial Cp of 0.3 $ng.mL^{-1}$ and then ranged between 0.2–1 $ng.mL^{-1}$ during the maintenance of anesthesia	TCI with Cp of 4 $ng.mL^{-1}$ at induction, and between 3–10 $ng.mL^{-1}$ during maintenance of anesthesia	176.45 (± 63.7)	156.16 (± 30.1)

of the technique of administering anesthetics. The differences in infusion techniques and dosages used in the various studies can be attributed to factors such as the variability in clinical practice, the individual characteristics of patients, the type of procedures performed and the specific objectives of each study. This heterogeneity contributes to a reduction in the certainty of evidence, as different opioid doses or methods of administration can significantly alter the depth and duration of anesthesia, as well as extubation time and associated side effect, highlighting the importance of future studies using more standardized methods.

Although most of the included studies used processed Electroencephalography (pEEG) monitoring to assist with propofol dosing to minimize the risk of overdose, it is important to note that such monitoring is not directly applicable to opioids. BIS is a valuable tool for assessing the effect of propofol on the level of hypnosis, but it does not directly indicate the intensity of pain,[21] which would be beneficial for titrating opioid infusion, which can vary greatly from patient to patient and affects both the depth and duration of anesthesia.

In the current landscape of anesthesia care, there has been a marked shift from reliance on opioids to a more balanced approach known as "multimodal general anesthesia". The rationale behind this approach is to use agents that act on different targets in the nociceptive system such as dexmedetomidine and non-specific agents such as magnesium, to ensure intraoperative control of nociception and postoperative pain management.[22] The multimodal approach may significantly reduce the opioid doses required, as highlighted in previous studies. Such a strategy would likely have resulted in better postoperative pain control and reduced the need for rescue analgesics. In addition, time to extubation, a critical parameter in assessing recovery from anesthesia, may have been influenced by the opioid doses used. In the case of sufentanil, with its longer duration of action, the use of adjuvants could have allowed dose reduction, resulting in a more predictable and potentially shorter extubation time.

A notable strength of our meta-analysis is the exclusive inclusion of Randomized Clinical Trials (RCTs), often considered the gold standard in clinical research. However, a major limitation was that we were unable to conduct a funnel plot analysis due to the inclusion of less than 10 studies. The lack of funnel plot analysis leaves a gap in our assessment of publication bias.

In summary, this meta-analysis provides valuable insight into the comparative efficacy and safety of sufentanil and remifentanil in propofol-based intravenous anesthesia. It shows a shorter extubation time with remifentanil and better postoperative analgesia with sufentanil, although the lack of TCI pumps and different dosages protocols in manual infusion is a significant limitation. Future studies with larger sample sizes and standardized methodologies are crucial to validate and extend our results. Additionally, it would be beneficial to incorporate other variables of interest, such as long-term safety outcomes. Such studies will enhance our understanding of the long-term implications of the opioid selection under consideration and help in establishing more robust guidelines for clinical practice.

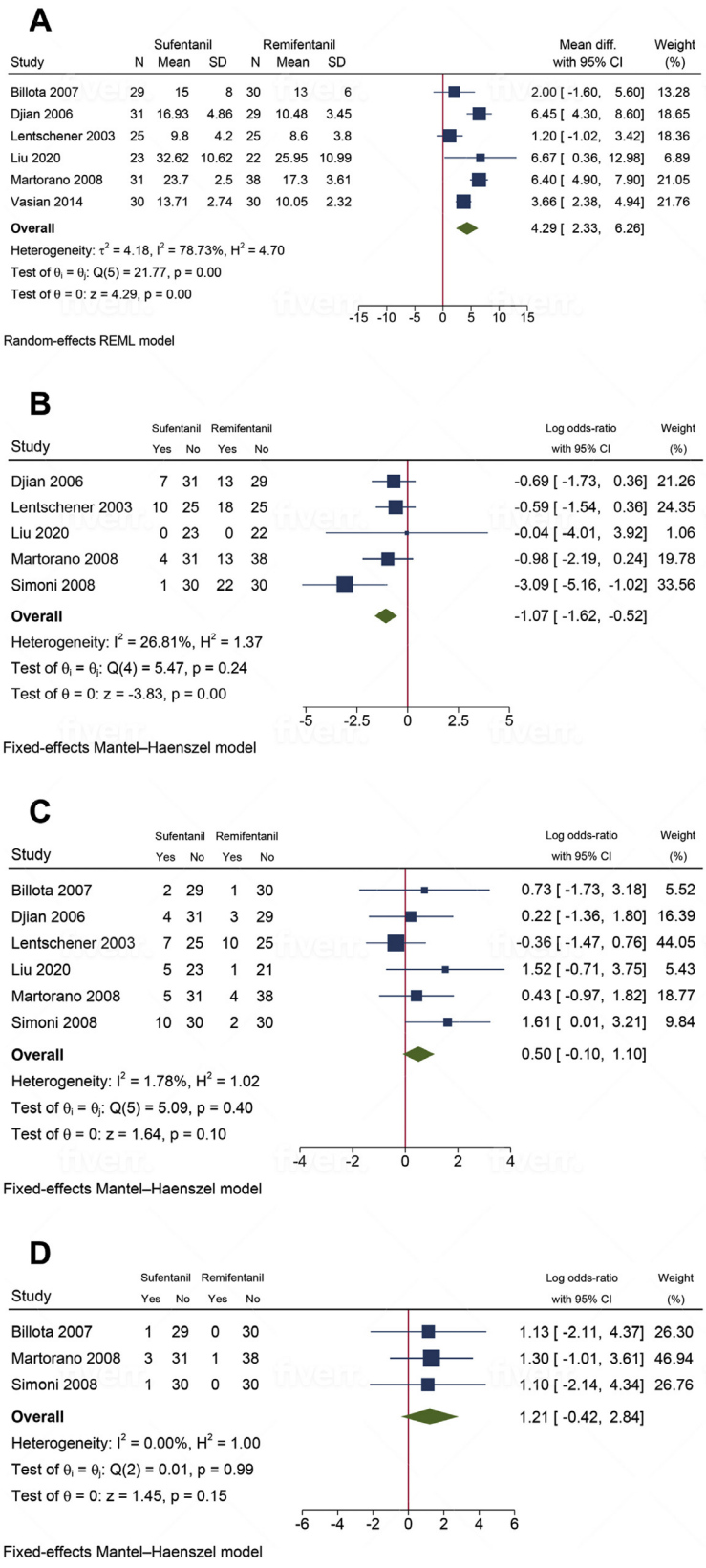

Figure 3 (A) Time to tracheal extubation was significantly longer in patients administered sufentanil compared to remifentanil. (B) The sufentanil group required significantly less postoperative rescue analgesics, indicating a lower need compared to the remifentanil group. (C) There were no significant differences in the incidence of PONV between the patient groups. (D) The incidence of respiratory depression was similar when sufentanil was compared to remifentanil in the setting of propofol-based TIVA.

Table 2 Certainty of the evidence (GRADE).

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sufentanil	Remifentanil	Relative (95% CI)	Absolute (95% CI)		
Extubation Time (assessed with: minutes)												
6	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	Publication bias strongly suspected[b]	169	174	–	MD **4.29 Min. higher** (2.33 higher to 6.26 higher)	⊕⊕◯◯ Low	Critical
Respiratory Depression												
3	Randomized trials	Not serious	Not serious	Not serious	Serious[c]	Publication bias strongly suspected[b]	5/95 (5.3%)	1/98 (1.0%)	**OR 1.21** (-0.42 to 2.84)	**2 more per 1.000** (from 15 fewer to 18 more)	⊕⊕◯◯ Low	Important
Postoperative Rescue Analgesia												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected[b]	22/162 (13.6%)	66/210 (31.4%)	**OR -1.07** (-1.62 to -0.52)	**1.000 fewer per 1.000** (from 1.000 fewer to 627 fewer)	⊕⊕⊕◯ Moderate	Important
Postoperative Nausea and Vomiting												
6	Randomized trials	Not serious	Not serious	Not serious	Serious[c]	Publication bias strongly suspected[b]	33/202 (16.3%)	21/194 (10.8%)	**OR 0.5** (-0.1 to 0.1)	**51 fewer per 1.000** (from 121 fewer to 96 fewer)	⊕⊕◯◯ Low	Important

CI, Confidence Interval; MD, Mean Difference; OR, Odds Ratio.
Explanations: (a) 78% heterogeneity; (b) less than ten studies were included in the meta-analysis, therefore it was not possible to assess publication bias; (c) Confidence interval includes the null value, it suggests significant uncertainty about the effect's direction and existence, indicating that observed effects could be due to chance, and necessitating cautious interpretation of these inconclusive results.

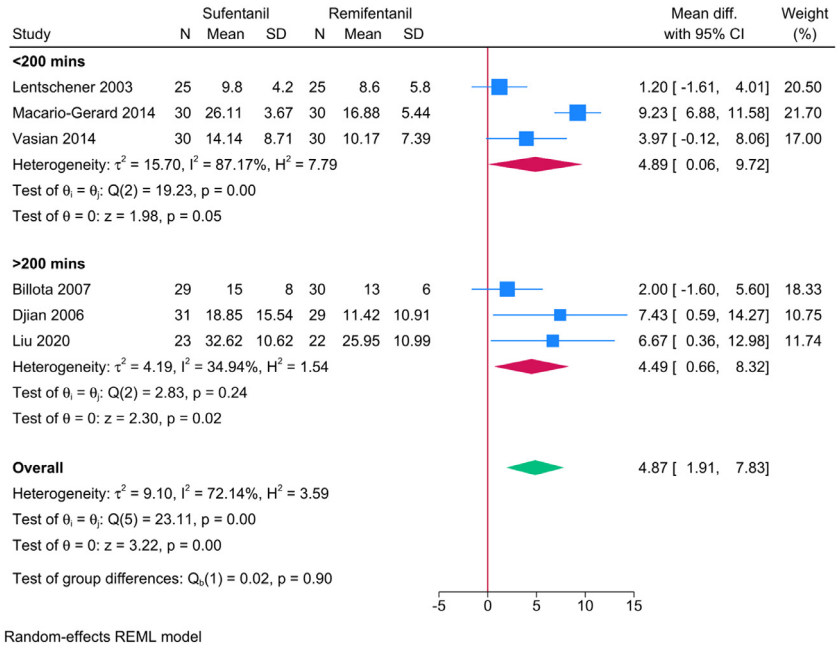

Figure 4 Subgroup analysis of tracheal extubation times under total intravenous anesthesia with remifentanil versus sufentanil, stratified by a 200-minute threshold. The analysis indicates reduced heterogeneity among patients receiving anesthesia for more than 200 minutes (I^2 = 34.94%) compared to those receiving anesthesia for less than 200 minutes (I^2 = 87.17%).

Conflicts of interest

The authors declare no conflicts of interest.

Presentation

This study was presented at the European Anaesthesiology Congress – Euroanaesthesia 2023 (Glasgow, Scotland, 2023).

Declaration of AI-assisted technologies in the writing process

The authors use Grammarly® in the writing process to improve readability and language of the manuscript.

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References

1. Al-Rifai Z, Mulvey D. Principles of total intravenous anaesthesia: basic pharmacokinetics and model descriptions. BJA Educ. 2016;16:92–7.
2. Glass PSA, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg. 1999;89 (4 Suppl):7.
3. Monk JP, Beresford R, Ward A. Sufentanil. Drugs. 1988;36:286–313.
4. Gepts E, Shafer SL, Camu F, Stanski DR, Woestenborghs R, Van Peer A, et al. Linearity of Pharmacokinetics and Model Estimation of Sufentanil. Anesthesiology. 1995;83:1194–204.
5. Wang JM, Xu F, Peng G, Lu S. Efficacy and Safety of Sufentanil-Propofol Versus Remifentanil-Propofol as Anesthesia in Patients Undergoing Craniotomy: A Meta-Analysis. World Neurosurg. 2018;119:e598–606.
6. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84. Jun 2.
7. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
8. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
9. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27:1785–805.
10. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
11. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401–6.
12. Liu YH, Hu XB, Yang XM, Wang YW, Deng M. Comparing remifentanil and sufentanil in stress reduction during neurosurgery: a randomised controlled trial. Int J Clin Pharm. 2020;42:1326–34.
13. Djian MC, Blanchet B, Pesce F, et al. Comparison of the time to extubation after use of remifentanil or sufentanil in combination with propofol as anesthesia in adults undergoing nonemergency intracranial surgery: A prospective, randomized, double-blind trial. Clin Ther. 2006;28:560–8.
14. Bilotta F, Caramia R, Paoloni FP, et al. Early postoperative cognitive recovery after remifentanil-propofol or sufentanil-propofol anaesthesia for supratentorial craniotomy: a randomized trial. Eur J Anaesthesiol. 2007;24:122–7.

15. Simoni RF, Simões DCP. Remifentanil versus Sufentanil em Infusão Contínua em Intervenções Cirúrgicas Videolaparoscópicas. Estudo Comparativo. Rev Bras Anestesiol. 2008;58:9.
16. Lentschener C, Ghimouz A, Bonnichon P, Pépion C, Gomola A, Ozier Y. Remifentanil-propofol vs. sufentanil-propofol: optimal combinations in clinical anesthesia: Computer simulation and clinical practice. Acta Anaesthesiol Scand. 2003;47:84—9.
17. Martorano PP, Aloj F, Baietta S, et al. Sufentanil-propofol vs. remifentanil-propofol during total intravenous anesthesia for neurosurgery. A multicentre study. MINERVA Anestesiol. 2008;74:11.
18. Vasian HN, Mărgărit S, Ionescu D, et al. Total Intravenous Anesthesia-Target Controlled Infusion for colorectal surgery. Remifentanil TCI vs sufentanil TCI. Rom J Anaesth Intensive Care. 2014;21:87—94.
19. Fletcher D, Pinaud M, Scherpereel P, Clyti N, Chauvin M. The efficacy of intravenous 0.15 versus 0.25 mg/kg intraoperative morphine for immediate postoperative analgesia after remifentanil-based anesthesia for major surgery. Anesth Analg. 2000; 90:666—71.
20. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91:693—700.
21. Takamatsu I, Ozaki M, Kazama T. Entropy indices vs the bispectral index™ for estimating nociception during sevoflurane anaesthesia. Br J Anaesth. 2006;96:620—6.
22. Brown EN, Pavone KJ, Naranjo M. Multimodal General Anesthesia: Theory and Practice. Anesth Analg. 2018;127:1246—58.

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REVIEW ARTICLE

Comparative effectiveness of anterior and posterior approaches for interscalene brachial plexus block: a systematic review and meta-analysis



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Nerve blockade;
Anesthesia;
Regional anesthesia

Abstract
Introduction: Interscalene Brachial Plexus Blocks (ISBPB) are highly effective forms of anesthesia for surgeries involving the upper arm, shoulder, and neck. Recently, there has been a growing interest in comparing the advantages and limitations of the anterior and posterior approaches.
Methods: This systematic review and meta-analysis aimed to determine whether the anterior or posterior approach to ISBPB offers a clinical advantage regarding complete block rates and time to block completion. We included randomized controlled trials comparing the anterior and posterior techniques for ISBPB while excluding studies with overlapping populations, comparisons of blocks other than interscalene, and articles written in a non-English language.
Results: The search strategy identified 2229 articles, of which six Randomized Controlled Trials (RCTs) met the inclusion criteria for the meta-analysis. A total of 414 patients were included, with 210 patients in the anterior group and 204 in the posterior group. The Odds Ratio (OR) for a complete sensory block between the two techniques did not reach statistical significance (OR = 0.56 [0.20, 1.58], 95% CI, p = 0.27). Similarly, the Standardized Mean Difference (SMD) for the time to complete the block also did not reach statistical significance (SMD: -0.77 [-2.12, 0.59], 95% CI, p = 0.27). Heterogeneity for complete block was not significant (I^2 = 0%), while procedure time showed high heterogeneity (I^2 = 97%).
Conclusion: Both techniques have shown effectiveness in providing surgical analgesia. The choice of technique should be determined by the provider's comfort and proficiency, as well as ensuring the highest level of safety for the patient.
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Introduction

Interscalene Brachial Plexus Block (ISBPB) is a highly effective form of anesthesia for surgical procedures on the upper arm, shoulder, and neck. It anesthetizes most of the territory innervated by the brachial plexus, sparing the inferior trunk.[1-6] Initially done using the landmark technique, the ISB technique has changed and, through ultrasound guidance, enhanced precision and accuracy.[7-12]

Pioneered by Winnie, the anterior technique for ISB involves injecting local anesthetic between the anterior and middle scalene muscles at the C6 level and has gained popularity.[13] However, in 1990, Pippa described a posterior approach to the ISBPB, which consisted of placing the needle where the levator scapulae's posterior border meets the trapezius muscle's anterior border and then advancing the needle towards the brachial plexus within the middle scalene muscle. Compared to the anterior approach, Pippa's technique prevents the local anesthetic from rapidly spreading along the anterior scalene muscle.[11,14,15]

Despite the extensive use of both techniques, there remains uncertainty regarding their comparative effectiveness and clinical utility. Previous studies show conflicting results, with some suggesting that the posterior approach may offer advantages in terms of block precision and reduced side effects, while others highlight the greater familiarity that physicians have with the anterior approach.[14,16,17] Furthermore, questions remain about the relative safety, cost-effectiveness, and required skill level for each technique, which are critical considerations in clinical practice. However, no consensus has emerged, underscoring the need for a rigorous comparison of these approaches.

To address these gaps in knowledge, we conducted a comprehensive systematic review and meta-analysis of randomized controlled trials to evaluate whether the anterior or posterior approach to ISBPB offers a clear clinical advantage. Specifically, we compared the two techniques in terms of time to finish the block and complete sensory block rate, with the goal of providing evidence-based guidance for anesthesiologists in choosing the most effective approach.

Methods

Search strategy

We conducted a systematic review of the literature from its inception [19,64] to June 2023, using three databases: Medline, Embase, and the Cochrane Library (Figure 1). The search strategy was as follows: "("brachial plexus" OR "scalene" OR "interscalene") AND ("block" OR blockades OR catheter) AND ("lateral" OR "posterior" OR anterolateral OR anterior OR pippa OR winnie)." No filters were applied. The search was supplemented by screening the references of included articles to identify any additional studies.

The systematic review and meta-analysis was performed in accordance with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines[18] The complete literature search strategy is listed in Table S1 (Supplementary Material).

This meta-analysis was registered on Prospero on October 3, 2023, under the inscription CRD42023469151.[19] No amendments to information provided at registration or in the protocol were done.

Eligibility criteria

Two authors independently conducted a literature review. Articles selected for full review by either author were then jointly assessed. We included randomized controlled trials comparing the anterior and posterior interscalene block techniques and their variations. Studies were excluded if they involved overlapping populations, compared non-interscalene blocks, or were published in languages other than English.

Statistical analysis and data collection

The outcomes of interest were modeled using a random effects model. Using a standardized extraction form, two authors independently extracted data on complete block rate, procedural time, study design, population characteristics, and intervention details.

Standardized mean difference was used to pool continuous outcomes with a 95% Confidence Interval, and Odds Ratio was used to pool categorical outcomes with a 95% Confidence Interval. Heterogeneity was evaluated with the Cochran Q test and I2 statistics; p-values inferior to 0.10, and $I2 > 25\%$ were considered significant for heterogeneity. DerSimonian and Laird's random effects model was used in pooled outcomes with high heterogeneity. Review Manager 5·4.1 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. Studies that reported results in terms of median and interquartile intervals had their mean and standard deviations calculated based on these values. Sensitivity analysis was performed for outcomes with high heterogeneity.

Quality assessment

The risk of bias was assessed for each included study using the Cochrane Collaboration's Risk of Bias Version 2 (RoB2). Each study was evaluated across five domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias (Figure 2). Bias in individual studies was categorized as high, low, or unclear risk based on predefined questions and flowgrams from each specific domain.

The assessment as performed independently by two reviewers. A spreadsheet was created for visual display of individual results. Disagreements were resolved through consensus or by a third reviewer who acted as a mediator. If consensus was not reached after discussion, the third reviewer would make a final decision.

Role of funding

There was no funding source for this study. All authors had full access to all the data, and the corresponding author had final responsibility for the decision to submit it for publication. There were no competing interests of any authors.

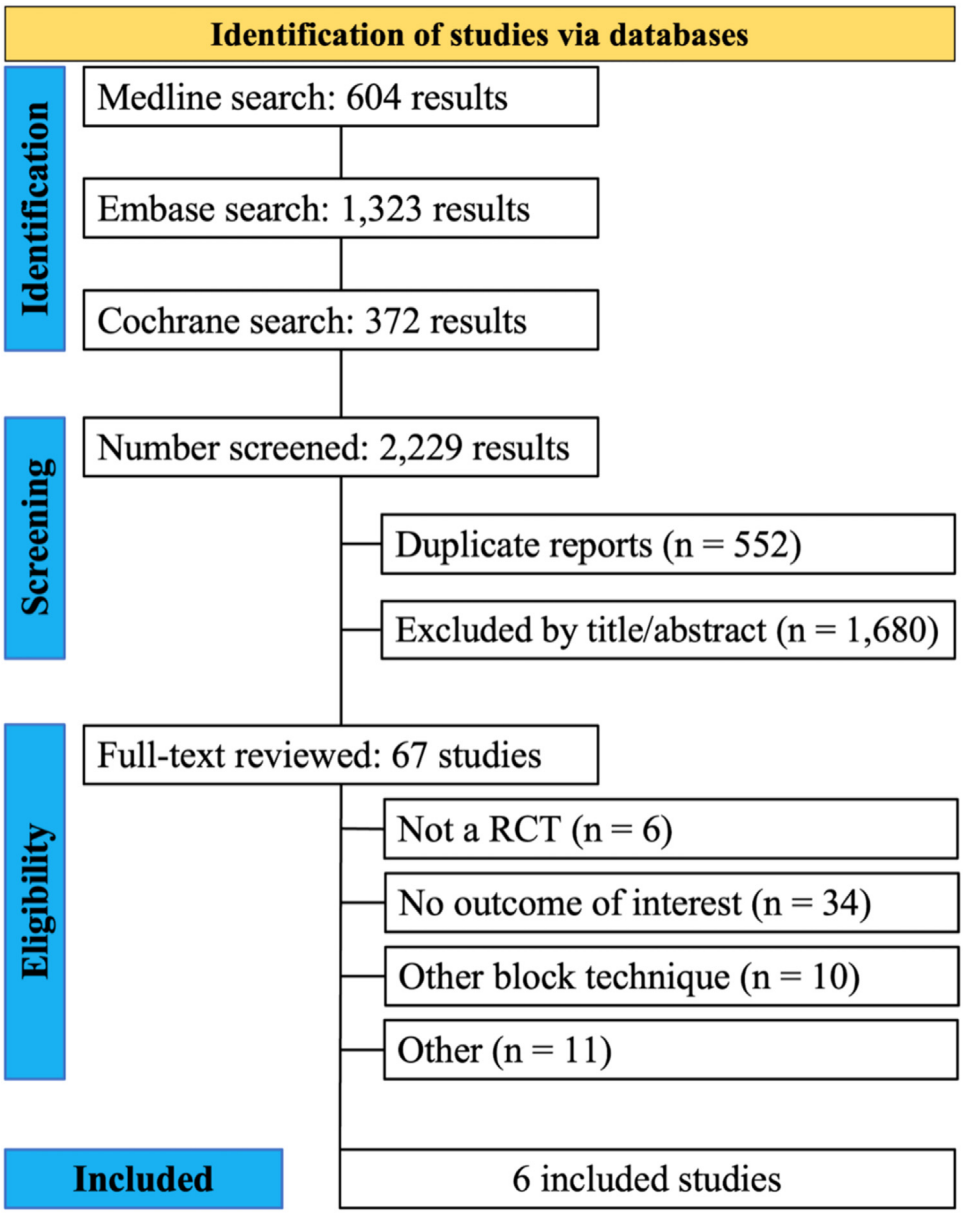

Figure 1 PRISMA flow diagram of study screening and selection.

Results

A total of 1747 articles were screened through Medline, Cochrane, and Embase databases (Figure 1). Of these, 1680 were excluded based on predetermined criteria, and 67 were read in full. Six randomized controlled trials were included for review and meta-analysis. The sum of patients from all studies was 414, with 210 patients in the anterior group and 204 in the posterior group. The mean age ranged from 38.3 to 63.8 years in the anterior group and from 37.7 to 67.1 years in the posterior group (Table 1).

Complete block was defined as the lack of need for sedation, adding a block supplement, or converting to general anesthesia due solely to pain in the brachial plexus distribution. Four studies reported complete blocks as an outcome. No study found a statistically significant difference in the number of complete blocks when comparing the two techniques. Studies' results and outcomes can be seen in Table 2.

In our meta-analysis, the odds ratio for complete blocks between the anterior and posterior approach did not reach statistical significance (OR = 0.56 [0.20, 1.58], 95% CI, p = 0.27), as shown in Figure 3. I^2 = 0, which is not statistically significant for heterogeneity. The risk of bias was of low concern for the studies included in this outcome.

Four studies reported procedure times ranging from 4.28 to 8.79 minutes in the anterior group and 4.93 to 9.6 minutes in the posterior group. No significant difference was observed for this outcome between the two groups (SMD: -0.77 [-2.12, 0.59], 95% CI, p = 0.27), as demonstrated in Figure 4. However, we obtained an I^2 = 97%, which is statistically significant for heterogeneity. The risk of bias was of low concern for the studies included in this outcome.

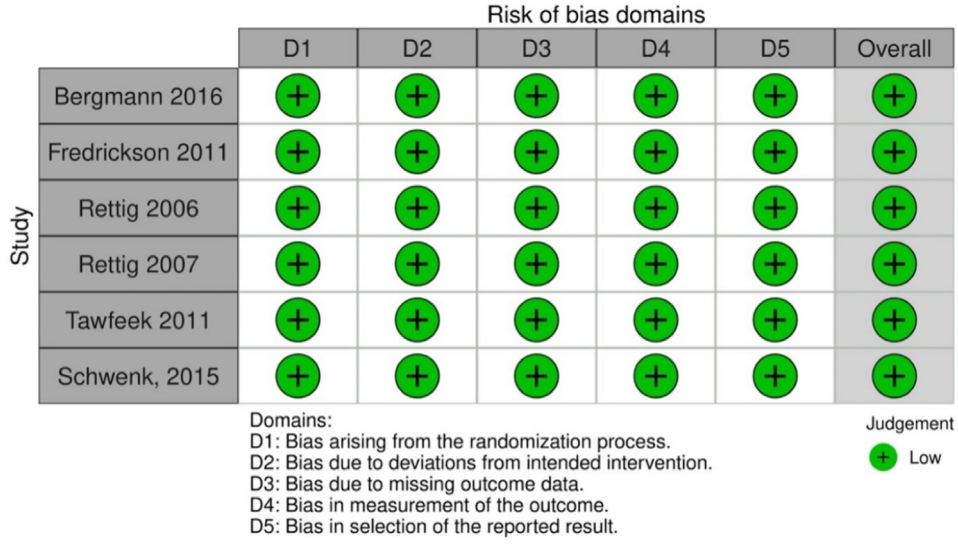

Figure 2 Quality assessment and risk of bias.

Given the substantial heterogeneity in procedure time (I2 = 97%), we performed a sensitivity analysis to explore potential sources of variability. We excluded the study with the fastest time for block completion (Schwenk, 2015) (SMD: -0.87 [-3.05, 1.18], 95% CI, p = 0.38; I2 = 97.66%). This analysis did not significantly alter the overall findings, suggesting that the heterogeneity is likely attributable to variability in practice techniques rather than data outliers.

One potential factor that contributed to the heterogeneity was the variability in operator experience. The included studies did not consistently report the experience level of the practitioners performing the blocks, which could significantly influence procedure time. Additionally, variations in local anesthetic volume may have influenced procedure times.

Discussion

Regional anesthesia techniques like the Interscalene Brachial Plexus Block (ISBPB) are widely recognized as effective and safe methods for surgical analgesia and postoperative pain management.[5,20] These techniques can enable outpatient surgical procedures and reduce hospital admissions for poorly controlled pain.[21-23]

The anterior approach for brachial plexus blockade, first described by Winnie in 1970, has been thoroughly studied and is known for its efficacy and relatively high safety profile.[14,15,24,25] Conversely, the posterior approach, as described by Pippa, has gained popularity for shoulder and upper arm surgeries.[26] Pippa's technique offers improved visualization of the needle shaft and tip, potentially allowing for more precise needle positioning and reducing the risk of complications.[27,28]

Table 1 Design and characteristics of studies included in the meta-analysis.

Study	Design	Patients[a]	Age[a,b]	Procedure	Intervention	Location; Period	Population
Bergmann, 2016[11]	RCT	42/42	49.9/48.9	Elective shoulder surgery	ISB	Germany, 2016	ASA I–II
Fredrickson, 2011[17]	RCT	56/52	48/47	Elective shoulder surgery	ISB	New Zealand, 2009-20010	ASA I–II
Tawfeek, 2011[31]	RCT	20/20	38.3/ 37.7	Elective shoulder surgery	ISB	Egypt, 20011	ASA I, II, III
Rettig, 2006[16]	RCT	40/40	49.6/46.4	Elective shoulder or upper arm surgery	ISB	Netherlands, 2006	ASA I–II
Rettig, 2007[44]	RCT	10/10	56/48	Elective shoulder surgery	ISB	Ireland, 2007	ASA I–II
Schwenk, 2015[45]	RCT	42/40	63.8/67.1	Open shoulder surgery	ISB	United States, 2015	ASA I, II, III

[a] Anterior Approach (AA) / Posterior Approach (PA).
[b] Age represented as mean.

Table 2 Studies' outcomes and procedures' characteristics.

Authors	Primary Outcome	Local Anesthetic	Intraoperative Management	Catheter Infusion	Findings
Bergmann, 2016[11]	Incidence of phrenic nerve block.	15 mL of ropivacaine 1%	Sedation: 0.033 $mg.kg^{-1}$ midazolam, 0.067 $\mu g.kg^{-1}$ sufentanil, and 0.0133 $mg.kg^{-1}$ propofol.	Non-available.	Both groups experienced significant decreases in respiratory function after an interscalene brachial plexus block, but no significant differences were found.
Fredrickson, 2011[17]	Pain free rates in the recovery room.	20 mL of ropivacaine 0.375% administered preoperatively.	General anesthesia: laryngeal mask airway, desflurane anesthesia, alfentanil 0.25 mg was administered as needed for a respiratory rate greater than 25 breaths per minute.	Ropivacaine 0.2% was administered via elastomeric pump delivering 2 $mL.hr^{-1}$ with patient-controlled boluses of up to 5 $mL.hr^{-1}$.	The anterior group had a statistically significant higher rate of pain relief in the recovery room compared to the posterior group. Rescue tramadol use was higher for the posterior group on the first day after surgery but not on the second day.
Tawfeek, 2011[31]	efficacy and safety of continuous posterior and anterior interscalene brachial plexus blockades.	Lidocaine 2% and Bupivacaine 0.5% (20 mL of both).	Premedication: 3.75—7.5 mg midazolam orally. General anesthesia: 1—2 $mcg.kg^{-1}$ fentanyl, 1.5—2 $mg.kg^{-1}$ propofol, and 0.5 $mg.kg^{-1}$ atracurium. Maintenance: mixture of nitrous oxide (50%—70%) and isoflurane (1%—1.5%) in oxygen, and incremental doses of atracurium.	Infusion of 8–10 mL. h^{-1} of bupivacaine 0.25% throughout the interscalene catheter was started postoperatively	There was no significant difference regarding the onset of anesthesia in both groups. Block procedure time and catheter placement time were faster in the posterior group.
Rettig, 2006[16]	Clinical efficacy of anterior versus posterior approach of brachial plexus block.	0.5 $mL.kg^{-1}$ of ropivacaine 7.5 $mg.mL^{-1}$	Sedation for the block: alfentanil 0.5 mg and, increment dose mg (0.5) or midazolam 1mg as needed. General anesthesia for surgery: propofol, 2 $mg.kg^{-1}$; fentanyl, 100–150 mcg for induction and maintained by propofol 4 to 6 $mg.kg^{-1}.h^{-1}$ and 70% N_2O in oxygen.	Non-available.	Anterior and posterior approaches of the brachial plexus were equal and comparable in clinical efficacy for shoulder and upper arm anesthesia.
Rettig, 2007[44]	Concentration of arterial plasma ropivacaine.	Single 3.75 $mg.kg^{-1}$ injection of ropivacaine 7.5 $mg.mL^{-1}$.	Sedation: alfentanil up to 1.0 mg and, if necessary, with midazolam up to 1.0 mg. Opioids were given during surgery as needed.	Non-available.	No statistically significant difference in plasma concentration of ropivacaine was observed between the anterior and posterior groups.
Schwenk, 2015[45]	Visual Analog Scale Pain Scores (VAS) at 24 and 48 hours.	Ropivacaine 0.5% (30 mL).	General anesthesia: propofol 1–2 $mg.kg^{-1}$, rocuronium, fentanyl 1–2 $mcg.kg^{-1}$. Maintenance: sevoflurane or desflurane in addition to fentanyl as needed.	Continuous 0.2% ropivacaine at 10 $mL.hr^{-1}$. Bolus of 5 mL of ropivacaine 0.2% was given by the pain team for pain score > 5/10.	No statistical difference in VAS at 24 hours and 48 hours, mean procedure time, and morphine consumption at 24 hours.

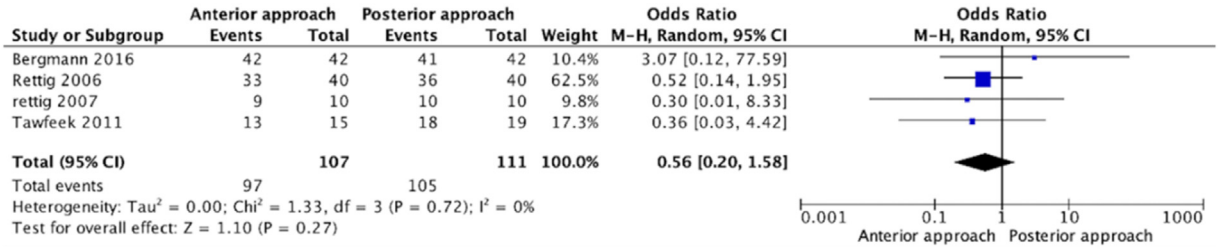

Figure 3 Odds ratio of complete sensory blocks.

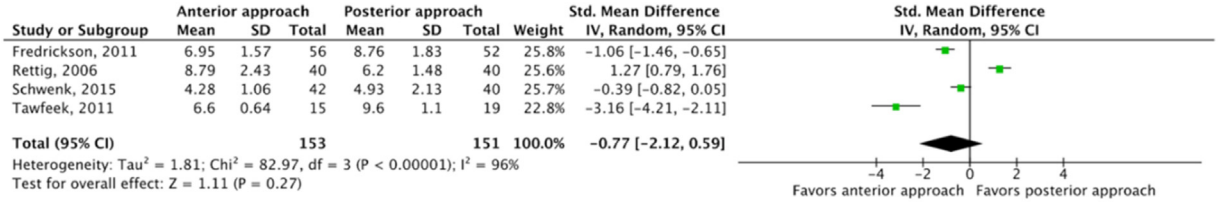

Figure 4 Standardized mean difference of procedure time.

Interpretation of results

A total of 1747 articles were screened, with six randomized controlled trials ultimately included in the meta-analysis, encompassing 414 patients (210 in the anterior group and 204 in the posterior group). The meta-analysis found no statistically significant difference between the anterior and posterior approaches regarding the odds ratio for complete blocks. Similarly, the procedure time did not differ significantly between the two groups.

Three studies reported a nonsignificant trend toward greater complete block rate with the anterior approach, while one suggested a nonsignificant advantage for the posterior approach. However, when pooling results from all studies, no significant difference was observed, demonstrating the effectiveness of both techniques. Regarding time to completion, three studies favored the anterior approach, with two reaching statistical significance. In contrast, only one study showed a statistically significant advantage for the posterior approach. Overall, there was no difference in the median time to perform the block when all studies were combined. This variability in results likely reflects differences in operator familiarity with each technique, leading to faster completion times when performing the more familiar method.

Our meta-analysis showed that both the anterior and posterior approaches for Interscalene Brachial Plexus Block (ISBPB) were equally effective in terms of complete block rates and procedure time. These findings have important implications for clinical practice. Since neither approach demonstrated a clear advantage, the choice between the two techniques should primarily be guided by the clinician's expertise, the surgical context, and patient-specific factors. For example, the anterior approach, which is more familiar to most anesthesiologists, may be the preferred technique in most cases. However, the posterior approach might be advantageous in cases where visualization of the needle tip and shaft is crucial, potentially reducing complications related to needle misplacement. Additionally, patient anatomy, co-existing conditions such as obesity, or previous neck surgeries may influence the feasibility of one approach over the other. Importantly, in patients with significant pulmonary compromise (e.g., chronic obstructive pulmonary disease), both techniques carry the risk of phrenic nerve block, requiring careful consideration of patient safety regardless of the technique chosen. Those findings align with current guidelines and best practices in regional anesthesia. Current guidelines do not prefer one approach over another but emphasize the need for safety considerations and an individualized approach.

Comparison with existing literature

The results of our study were consistent with some previous research but differ from others, highlighting the ongoing debate in the literature about the superiority of different approaches. Previous studies show varying success rates for anterior interscalene non-stimulating catheter techniques, with some achieving 100% success while others report failure rates as high as 20%.[29,30] These mixed results have led to debates about the relative merits of the anterior and posterior approaches. There is no clear consensus on which technique is superior in terms of time to completion or success rate.

Comparative studies on postoperative outcomes, such as opioid consumption, procedure time, and patient satisfaction, also yield inconsistent findings. For example, Fredrickson et al. reported that Pippa's technique has more difficulty with catheter threading and longer placement time. In contrast, patients in the anterior group experience higher rates of pain relief and lower opioid consumption within the first 24 hours post-surgery.[17] However, potential bias is noted due to the operator's greater experience with Winnie's technique. On the other hand, Tawfeek et al. reported faster block procedure times, lower pain scores, and higher patient satisfaction with the posterior approach. It should be noted that this study did not include subcutaneous tunneling in the anterior approach, which may have influenced the results.[31]

Similarly, Fredrickson et al. suggested that the anterior approach may provide better postoperative pain control, with patients requiring less rescue analgesia in the Post-Anesthesia Care Unit (PACU) compared to the posterior approach.[17] However, our meta-analysis found no significant differences in the number of complete blocks or procedure times between the two techniques. These findings, however, suggest potential advantages of the anterior approach in managing postoperative pain.

Regarding catheter stability, Aoyama et al. did not observe any significant differences between the anterior and posterior approaches concerning catheter tip migration.[32] Although this outcome was not directly addressed in our meta-analysis, our findings support that both techniques are mechanically equivalent in achieving a complete block, implying that the choice of technique may not significantly affect block success when using catheters.

Rettig et al. did not find any significant differences in block success or patient satisfaction between the approaches.[16] Overall, most randomized trials, including this meta-analysis, do not favor one technique over the other. Neither approach showed a significant difference regarding complete block rate, procedure time, patient satisfaction, catheter tip migration, phrenic nerve block rate, or local anesthetic plasma concentration. Both techniques are equally effective in achieving a successful block and ensuring patient satisfaction.

Complications

Despite the long-standing use of Winnie's technique, complications such as subdural anesthesia, subarachnoid injection of local anesthetic, and recurrent laryngeal nerve blockade have been reported.[33-37] Similarly, Pippa's technique has been associated with complications, including intrathecal and epidural injections, raising safety concerns.[27,33,38,39]

The anterior and posterior approaches risk accidental phrenic nerve blockade, leading to hemidiaphragmatic paresis.[40-43] This complication is particularly concerning for patients with severe Chronic Obstructive Pulmonary Disease (COPD). Studies, such as those by Bergmann et al., show no difference between the two approaches regarding the frequency of unintentional phrenic nerve block, suggesting neither technique offers a clear safety advantage.[11]

Catheter dislodgment is another concern with continuous neuraxial and regional anesthesia. The posterior approach is theorized to be more favorable for maintaining the catheter tip position due to its longer insertion length and passage through multiple muscle layers.[24,25] However, Aoyama et al. did not find any difference in catheter tip migration between the two approaches in their study of continuous interscalene plexus blocks.[32]

Rettig et al. compared Winnie's and Pippa's approaches and found no significant clinical differences, except for a thoracic epidural block complication observed in one patient with the anterior technique.[16] Transient symptoms of paresthesia and dysesthesia were reported in both groups, with a higher incidence in the anterior group, though these symptoms generally resolved within 6 to 8 weeks after surgery. In a following study, Rettig et al. analyzed the difference in plasma concentration of local anesthetic following brachial plexus blockade using Winnie's or Pipa's technique. Rettig et al. concluded that both the anterior and posterior techniques yield similar results.[44] Consequently, as plasma levels of local anesthetics are similar between the two groups, no method, most likely, provides a better safety profile to local anesthetic systemic toxicity, and standard precautions should be taken irrespective of the approach used.

Limitations

Our study has several limitations that should be considered when interpreting the findings. First, despite including multiple Randomized Controlled Trials (RCTs), the final sample size of 414 patients is relatively small. This limited sample size may restrict the statistical power of our analyses, potentially affecting the generalizability of the results. Larger trials would be needed to confirm these findings and detect more subtle differences between the anterior and posterior approaches.

Second, there is significant heterogeneity in the procedure time analysis (I^2 = 97%), suggesting variability in operator experience, technique, and study methodologies. This variability could introduce bias, impacting the reliability of our findings. Differences in ultrasound-guided techniques, needle orientation, or local anesthetic volume may have contributed to the variation across studies. Although sensitivity analyses were conducted to mitigate this, the potential for bias remains a concern.

Third, the exclusion of non-English studies introduces the possibility of language bias. It is possible that relevant studies published in other languages were missed, which could limit the comprehensiveness of our review. Similarly, publication bias should also be considered, particularly the non-reporting of negative or inconclusive results. Studies showing no significant differences between techniques may be less likely to be published, skewing the evidence base in favor of either approach.

Moreover, while the included studies were generally classified as having low concerns for bias according to the Cochrane Collaboration tool, significant potential biases were identified in the studies by Fredrickson et al. and Tawfeek et al. These biases, which included variations in operator experience and the use of different adjuncts or techniques (e.g., subcutaneous tunneling), could undermine the strength of their findings. These factors should be accounted for when interpreting the results of this meta-analysis.

Lastly, the generalizability of our findings may be limited by the relatively narrow range of patient populations included in the analyzed RCTs. Most studies focused on elective surgery populations, and the outcomes may not be applicable to patients with more complex medical conditions or those undergoing emergency procedures.

To the best of our knowledge, this meta-analysis represents the only comparative analysis of Pippa's and Winnie's techniques to date. Our study aimed to investigate whether these two techniques led to different outcomes, such as procedure time and complete sensory block. Our findings indicate no significant difference in complete block rate or procedure time between the two techniques. Consequently, contrary to some randomized controlled trials, this meta-analysis demonstrates no obvious superiority of one technique. The observed differences in previous randomized

trials can largely be attributed to biases, such as differences in expertise or failure to implement specific steps in one approach.

Conclusion

Our meta-analysis compared the anterior and posterior approaches for Interscalene Block (ISB), finding no significant differences in speed or success rates between the two techniques. However, our findings suggest that the anterior approach, followed by catheter placement, may offer superior postoperative pain control, and reduced opioid consumption in PACU. Patients with large anterior neck masses, such as those with goiter or thyroid cancer, may benefit more from the posterior approach due to anatomical considerations. Each technique has distinct advantages and risks, so the choice of approach should be tailored to the provider's expertise and the individual patient's clinical scenario. Further research is needed to evaluate long-term outcomes, including complication rates and patient satisfaction.

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.2024.844574.

References

1. Bowens C, Sripada R. Regional Blockade of the Shoulder: Approaches and Outcomes. Anesthesiol Res Pract. 2012;2012:1—12.
2. Jiangping W, Xiaolin Q, Han S, et al. Network Meta-Analysis of Perioperative Analgesic Effects of Different Interventions on Postoperative Pain After Arthroscopic Shoulder Surgery Based on Randomized Controlled Trials. Front Med. 2022;9:921016.
3. Bishop JY, Sprague M, Gelber J, et al. Interscalene regional anesthesia for arthroscopic shoulder surgery: A safe and effective technique. J Shoulder Elbow Surg. 2006;15:567—70.
4. Bishop JY, Sprague M, Gelber J, et al. Interscalene Regional Anesthesia for Shoulder Surgery. J Bone Jt Surg. 2005;87:974—9.
5. Urban MK, Urquhart B. Evaluation of brachial plexus anesthesia for upper extremity surgery. Reg Anesth. 1994;19:175—82.
6. Singelyn FJ, Lhotel L, Fabre B. Pain Relief After Arthroscopic Shoulder Surgery: A Comparison of Intraarticular Analgesia, Suprascapular Nerve Block, and Interscalene Brachial Plexus Block. Anesth Analg. 2004;99:589—92.
7. Thomas LC, Graham SK, Osteen KD, Porter HS, Nossaman BD. Comparison of ultrasound and nerve stimulation techniques for interscalene brachial plexus block for shoulder surgery in a residency training environment: a randomized, controlled, observer-blinded trial. Ochsner J. 2011;11:246—52.
8. Hopkins PM. Ultrasound guidance as a gold standard in regional anaesthesia. Br J Anaesth. 2007;98:299—301.
9. McCartney CJL, Lin L, Shastri U. Evidence Basis for the Use of Ultrasound for Upper-Extremity Blocks. Reg Anesth Pain Med. 2010;35(Suppl 1):S10—5.
10. Choi S, McCartney CJL. Evidence Base for the Use of Ultrasound for Upper Extremity Blocks: 2014 Update. Reg Anesth Pain Med. 2016;41:242—50.
11. Bergmann L, Martini S, Kesselmeier M, et al. Phrenic nerve block caused by interscalene brachial plexus block: breathing effects of different sites of injection. BMC Anesthesiol. 2015;16:45.
12. Winnie AP. Interscalene brachial plexus block. Anesth Analg. 1970;49:455—66.
13. Zisquit J, Nedeff N. Interscalene Block. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. 2022 Sep 19.
14. McNaught A, McHardy P, Awad IT. Posterior interscalene block: an ultrasound-guided case series and overview of history, anatomy and techniques. Pain Res Manag. 2010;15:219—23.
15. Mariano ER, Loland VJ, Ilfeld BM. Interscalene Perineural Catheter Placement Using an Ultrasound-Guided Posterior Approach. Reg Anesth Pain Med. 2009;34:60—3.
16. Rettig H, Gielen M, Jack N, Boersma E, Klein J. A Comparison of the Lateral and Posterior Approach for Brachial Plexus Block. Reg Anesth Pain Med. 2006;31:119—26.
17. Fredrickson MJ, Ball CM, Dalgleish AJ. Posterior Versus Anterolateral Approach Interscalene Catheter Placement: A Prospective Randomized Trial. Reg Anesth Pain Med. 2011;36:125—33.
18. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst Rev. 2022;18:e1230.
19. TB Mauren Carbonar, Catreen Abouelsaad, Michael Mahla, Luis Ciconini. Anterolateral and posterior approach for interscalene brachial plexus block: a systematic review and meta-analysis. PROSPERO. from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023469151.
20. Singh A, Kelly C, O'Brien T, Wilson J, Warner JJ. Ultrasound-Guided Interscalene Block Anesthesia for Shoulder Arthroscopy: A Prospective Study of 1319 Patients. J Bone Joint Surg Am. 2012;94:2040—6.
21. Kinnard P, Truchon R, St-Pierre A, Montreuil J. Interscalene block for pain relief after shoulder surgery. A prospective randomized study. Clin Orthop Relat Res. 1994(304):22—4.
22. Tetzlaff JE, Yoon HJ, Brems J. Interscalene brachial plexus block for shoulder surgery. Reg Anesth. 1994;19:339—43.
23. D'Alessio JG, Rosenblum M, Shea KP, Freitas DG. A retrospective comparison of interscalene block and general anesthesia for ambulatory surgery shoulder arthroscopy. Reg Anesth. 1995;20:62—8.
24. Antonakakis JG, Sites BD, Shiffrin J. Ultrasound-guided posterior approach for the placement of a continuous interscalene catheter. Reg Anesth Pain Med. 2009;34:64—8.
25. Mariano ER, Afra R, Loland VJ, et al. Continuous Interscalene Brachial Plexus Block via an Ultrasound-Guided Posterior Approach: A Randomized, Triple-Masked, Placebo-Controlled Study. Anesth Analg. 2009;108:1688—94.
26. Sandefo I, Iohom G, Vanelstraete A, Lebrun T, Polin B. Clinical Efficacy of the Brachial Plexus Block via the Posterior Approach. Reg Anesth Pain Med. 2005;30:238—42.
27. Grefkens JM, Bürger K. Total spinal anaesthesia after an attempted brachial plexus block using the posterior approach. Anaesthesia. 2006;61:1105—8.
28. Klein SM, Grant SA, Greengrass RA, et al. Interscalene Brachial Plexus Block with a Continuous Catheter Insertion System and a Disposable Infusion Pump. Anesth Analg. 2000;91:1473—8.
29. Borgeat A. All Roads Do Not Lead to Rome. Anesthesiology. 2006;105:1—2.

30. Borgeat A, Dullenkopf A, Ekatodramis G, Nagy L. Evaluation of the Lateral Modified Approach for Continuous Interscalene Block after Shoulder Surgery. Anesthesiology. 2003;99:436—42.
31. Tawfeek MM, Hassanin MA. Comparison between continuous posterior and lateral interscalene brachial plexus blockades for major shoulder surgery. Egypt J Anaesth. 2011;27. sc.
32. Aoyama Y, Sakura S, Kitajo A, Saito Y. Incidence and effects of postoperative migration of interscalene catheter tips placed using ultrasound-guided anterior and posterior approaches. J Anesth. 2021;35:175—83.
33. Park HS, Kim HJ, Ro YJ, Yang HS, Koh WU. Delayed bilateral vocal cord paresis after a continuous interscalene brachial plexus block and endotracheal intubation: A lesson why we should use low concentrated local anesthetics for continuous blocks. Medicine (Baltimore). 2017;96:e6598.
34. Passannante AN. Spinal Anesthesia and Permanent Neurologic Deficit After Interscalene Block. Anesth Analg. 1996;82:873—4.
35. Thukral S, Gupta P, Gupta M, Lakra A. Recurrent laryngeal nerve palsy following interscalene brachial plexus block: How to manage and avoid permanent sequelae? J Anaesthesiol Clin Pharmacol. 2015;31:282.
36. Villar T, Pacreu S, Zalbidea M, Montes A. Prolonged dysphonia as a complication of interscalene block. Injury. 2015;46:1409—10.
37. Franco CD, Williams JM. Ultrasound-Guided Interscalene Block: Reevaluation of the "Stoplight" Sign and Clinical Implications. Reg Anesth Pain Med. 2016;41:452—9.
38. Gupta A, Procopio GL, Charles PH, Hernandez M, Patel R. Inadvertent Intrathecal Administration of Local Anesthetics Leading to Spinal Paralysis with Lipid Emulsion Rescue. Clin Pract Cases Emerg Med. 2017;1:81—3.
39. Whitaker EE, Edelman AL, Wilckens JH, Richman JM. Severe hypotension after interscalene block for outpatient shoulder surgery: a case report. J Clin Anesth. 2010;22:132—4.
40. Riazi S, Carmichael N, Awad I, Holtby RM, McCartney CJL. Effect of local anaesthetic volume (20 vs. 5 mL) on the efficacy and respiratory consequences of ultrasound-guided interscalene brachial plexus block. Br J Anaesth. 2008;101:549—56.
41. Rose M, Ness T. Hypoxia following interscalene block☆. Reg Anesth Pain Med. 2002;27:94—6.
42. Ferré F, Pommier M, Laumonerie P, et al. Hemidiaphragmatic paralysis following ultrasound-guided anterior vs. posterior suprascapular nerve block: a double-blind, randomised control trial. Anaesthesia. 2020;75:499—508.
43. Oliver-Fornies P, Ortega Lahuerta JP, Gomez Gomez R, et al. Diaphragmatic paralysis, respiratory function, and postoperative pain after interscalene brachial plexus block with a reduced dose of 10 ml levobupivacaine 0.25% versus a 20 mL dose in patients undergoing arthroscopic shoulder surgery: study protocol for the randomized controlled double-blind REDOLEV study. Trials. 2021;22:287.
44. Rettig HC, Lerou JGC, Gielen MJM, Boersma E, Burm AGL. The pharmacokinetics of ropivacaine after four different techniques of brachial plexus blockade. Anaesthesia. 2007;62:1008—14.
45. Schwenk ES, Gandhi K, Baratta JL, et al. Ultrasound-Guided Out-of-Plane vs. In-Plane Interscalene Catheters: A Randomized, Prospective Study. Anesthesiol Pain Med. 2015;5:e31111.

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REVIEW ARTICLE

The impact of patient- and family-centered care interventions on intensive care unit outcomes: a meta-analysis of randomized controlled trials

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KEYWORDS
Critical care;
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Patient centered care

Abstract
Background: Patient and Family-Centered Care (PFCC) interventions are increasingly recognized as a viable approach to address various mental health issues among patients in Intensive Care Units (ICUs). Therefore, this review aims to estimate the effect of Patient and Family-Centered Care Interventions on specific outcomes in adult patients admitted to Intensive Care Units (ICUs).
Methods: We systematically searched four major databases for parallel arm Randomized Controlled Trials (RCTs). The PRISMA framework was used to report our review. We included studies involving adult patients (> 18-years) admitted to ICUs and examined the effects of any type of Patient and Family-Centered Care intervention (PFCC) on outcomes such as depression, anxiety, delirium, and length of hospital stay. Data extraction was performed independently by two authors in Medline, Google Scholar, and ScienceDirect, from inception to July 2024. Random effects model was used to pool the data.
Results: A total of 11 studies were included in our systematic review and meta-analysis, with a combined sample size of 3352 patients (PFCC group, n = 1681; usual care group, n = 1671). A random-effects model revealed a significant reduction in delirium prevalence in the PFCC group, with a pooled Risk Ratio (RR) of 0.54 (95% CI 0.36 to 0.81). However, no statistical significance was found for other outcomes such as depression, length of ICU stay, and anxiety. It is important to note that all the included studies were assessed to have either a high or unclear risk of bias.
Conclusion: PFCC interventions may significantly reduce delirium rates among ICU patients; however, their effects on other outcomes, such as depression, anxiety, and length of stay, were not statistically significant.
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Introduction

Admission to an Intensive Care Unit (ICU) due to critical or terminal illness is a stressful experience for both patients and their relatives.[1,2] These stressful situations have been shown to increase physical and psychological stress among patients, leading to delirium, depression, and anxiety.[3] Studies have even demonstrated that these events further complicate ICU admissions, resulting in longer stays, increased post-traumatic stress, and even mortality.[3] Recent research has also highlighted the impact of these consequences on the families and relatives of patients, who may experience anxiety, depression, and Post-Traumatic Stress Disorder (PTSD) during their time in the ICU.[4,5]

The Institute of Patient and Family-Centered Care defines family-centered care as an approach that involves planning, evaluation, and the delivery of mutually beneficial care between healthcare providers, patients, and their family members.[6] PFCC interventions are based on four core principles: dignity and respect, information sharing, patient and family participation in care, and collaboration between healthcare providers and families.[7] This approach emphasizes the involvement of family members in the delivery of healthcare.[8] Recent studies have suggested that PFCC can be a viable intervention for improving psychological and clinical outcomes, given they empower patients, improve coping mechanisms and satisfaction, prominently reduce psychological distress and streamline the care process.[9-11] As a result, PFCC has become an integral part of hospital care, encompassing the implementation of management protocols, counseling, and specific interventions.[12] In an ICU setting, effective patient and family communication is a crucial challenge, as we heavily rely on families for decision-making and support.[13] However, some studies have raised concerns about the potential for PFCC to contribute to additional cases of delirium among patients and family members. As of now, there has been no comprehensive review examining the effects of PFCC on ICU outcomes, specifically delirium, depression, anxiety, and mortality. Therefore, we conducted this review to estimate the impact of Patient and Family-Centered Care Interventions on specific outcomes in adult patients admitted to intensive care units.

Methods

Research question

Among adult patients admitted to the Intensive Care Unit, what is the effect of Patient and Family-Centered Care Interventions on ICU outcomes?

Inclusion and exclusion criteria

For this review, we included all parallel-arm individual randomized, or cluster randomized controlled trials. Studies reported as full text were included, while studies published only as abstracts or unpublished data were excluded. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to report our results.[14] We only included studies reported in English from the following databases: Medline, Google Scholar, and ScienceDirect, from inception to July 2024. The detailed search strategy is explained in the supplemental material.

Participants

We included studies with adult patients (> 18-years) admitted to ICUs, assessing the impact of any PFCC interventions on outcomes like depression, anxiety, delirium, and length of hospital stay. We excluded studies conducted among pediatric and neonatal patients and specialized ICUs. A family member, defined based on individual studies, could be an adult (> 18-years), spouse, partner, friend, or blood or non-blood relative of the adult ICU-admitted patients.[15]

Type of intervention and comparator

Our review included studies involving any type of Patient and Family-Centered Care Interventions (PFCC) aimed at improving outcomes in adult ICU patients. We included studies that provided PFCC to adult patients regardless of their disease severity. We excluded studies that focused on interventions for family members, interventions implemented before improvement in study outcomes prior to ICU admission, interventions targeting specific subgroups such as dying patients or patients with cognitive impairment, and interventions that did not involve the active participation of family members during their ICU stay. The intervention was compared to a control group receiving standard medical care without any form of PFCC intervention during their ICU stay.

Type of outcome measure

The primary outcome of interest was to examine the difference in the rate of depression in the intervention and comparator group. Secondary outcome were anxiety, delirium and length of hospital stay (in days).

We included studies reporting any of the above-mentioned outcomes in either arm.

Data collection and analysis

Two independent investigators (YL and PL) conducted the literature search, and screened titles, abstracts, and keywords of all selected studies for inclusion in our review. Relevant full-text articles were extracted. The abstracts and full texts of retrieved articles were further screened independently by the primary and secondary investigators. We used the PICOS (Population, Intervention, Control, and Outcome Study) design for identifying and extracting potential studies for inclusion in our analysis. Any disagreements between the two investigators during the selection process were resolved through consensus or consultation with a third investigator (KC). The third investigator also monitored the quality of the overall review process.

The primary investigator extracted relevant study characteristics for the review from the included studies. Only

the relevant arms were included for studies reporting multiple arms from a single trial. The primary investigator entered the data into Microsoft Excel, and the third investigator double-checked the data entry for accuracy.

Two independent investigators (RL and TZ) assessed the risk of bias in the included studies using the Cochrane risk of bias tool for Randomized Controlled Trials.[16] Randomization was used for the allocation of study participants into intervention and control arms in all the included studies. However, none of the included studies provided a clear description of blinding of participants and outcome assessment. Five out of the eleven included studies had a high risk of bias with respect to blinding and were categorized as high risk, while the remaining six were categorized as an unclear risk due to insufficient information on blinding and outcome assessment. We summarized the risk of bias using the criteria established by Higgins et al.[17]

Statistical analysis

We evaluated the pooled effect of PFCC on the outcome such as a change in the rate of delirium, anxiety, depression, and length of ICU stay through the inverse variance method using the Mean Difference (MD) and standard deviation. Binary outcomes such as delirium were summarized using Risk Ratios (RR) with a 95% Confidence Interval (95% CI) using the Mantel-Haenszel method. Finally, the pooled estimate was reported as mean difference with 95% Confidence Interval. Analysis was performed in STATA version 14.2.

Assessment of heterogeneity

Chi-Square test of heterogeneity and I^2 statistic (to quantify heterogeneity) were used to assess the between-study variance due to heterogeneity. I^2 less than 25% was considered mild, 25%—75%, moderate, and more than 75% as substantial heterogeneity. Study details and pooled estimates were graphically represented through a forest plot. Heterogeneity often indicates significant variability in study design, populations, interventions, or other factors.

Since we collected information from openly available sources, we do not warrant an Ethical clearance

Certainty of evidence

The quality of evidence in the included studies was evaluated following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. As per GRADE guidelines, Randomized Controlled Trials (RCTs) initially provide high-certainty evidence. However, the certainty of evidence was downgraded based on our evaluation of five key domains: study limitations, inconsistency, imprecision, indirectness, and publication bias. For each outcome, the evidence was classified as high, moderate, low, or very low certainty. Additionally, the GRADE criteria account for both the certainty of evidence and the magnitude of the observed effect.

Results

Study selection

Through our systematic review, a total of 1906 articles were identified and screened, of which 1295 duplicates were removed. During the primary screening, 521 articles were excluded as they did not meet our inclusion criteria. Thus, finally, 90 articles were chosen for secondary screening, of which 11 were included for the systematic review and meta-analysis.[18-28] The total number of participants was n = 3352, with the PFCC group consisting of n = 1681 and the usual care group consisting of n = 1671. The PRISMA flow diagram explaining the process is presented in Figure 1.

Included and excluded studies

Table 1 provides the study characteristics of the individual articles included in the review. The intervention mainly focused on any intervention that included Patient and Family-Centered Care Interventions (PFCC) aimed at improving outcomes of adult patients in the ICU. The most commonly studied primary outcome was depression, anxiety, and delirium, while other commonly studied secondary outcomes included in-hospital mortality and length of ICU stay. Sample sizes across these studies ranged from as small as 35 participants (Sayde 2020 in the USA) to as large as 1685 participants (Rosa 2019 in Brazil). The interventions typically involved diaries, educational booklets, and structured communication between healthcare providers, patients, and their families, aiming to reduce psychological stressors such as anxiety, depression, and delirium during and after ICU stays. The primary outcomes measured across the studies largely focused on psychological effects, particularly the reduction of delirium, anxiety, and depression, with tools like the Hospital Anxiety and Depression Scale (HADS) and Confusion Assessment Method for ICU (CAM-ICU) commonly employed. Secondary outcomes frequently included length of ICU stay and overall hospital stay, although reductions in these outcomes were not uniformly observed across all studies.

Out of the 76 full-text articles that we extracted; we excluded 65 studies. Among them, 42 were conducted among non-ICU populations, 13 had no clear definition of PFCC, four were non-Randomized Controlled Trials (non-RCTs), three had different outcome measures, two were study protocols, and the remaining one was in Arabic.

Effects of interventions

Effect of PFCC on anxiety among patients admitted to the ICU: Four studies reported anxiety among patients (n = 690, PFCC group: n = 339, control group: n = 351). The Pooled Mean Difference (PMD) was estimated as -0.10 (95% CI: -0.70 to 0.50), indicating no significant reduction in anxiety levels across the groups (Fig. 2). We found moderate heterogeneity among the studies in reporting this outcome (I^2 = 59.9%, p = 0.058). The data was extracted as mean (SD) from all four studies that utilized the Hospital Anxiety and Depression Scale (HADS) questionnaire to measure anxiety. Another study by Neilson et al. was not included in the analysis as it failed to report the mean (SD) of the depression and anxiety

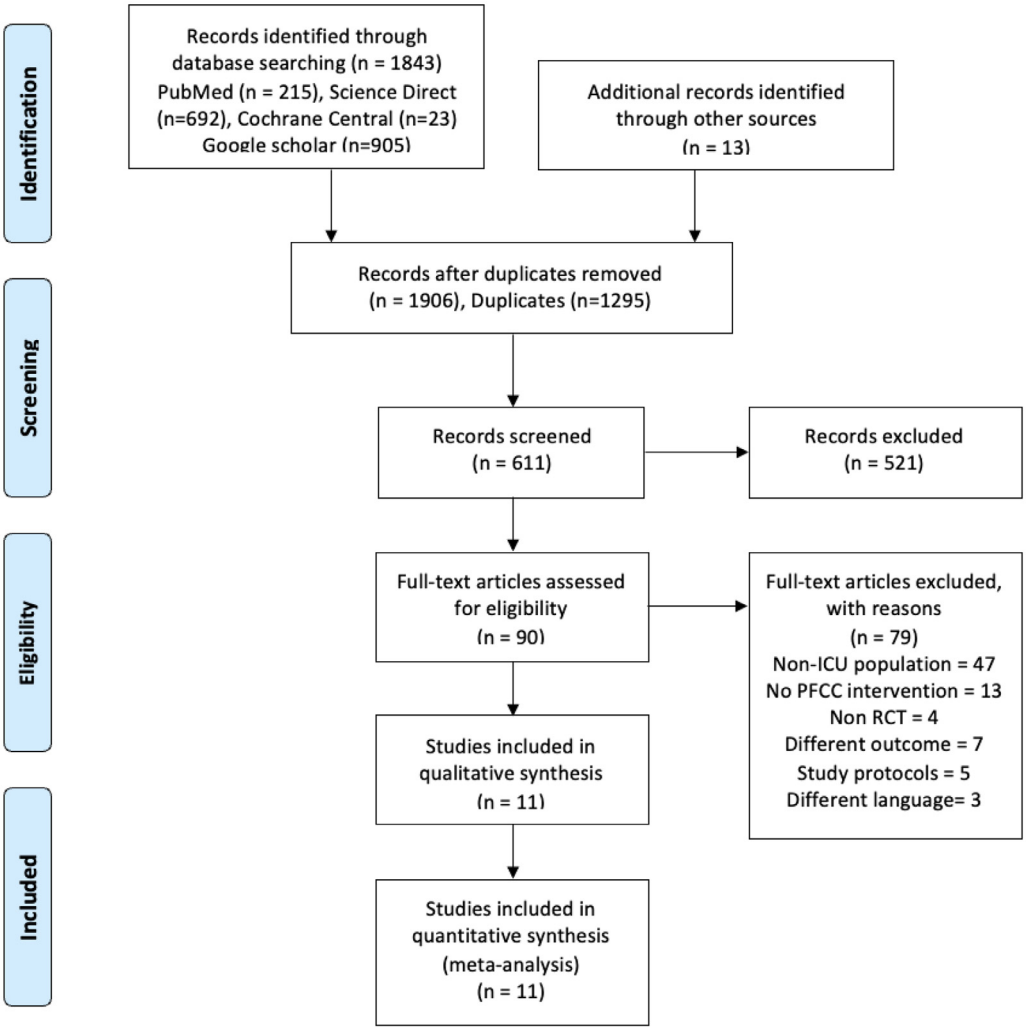

Figure 1 PRISMA flow diagram explaining the search flow.

scores between the groups, reporting anxiety as a binary outcome with a cut-off > 11 as anxiety.[29]

Effect of PFCC on depression among patients admitted to the ICU: The same four studies that reported anxiety among patients (n = 690, PFCC group: n = 339, control group: n = 351) also reported depression measured using the same HADS questionnaire. The pooled mean difference (PMD) was -0.19 (95% CI: -0.50 to 0.11), indicating that PFCC did not significantly reduce depression between the intervention group and the control group (Fig. 3). We found nil heterogeneity among the studies in reporting this outcome (I^2 = 0.0%, p = 0.60).

Effect of PFCC on delirium among patients admitted to ICU: Of the 11 included studies, seven reported delirium prevalence as an outcome measure at the study endpoint (n = 2662; PFCC group: n = 1342; control group: n = 1320). Using the random-effects model, we observed a significant reduction in delirium prevalence in the PFCC group, with a pooled Risk Ratio (RR) of 0.54 (95% CI 0.36 to 0.81), although there was significant heterogeneity among the studies (I^2 = 86.8%, p < 0.001) (Fig. 4).

Effect of PFCC on length of ICU stay among patients admitted to the ICU: Five studies reported the change in the duration of ICU stay for both groups (n = 2762; PFCC group: n = 1375; control group: n = 1387). The Pooled Mean Difference (PMD) was -0.97 (95% CI: -3.05 to 1.10), indicating no significant reduction in ICU stay duration among the groups (Fig. 5). We found very high heterogeneity among the studies in reporting this outcome (I^2 = 97.8%, p < 0.001).

Sensitivity analysis

We did not perform a sensitivity analysis as we did not find any low-risk studies included in our review. Out of the eleven studies included in our review, five had a high risk of bias, while the remaining six had an unclear risk of bias. GRADE evidence showed that all studies included in our review were of low quality of evidence.

Discussion

In our systematic review and meta-analysis, we pooled findings from various studies conducted across countries to estimate the effect of Patient and Family-Centered Care Interventions (PFCC) on specific outcomes among adult

Table 1 Characteristics of included studies (n = 11).

Study and study design	Country	Study population	Sample size	Type of ICU and number of sites	Primary and Secondary outcomes	Description
Garrouste 2019 (RCT)	France	Patients aged more than 18-years on mechanical ventilation for > 48 hours, who were initiated on ventilation within 48 hours of ICU admission	n = 339 (Intervention = 164, Control = 175)	Multicentric study including 35 ICUs	Primary outcomes: The proportion of patients who had PTSD symptoms after 3-months of ICU discharge, evaluated through Impact of Event Scale-Revised (IES-R) questionnaire. Secondary outcomes: Secondary outcomes measured included anxiety and depression measured using HADS (Hospital Anxiety and Depression Scale (HADS) score) evaluated 3-months after ICU discharge and length of ICU stay	The intervention was basically a diary that was filled out duly by the clinicians and the family members, while the concluding note was written by the clinician before patients were transferred to the ICU. The diary details were explained to the patients before they were discharged and in case, they were not able to comprehend it or understand it, it was detailed to the family member or the caretaker. The comparator group did not receive any diary intervention.
Bench 2015 (Cluster RCT)	United Kingdom	Patients over 18-years of age who were at least 72h in the ICU and declared fit to be transferred to the general ward.	n = 158 (Intervention - user-centered critical care discharge information pack (UCCDIP; n = 51), control 1: ad hoc verbal information (n = 59), control 2: booklet published by ICU steps (n = 48).	A multicentric study including 2 ICUs with mixed patients (medical, surgical and trauma care)	Primary outcomes: Patient Anxiety and depression were measured using HADS (Hospital Anxiety and Depression Scale-HADS score) post 28-days of ICU stay. Secondary outcomes: Length of Stay (LOS).	The patients were provided with discharge information booklets which either had UCCDIP or the ICU steps; one each for the patient and the family prior to discharge. The booklet had information regarding discharge summary, diary pages to write about patient's thoughts and feelings that they felt during the hospital stay. The comparator group received the usual care with adhoc verbal information on ICU discharge

Table 1 (*Continued*)

Study and study design	Country	Study population	Sample size	Type of ICU and number of sites	Primary and Secondary outcomes	Description
Sayde 2020 (RCT)	USA	The study included patients who were over 18-years of age and had an ICU stay of more than 72h, and also who were sedated and intubated for more than 24h, with any pre-existing PTSD, dementia, or intracranial injury	n = 35 (Intervention = 18, Control = 17)	Single, mixed ICU with both medical and surgical patients	Primary outcomes: Post traumatic stress measured using IES-R, general well-being using the Patient Health Questionnaire (PHQ-8) Anxiety and depression using Hospital Anxiety and Depression Scale (HADS), and Generalized Anxiety Disorder 7-item (GAD-7) at 1-week of ICU discharge, and again at 4-weeks, 12-weeks and 24-weeks following discharge. Secondary outcomes: Length of hospital stay	All patients who were enrolled into the intervention group were provided with a bedside diary, and the patients and family were asked to write down the changes and daily events. PTSD education was provided to the participants starting within 1-week of admission.
Azoulay 2018 (RCT)	France	Patients were enrolled into the study if they were > 18-years and had received mechanical ventilation before 48hrs of ICU admission. For every patient one relative was included.	n = 302 (Intervention = 148, Control = 154)	Multicentric study with included data from 14 ICUs	Primary outcomes: Anxiety and depression measured using HADS after 5-days of intervention. Secondary outcomes: Family satisfaction	Validated list of 21 questions were given to relatives so they could ask questions to help improve comprehension of patient diagnosis and treatment. Usual care had family and staff conferences with no intervention list.

Table 1 (*Continued*)

Study and study design	Country	Study population	Sample size	Type of ICU and number of sites	Primary and Secondary outcomes	Description
Black 2010 (RCT)	Ireland	Patients were enrolled into the study if they are > 18-years and provided consent for the study Patients and family members who were not able to participate physically in the intervention were excluded.	n = 170 (83 in the control group and 87 in the intervention group)	A single center study including mixed ICUs	Primary: Intensive Care Delirium Screening Checklist (ICDSC) was used to measure delirium, Therapeutic Intervention Scoring System-28 to measure severity of illness, and Sickness Impact Profile for psychological recovery measured on day 1, 14 and at months 1, 2 and 3.	The intervention was provided to all patients in the intervention group through voice messages that were aimed to reduce the stressors during the stay in ICU. The intervention included a booklet that contained information on delirium guide and psychological care. Information on how to deliver the information verbally and written ways were outlined and explained to the intervention group. Control group received usual care.
Gan Xioaqing 2017 (RCT)	China	Patients were enrolled into the study if they were > 18-years and who provided consent for the study with no previous history of diagnosed delirium	n = 391 (178 in the control group and 213 in the intervention group)	A single center study including mixed ICUs	Primary: Delirium measured during follow up after discharge and 14-days after, measured using Confusion Assessment Method—ICU (CAM—ICU) tool. Secondary outcomes: Length of hospital stay	The intervention group received a booklet that had instructions to the patient and the family member on prevention of delirium. The control group received usual care.
Jiao Xueping 2021 (RCT)	China	Patients were enrolled into the study if they were > 18-years and who provided consent for the study with no previous history of diagnosed delirium	n = 164 (82 in the control group and 82 in the intervention group)	A single center study including mixed ICUs	Primary: Delirium measured during follow up after discharge and 14-days after, and post 3-months of discharge. Secondary outcomes: Length of hospital stay	The intervention group received a diary that was provided to note down the daily happenings and proceedings by the patient, and by the family member, in case the patient. Health education on delirium and anxiety prevention was provided to them three days post admission in ICU. The control group received usual care.

Table 1 (*Continued*)

Study and study design	Country	Study population	Sample size	Type of ICU and number of sites	Primary and Secondary outcomes	Description
Eghbali Babadi 2017 (RCT)	Iran	Patients between 18–70-years, who were accompanied by their family members, with no history of addictions, delirium, cognitive or mental disorders	n = 68 (34 in both control group and intervention group)	A single center study including patients who were admitted following open heart surgery in the ICU	Primary: Development of delirium, assessed using the Confusion Assessment Method —ICU (CAM—ICU) tool designed to assess the patients concerning delirium (twice a day assessed). Secondary outcomes: Level of irritability measured using the Richmond Agitation Sedation Scale (RASS)	The next day after surgery, one among the family members in the intervention group who received education (which focused on the goal, signs, causes and methods of prevention of delirium) prior visited the patient. Pamphlets were also distributed to them. In the control group, patients received routine care and no special visit was made
Ma Hong 2015 (RCT)	China	Patients above 18-years of age, who were admitted for more than 72 hours in ICU, with no prior diagnosed delirium or cognitive dysfunction	n = 164 (Intervention = 84 and Control = 80)	A single center study including patients from mixed ICU	Primary outcomes: Delirium rates measured using CAM-ICU	The intervention included a booklet that was provided to the family member, that consisted of educational information on guidance to alleviate stress response and improve psychological stability. In the control group, patients received routine care

Table 1 (*Continued*)

Study and study design	Country	Study population	Sample size	Type of ICU and number of sites	Primary and Secondary outcomes	Description
Mitchell 2017 (RCT)	Australia	The study participants included patients aged more than 16-years, with more than 96 hours ICU stay, and willing to get screened for delirium, and a family member attending them. One family member per patient was selected	434	A single center study including patients from mixed ICU	Primary: Delirium rates measured using CAM-ICU. Secondary outcomes: Level of irritability measured using the Richmond Agitation Sedation Scale (RASS)	The intervention consisted of an educational protocol that had the template on description of intervention and a guide that helps in implementation which was adopted from previous studies. The protocol had details on orientation on memory, therapeutic engagement for cognitive stimulation and has activities to discuss family events, finally a sensory tool which has hearing aids and glasses. The control group received only usual care.
Rosa 2019 (Cluster randomized trial)	Brazil	Patients more than 18-years admitted to the ICUs with more than 96 hours stay were included.	n = 1685 (Intervention = 837 and Control = 848)	Cluster-crossover RCT including 36 mixed ICUs	Primary: Delirium rates measured using CAM-ICU. Secondary outcomes: Length of ICU stay, ICU acquired infections	The intervention included a model through which the flexible visits to ICU were advocated for family education. Family members attended the meeting regularly to learn about ICU environment, palliative care and delirium prevention.

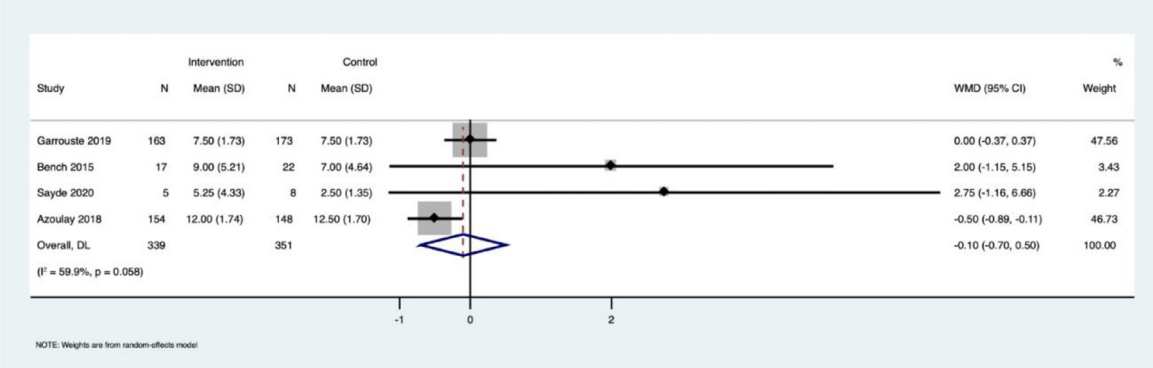

Figure 2 Forrest plot describing the effect of PFCC on anxiety among patients admitted in ICU.

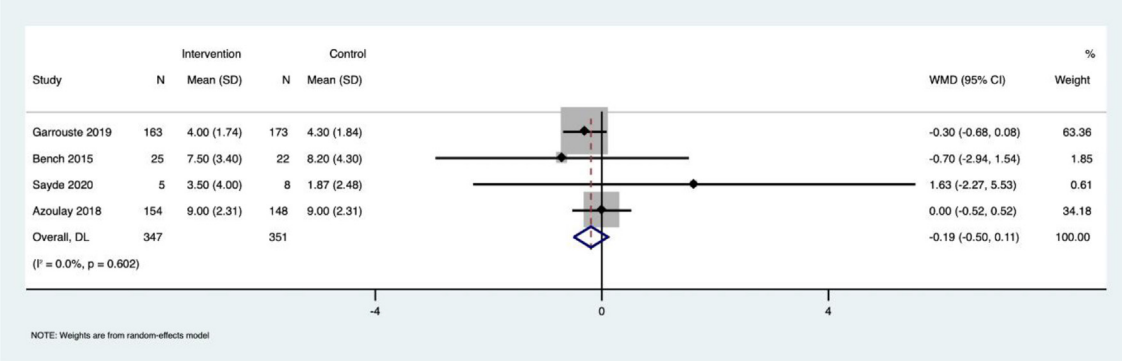

Figure 3 Forrest plot describing the effect of PFCC on depression among patients admitted in ICU.

patients admitted to Intensive Care Units (ICUs). We included eleven Randomized Controlled Trials (RCTs) to evaluate the impact of PFCC on outcomes such as patient depression, anxiety, delirium, and length of hospital stay. However, we only observed a significant reduction in ICU stay in the PFCC group compared to the control group.

The ICU environment is known to induce fear and emotional distress among family members of admitted patients due to factors like inaccessibility, lack of information, absence of joint decision-making, and uncertainty of life.[30] Frequent communication and involving family members in the healthcare decision-making process can enhance family understanding of the patient's health condition and provide hope. Additionally, including family members in the decision-making process can improve risk communication by healthcare personnel.[31]

Previous studies have shown that ICU-related delirium primarily stems from fear of the ICU environment and patients' medical condition. Furthermore, patients without family visits tend to have a threefold higher risk of

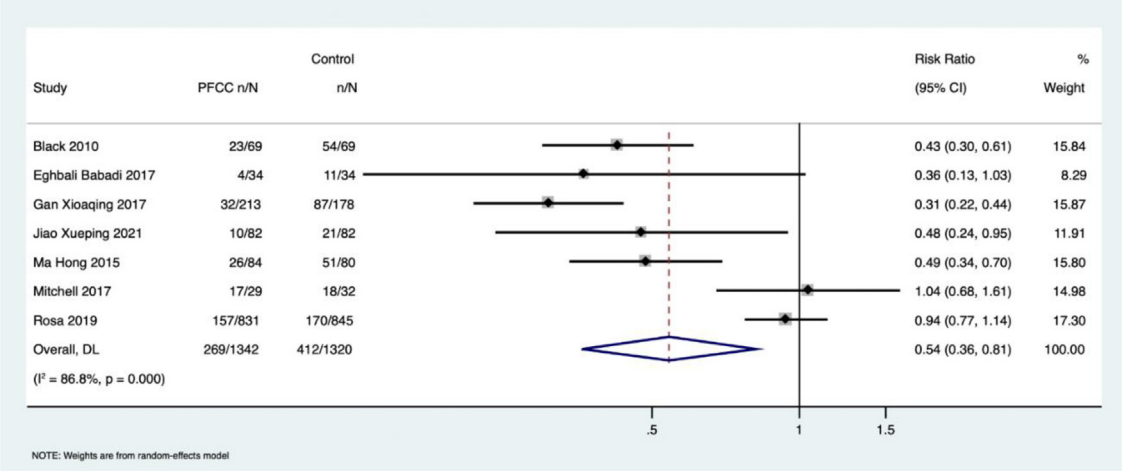

Figure 4 Forrest plot describing the effect of PFCC on delirium among patients admitted in ICU.

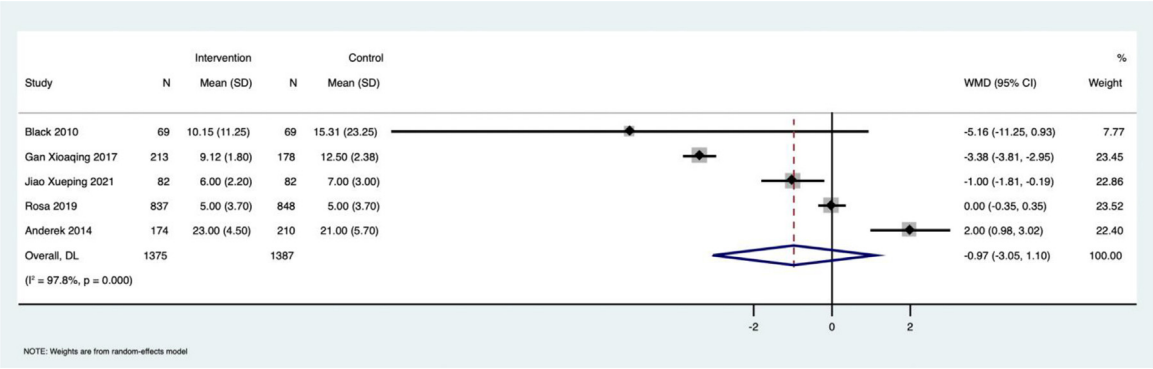

Figure 5 Forrest plot describing the effect of PFCC on length of ICU stay among patients admitted in ICU.

developing delirium.[32] While previous studies have demonstrated the effectiveness of PFCC interventions in preventing delirium among non-ICU populations, they did not observe a significant change in the duration of delirium. Our study, on the other hand, showed that PFCC had a significant impact on reducing delirium in ICU patients. Another interprofessional multinational perspective document by Pandharipande in 2017 advocates for RCTs exploring the effect of PFCC on delirium reduction.[33] Our results align with previous studies by Lin et al. and McKenzie et al.[34-36]

In terms of depression and anxiety reduction, our study did not observe statistically significant results through PFCC intervention. However, contrasting results were shown in studies by Neilson et al. and Sayde et al.[18,29] These discrepancies could be attributed to differences in study population, comorbidity patterns, intervention types and durations, as well as variations in outcome assessment scales. Our findings are consistent with a meta-analysis conducted by Bohart et al. in 2021, which similarly demonstrated a non-significant reduction in anxiety and depression following PFCC.[37]

Regarding the duration of ICU stay, our study did not find a significant association with PFCC interventions, which aligns with the results of other studies.[38-41] Some studies have also indicated that PFCC can alleviate depression and anxiety even among family members participating in the intervention.

Our study has several strengths. It is one of the few studies that has attempted to generate evidence on the effectiveness of PFCC interventions on various ICU outcomes. Compared to previous reviews on the same topic, our review is more comprehensive as we included newer research articles with diverse outcomes and a larger sample size. All studies were independently screened and assessed for risk of bias by two authors. We exclusively included RCTs, further enhancing the quality of the pooled evidence.

However, our review also possesses several limitations.

1. Risk of bias in included studies: The review acknowledges that all included studies were assessed to have either a high or unclear risk of bias. Five out of the eleven studies had a high risk of bias concerning blinding, while the remaining six had an unclear risk due to insufficient information on blinding and outcome assessment. This high risk of bias significantly limits the validity and reliability of the meta-analysis findings.
2. Limited scope of databases: The systematic search was conducted only in three databases: Medline, Google Scholar, and ScienceDirect. Key databases such as Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were not included. This restricted search may have resulted in the omission of relevant studies, potentially introducing selection bias.
3. Language bias: The review only included studies reported in English. This introduces language bias and may have excluded high-quality studies published in other languages, potentially impacting the comprehensiveness of the review.
4. Inconsistent outcome measures: Different studies utilized various tools and scales to measure the same outcomes (e.g., anxiety, depression). Although the authors pooled estimates using a weighted mean difference, the inconsistency in outcome measures could contribute to the observed heterogeneity and affect the validity of the pooled results.
5. Heterogeneity among studies: There was significant heterogeneity observed in the meta-analysis, particularly concerning the effects on delirium (I^2 = 86.8%) and length of ICU stay (I^2 = 97.8%). Such substantial heterogeneity suggests variability in study designs, populations, interventions, and outcome assessments, which complicates the interpretation of pooled effects and reduces the overall strength of the conclusions.
6. Focus on freely available full-text articles: The inclusion criteria were limited to freely available full-text articles. This restriction may have excluded potentially relevant studies not freely accessible, contributing to selection bias and reducing the comprehensiveness of the review.
7. Limited exploration of patient characteristics: The review did not account for the primary diagnoses or characteristics of the ICU patients in the included studies. Differences in patient demographics and clinical conditions could influence outcomes, and without this consideration, the applicability of the review's findings to diverse patient populations is limited.
8. Lack of sensitivity analysis: No sensitivity analysis was performed to assess the robustness of the findings. Given the high risk of bias in many studies, a sensitivity analysis could have provided valuable insights into how different studies or methodological choices affect the overall results.

While the systematic review provides valuable insights into the potential benefits of Patient and Family-Centered Care interventions in reducing delirium among ICU patients, the findings are substantially limited by high risk of bias, language restrictions, heterogeneity, and a limited scope of included studies. Future systematic reviews should aim to include a broader range of databases, consider studies in multiple languages, account for patient characteristics, and perform sensitivity analyses to enhance the reliability and applicability of the findings.

Conclusion

This systematic review and meta-analysis suggests that PFCC interventions are effective in reducing the incidence of delirium among ICU patients. However, these interventions do not appear to significantly impact other psychological outcomes, such as anxiety and depression, or reduce the length of ICU stay. Given the high risk of bias and variability in study designs, future research should focus on high-quality, well-powered randomized controlled trials to more definitively determine the benefits of PFCC interventions in ICU settings. Further studies should also explore tailored interventions that address specific patient needs and consider the diverse settings of ICUs globally.

Authors' contributions

Conceptualization: Kaifang Cai. Data curation: Yangjin LV, Peng Li, Peng Li, Ronghui Li, Ting Zhang, Kaifang Cai. Formal analysis: Yangjin LV, Peng Li. Investigation: Ting Zhang. Methodology: Yangjin LV, Peng Li, Ronghui Li, Ting Zhang. Project Administration: Yangjin LV, Peng Li, Ronghui Li, Kaifang Cai. Resources: Peng Li. Software Yangjin LV, Ronghui Li. Supervision: Yangjin LV, Ting Zhang, Kaifang Cai. Validation: Yangjin LV, Peng Li, Ronghui Li, Ting Zhang, Kaifang Cai. Visualization: Peng Li, Kaifang Cai. Writing-original draft: Yangjin LV. Writing-review & editing: Yangjin LV, Peng Li, Ronghui Li, Ting Zhang, Kaifang Cai.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. van Beusekom I, Bakhshi-Raiez F, de Keizer NF, Dongelmans DA, van der Schaaf M. Reported burden on informal caregivers of ICU survivors: a literature review. Crit Care. 2016;20:16.
2. Rose L, Muttalib F, Adhikari NK. Psychological consequences of admission to the ICU: helping patients and families. JAMA. 2019;322:213–5.
3. Rengel KF, Hayhurst CJ, Pandharipande PP, Hughes CG. Long-term cognitive and functional impairments after critical illness. Anesth Analg. 2019;128:772–80.
4. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome–family. Crit Care Med. 2012;40:618–24.
5. McAdam JL, Fontaine DK, White DB, Dracup KA, Puntillo KA. Psychological symptoms of family members of high-risk intensive care unit patients. Am J Crit Care. 2012;21:386–94.
6. Institute of Patient and Family Centred-Care, 2018. Patient- and Family-Centered Care. https://www.ipfcc.org/about/pfcc.html. Accessed June 2022.
7. Baas LS. Patient-and family-centered care. Heart Lung. 2012; 41:534–5.
8. Wong P, Redley B, Digby R, Correya A, Bucknall T. Families' perspectives of participation in patient care in an adult intensive care unit: A qualitative study. Aust Crit Care. 2020;33:317–25.
9. Martín Delgado MC, García de Lorenzo Y, Mateos A. Surviving the Intensive Care Units looking through the family's eyes. Med Intensiva. 2017;41:451–3.
10. McAdam J, Dracup K, White D, Fontaine DK, Puntillo KA. Symptom experiences of family members of intensive care unit patients at high risk for dying. Crit Care Med. 2010;38:1078–85.
11. Gooding J, Cooper L, Blaine A, Franck L, Howse J, Berns S. Family Support and Family-Centered Care in the Neonatal Intensive Care Unit. Origins Advances Impact Semin Perinatol. 2011; 35:20–8.
12. Frakking T, Michaels S, Orbell-Smith J, Le Ray L. Framework for patient, family-centred care within an Australian Community Hospital: development and description. BMJ Open Qual. 2020;9:e000823.
13. Ten Hoorn S, Elbers PW, Girbes AR, Tuinman PR. Communicating with conscious and mechanically ventilated critically ill patients: a systematic review. Crit Care. 2016;20:333.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Int Med. 2009;151: 264–9.
15. Davidson JE, Aslakson RA, Long AC, et al. Guidelines for family-centered care in the neonatal, pediatric, and adult ICU. Crit Care Med. 2017;45:103–28.
16. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane Database Syst. Rev. 2019: 205–28.
17. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
18. Garrouste-Orgeas M, Flahault C, Vinatier I, et al. Effect of an ICU diary on posttraumatic stress disorder symptoms among patients receiving mechanical ventilation: a randomized clinical trial. JAMA. 2019;322:229–39.
19. Bench S, Day T, Heelas K, Hopkins P, White C, Griffiths P. Evaluating the feasibility and effectiveness of a critical care discharge information pack for patients and their families: a pilot cluster randomised controlled trial. BMJ Open. 2015;5: e006852.
20. Sayde GE, Stefanescu A, Conrad E, Nielsen N, Hammer R. Implementing an intensive care unit (ICU) diary program at a large academic medical center: Results from a randomized control trial evaluating psychological morbidity associated with critical illness. Gen Hosp Psychiatry. 2020;66:96–102.
21. Azoulay E, Forel JM, Vinatier I, et al. Questions to improve family-staff communication in the ICU: a randomized controlled trial. Intensive Care Med. 2018;44:1879–87.
22. Black P, Boore JR, Parahoo K. The effect of nurse-facilitated family participation in the psychological care of the critically ill patient. J Adv Nurs. 2011;67:1091–101.
23. Xiaoqing G, Cao U, Zeya S. Application of families participatory nursing in the prevention of delirium in ICU patients. J Qilu Nurs. 2017;23:1–3.
24. Xueping J, Ruiyun L, Wenjuan L, Hua J, Yuting Z, Jing H. Effect of family-centred visitation on delirium in ICU patients with cancer. J Nurs Sci. 2021;36:1–4.

25. Eghbali-Babadi M, Shokrollahi N, Mehrabi T. Effect of family-patient communication on the incidence of delirium in hospitalized patients in cardiovascular surgery ICU. Iran J Nurs Midwifery Res. 2017;22:327—31.
26. Hong M, Xiaojing I, Qixia Z, Xiaoyan Z. Effect of family participated three stages nursing model in the prevention of delirium for patients in ICU. Nurs J Chin People's Liberation Army. 2015;32:52—4.
27. Mitchell M, Kean S, Rattray E, et al. A family intervention to reduce delirium in hospitalised ICU patients: A feasibility randomised controlled trial. Intensive Crit Care Nurs. 2017; 40:77—84.
28. Rosa R, Falavigna M, DaSilva B. Effect of flexible family visitation on delirium among patients in the intensive care unit: The ICU visits randomized clinical trial. JAMA. 2019;322:216—28.
29. Nielsen AH, Angel S, Egerod I, Lund TH, Renberg M, Hansen TB. The effect of family-authored diaries on posttraumatic stress disorder in intensive care unit patients and their relatives: a randomised controlled trial (DRIP-study). Aust Crit Care. 2020;33:123—9.
30. Roze des Ordons A, Stelfox H, Sinuff T, et al. Spiritual distress in family members of critically ill patients: Perceptions and experiences. J Palliative Med. 2020;23(2):198—210.
31. Kang J, Cho Y, Choi S. State anxiety, uncertainty in illness, and needs of family members of critically ill patients and their experiences with family-centered multidisciplinary rounds: A mixed model study. PLoS One. 2020;15:e0234296.
32. Van Rompaey B, Elseviers M, Schuurmans J, et al. Risk factors for delirium in intensive care patients: A prospective cohort study. Critl Care. 2009;13:R77.
33. Pandharipande P, Ely E, Arora R, et al. The intensive care delirium research agenda: A multinational, interprofessional perspective. Intensive Care Med. 2017;43(9):1329—39.
34. McKenzie J, Joy A. Family intervention improves out- comes for patients with delirium: Systematic review and meta- analysis. Australas J Ageing. 2020;39:21—30.
35. Lin L, Peng Y, Zhang H, Huang X, Chen L, Lin Y. Family-centred care interventions to reduce the delirium prevalence in critically ill patients: A systematic review and meta-analysis. Nurs Open. 2022;00:1—10.
36. Balas M, Devlin J, Verceles A, Morris P, Ely E. Adapting the ABCDEF bundle to meet the needs of patients requiring prolonged mechanical ventilation in the long-term acute care hospital setting: Historical perspectives and practical implications. Semin Respir Crit Care Med. 2016;37:119—35.
37. Bohart S, Møller A, Andreasen A, Waldau T, Lamprecht C, Thomsen T. Effect of Patient and Family Centred Care interventions for adult intensive care unit patients and their families: A systematic review and meta-analysis. Intensive Crit Care Nurs. 2021:103156.
38. Goldfarb M, Bibas L, Bartlett V, Jones H, Khan N. Outcomes of patient- and family-centered care interventions in the ICU: A systematic review and meta-analysis. Crit Care Med. 2017;45 (10):1751—61.
39. Bibas L, Peretz-Larochelle M, Adhikari NK, et al. Association of surrogate decision-making interventions for critically ill adults with patient, family, and resource use outcomes: a systematic review and meta-analysis. JAMA Netw Open. 2019;2. e197229-.
40. Barreto BB, Luz M, Rios MN, Lopes AA, Gusmao-Flores D. The impact of intensive care unit diaries on patients' and relatives' outcomes: a systematic review and meta-analysis. Crit Care. 2019;23. 1-0.
41. Wang G, Antel R, Goldfarb M. The Impact of Randomized Family-Centered Interventions on Family-Centered Outcomes in the Adult Intensive Care Unit: A Systematic Review. J Intensive Care Med. 2023;38:690—701.

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REVIEW ARTICLE

Pharmacological and non-pharmacological interventions in patients undergoing nasal surgeries for prevention of emergence agitation: a systematic review and network meta-analysis

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Abstract

Background: Emergence agitation is a common complication after nasal surgeries, marked by increased agitation and a heightened risk of injuries. Factors like urinary catheter, endotracheal tube, postoperative pain, and younger age contribute to its occurrence. Due to the variety of preventive approaches reported in the literature, a network meta-analysis is essential.

Methods: This systematic review employs a network meta-analysis design, following Cochrane Handbook and PRISMA-NMA criteria. Inclusion criteria involve randomized controlled studies on pharmacological and non-pharmacological interventions for preventing emergence agitation in nasal surgeries. Electronic searches, including PubMed, Scopus, Embase, Cochrane Library, and Web of Science, without language or date restrictions, were conducted. Two independent reviewers selected studies, and data extraction was performed using standardized tables. Bayesian NMA, MetaInsight web app, and Cochrane Foundation Risk of Bias Assessment Tool were applied for data analysis and bias assessment.

Results: After a rigorous selection process, 17 Randomized Controlled Trials (RCTs) encompassing 2,122 patients and 14 interventions were included. The best ranked treatments identified were intraoperative dexmedetomidine (1 μg.kg^{-1} for 10 minutes as a bolus, followed by 0.4 μg.kg^{-1}.h^{-1}), bilateral nasociliary and maxillary nerve block, ketamine (0.5 mg.kg^{-1} administered 20 minutes before the end of surgery), nasal compression for 40 minutes before anesthesia induction, and suction above the cuff of the endotracheal tube.

Conclusions: Both pharmacological and non-pharmacological interventions emerged as effective strategies in mitigating emergence agitation after nasal surgeries,

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offering clinicians valuable options for improving postoperative outcomes in this patient population.

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Introduction

Postanesthetic emergence agitation, also called emergence delirium, is a common complication after nasal surgeries, leading to increased risks of injury, pain, bleeding, and self-extubation. The most commonly known risk factors are the presence of urinary catheters, endotracheal tubes, postoperative pain, younger age, and inhalation anesthesia. With prevalence rates ranging from 22.2% to 55.4% in nasal surgeries, emergence agitation poses significant challenges to patient safety and adds substantial costs to healthcare.[1] The costs arise from prolonged hospital stays and the need for additional interventions, highlighting the importance of identifying effective preventive measures.

Understanding the physiopathology of emergence agitation is crucial for developing targeted interventions. The literature suggests a multifactorial interaction, with disruption of the cholinergic system being a central component.[2] Other contributing factors include neurotransmitter imbalances, inflammatory dysregulations, and stress responses.[3]

Preventive strategies for emergence agitation have been preliminarily explored. Dexmedetomidine shows promise due to its ability to modulate the inflammatory response and mitigate hyperactivity of the sympathetic nervous system, essential for preventing acute postoperative cognitive changes.[4,5] Other pharmacological agents, such as ketamine and butorphanol, have also been investigated for their potential to reduce the incidence of emergence agitation.[6-8]

In addition to pharmacological approaches, regional anesthetic blocks may help prevent emergence agitation by minimizing the need for systemic agents.[9-11] Furthermore, non-pharmacological interventions have been associated with lower incidences of emergence agitation, representing cost-effective therapeutic tools that could improve clinical outcomes.[12-14]

The diverse approaches proposed in the literature for preventing emergence agitation necessitate a comprehensive, systematic analysis. Network meta-analysis is a valuable tool for this purpose, as it allows for direct and indirect comparisons of intervention effectiveness and establishes a relative hierarchy.[15] Consequently, our analysis aims to differentiate between the various explored interventions and their efficacy in preventing emergence agitation, potentially providing a solid foundation for enhancing perioperative management and clinical outcomes for patients undergoing nasal surgeries.

Methods

This systematic review and network meta-analysis were conducted and reported based on the Cochrane Handbook and to the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[16,17] The review protocol was registered on PROSPERO (CRD42023464926).

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: (1) Randomized controlled studies; (2) Those describing pharmacological or non-pharmacological interventions for prevention of emergence agitation; (3) Those in patients American Society of Anesthesiologists (ASA) physical status I or II undergoing nasal surgeries; and (4) Those with emergence agitation assessed by the Riker Sedation/Agitation Scale or the Richmond Agitation Sedation Scale. We excluded studies: (1) With insufficient information or data that could not be retrieved by contacting the corresponding authors; (2) That did not present interventions suitable for comparison in the network meta-analysis; and (3) That did not meet the transitivity assumption.

Search strategy

We conducted a comprehensive literature search across multiple electronic databases, including MEDLINE, Scopus, Embase, Cochrane Library, and Web of Science. The search was conducted on June 11th, 2024. There was no restriction on language or publication date.

The search strategy consisted of: ("Nasal surgery" OR "Nose surgery" OR "Nasal endoscopy" OR "Nasoendoscopy" OR "endoscopic sinus" OR "Sinus surgery" OR "Rhinoplasty" OR "Sinuplasty" OR "Septoplasty" OR "Turbinoplasty" OR "Nasal polyp removal" OR "Nasal polypectomy" OR "Nasal polyp resection" OR "Ethmoidectomy" OR "Rhinoseptoplasty") AND ("Delirium" OR "Emergence delirium" OR "Emergence agitation" OR "Postoperative delirium" OR "Post-operative delirium" OR "Post operative delirium" OR "Postoperative agitation" OR "Post-operative agitation" OR "Post operative agitation" OR "Postanesthesia delirium" OR "Post-anesthesia delirium" OR "Post anesthesia delirium" OR "Postanaesthesia delirium" OR "Post-anaesthesia delirium" OR "Post anaesthesia delirium" OR "Postanesthesia agitation" OR "Post-anesthesia agitation" OR "Post anesthesia agitation" OR "Postanaesthesia agitation" OR "Post-anaesthesia agitation" OR "Post anaesthesia agitation").

The included documents were exported to a reference manager (Mendeley 1.19.8®) to remove duplicates. The reference lists of all the included articles were also reviewed for potential citation eligibility.

Selection of studies

Two reviewers (GRMW and HGO) independently performed the two-step selection. Titles and abstracts of all results

were initially screened; after this, the full text of the selected studies was obtained and independently assessed for eligibility. In cases of disagreement, a third reviewer was consulted.

Data extraction and synthesis

Data extraction was performed in duplicate using standardized data extraction tables in Google Sheets containing article identification, sample numbers, characteristics, and outcome measures. The data was initially collected in an inclusive way, and the relevant data was then synthesized by generating new tables for better comprehension. After the preliminary search, a network meta-analysis approach was considered appropriate.

Risk of bias assessment

Quality assessment of all the Randomized Controlled Trials (RCTs) was performed with Cochrane's tool, wherein studies are scored as high, low, or unclear risk of bias in 5 domains: selection, performance, detection, attrition, and reporting.[18]

Data analysis

A Network Meta-Analysis (NMA) was conducted utilizing a Bayesian NMA model with the assumption of evidence consistency. We estimated and reported risk ratios along with their associated 95% Bayesian credible intervals. Treatments were ranked using rank probabilities, and the Surface Under the Cumulative Ranking (SUCRA) and Litmus Rank-O-Gram were calculated in relation to individual outcomes.[19]

The quantitative synthesis was conducted by GRMW using the MetaInsight web app, which incorporated R packages such as "netmeta", "gemtc", "BUGSnet", "rjags", and "coda".[20-25] The different interventions covered by the network meta-analysis were mapped onto graphs. Generalized Linear Models (GLMs) with a random-effects model were utilized, based on a priori noninformative distributions, binomial likelihood distributions, and a log link function. Markov Chain Monte Carlo (MCMC) simulations, involving 4 chains, were employed with a burn-in phase of 5,000 iterations followed by 20,000 iterations and a thinning factor of one. Model selection was based on trial and error, guided by MCMC convergence diagnostics, including Gelman-Rubin trace plots and potential scale reduction factors, as well as leverage plots.[26] Model fit was assessed using the posterior mean of the residual Deviance (Dbar), effective degrees of freedom (pD), and Deviance Information Criterion (DIC), and was visually represented through residual deviance plots of the network Meta-Analysis Model (NMA), Unrelated Mean Effect Model (UME), stem plots, and leverage plots. The precision of estimates was indicated by 95% Credibility Intervals (95% CrIs). A comprehensive explanation of the statistical terms is provided in the supplementary material (Supplementary Methods).

Results

The selection process included 294 manuscripts, as presented by the PRISMA flowchart (Fig. 1). After all selection steps, 17 RCTs were included, totaling 2,122 patients and 14 different interventions (Supplementary Table S1). The timing of each intervention administration was better described in the Supplementary Material. Different control settings, such as saline solution administration, placebo, and not performing the intervention, were considered equivalent.

Network meta-analysis

We conducted a network meta-analysis on patients undergoing nasal surgeries under general anesthesia maintained with inhalational anesthetics. The literature indicates that sevoflurane is a risk factor for emergence agitation in nasal surgeries.[1,27] Additionally, a recent meta-analysis identified inhalational anesthesia, particularly sevoflurane, as a risk factor for emergence agitation in adult patients.[28] Although only inhalational anesthesia with sevoflurane was explicitly identified as a risk factor, the reviewed studies predominantly utilized sevoflurane. For instance, in the cited meta-analysis, out of 12 RCTs comparing TIVA to inhalational anesthetics, 9 studies used sevoflurane. Consequently, the absence of other inhalational agents as identified risk factors may result from limited available evidence. Therefore, we conducted an analysis including articles that utilized inhalation anesthetics for maintenance anesthesia without discriminating between the use of sevoflurane and assessed our findings through two subgroup analyses: one for general anesthesia maintained with sevoflurane and another for general anesthesia maintained with non-sevoflurane inhalational agents.

Regarding other pertinent analyses, intervention analysis on patients undergoing general anesthesia with propofol could not be performed due to the limited and insufficient number of studies. Additionally, a network meta-analysis comparing different anesthetic regimens was not feasible due to the limited number of studies addressing this comparison.

The full details, including the number of patients, number of comparisons, number of studies, and summary statistics of each outcome for each comparison, were reported in supplementary tables. The results for the analyses were summarized in graphs, forest plots, SUCRA plots and Litmus Rank-O-Gram in relation to individual outcomes.

Inhalation agents for anesthesia maintenance analysis

Seventeen RCTs[6-13,29-36] involving 2,122 patients across 14 different interventions were included in the analysis. Of the 91 possible pairwise comparisons, 14 were direct. All studies provided event data, and the network graph was connected. A random-effects model was used for the analysis. Detailed information on the quantitative synthesis is available in Supplementary Tables 1, 2, 3, 4, and Supplementary Figures 1, 2, 3, 4, and 13. The inhalation anesthetic agents studied were Sevoflurane,[7-12,33,36] Desflurane,[6,13,30-32,34] and Isoflurane.[14,29,35]

Subgroup analysis

Sevoflurane maintenance group

Eight RCTs involving 1,275 patients used sevoflurane[7-12,33,36] across nine different interventions (Fig. 2). Of the 36 possible pairwise comparisons, eight were direct. All studies had

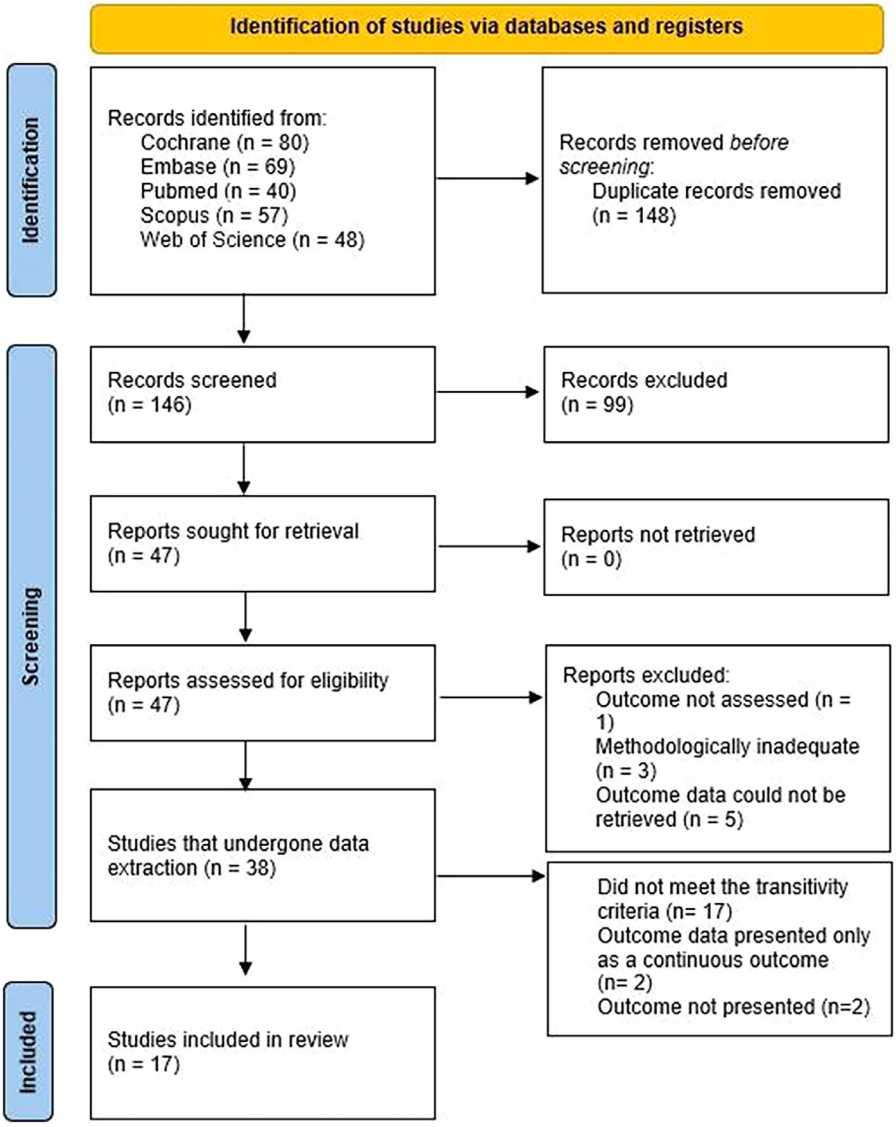

Figure 1 Study Flow Diagram.

event data, and the network graph was connected. The analysis followed a random-effects model. More details on the quantitative synthesis can be found in Supplementary Tables 1, 2, 5, 6, and Figures 5, 6, 7, 8, and 14.

Non-sevoflurane inhalation agents' maintenance group

Nine RCTs involving 864 patients used non-sevoflurane inhalation anesthetics across nine different procedures (Fig. 3).[6,13,14,29-32,34,35] Of the 21 possible pairwise comparisons, seven were direct. All studies had event data, and the network graph was connected. A random-effects model was used for the analysis. Further information on the quantitative synthesis is available in Supplementary Tables 1, 2, 5, and 6, and Supplementary Figures 9, 10, 11,12, and 15. The inhalation anesthetic agents included were Desflurane,[6,13,30-32,34] and Isoflurane.[14,29,35]

Best ranked treatments

We chose to describe only the five best-ranked treatments in the overall analysis (Fig. 4). The ranking based on Surface Under the Cumulative Ranking (SUCRA) scores provides a comprehensive measure of the effectiveness of each intervention. SUCRA scores range from 0% to 100%, where a higher percentage indicates a higher probability of an intervention being among the best treatments. This ranking system considers the entire distribution of effect estimates, allowing for a more nuanced comparison of treatments. By incorporating the probability of each intervention occupying each rank, SUCRA scores offer a detailed understanding of how each treatment performs relative to others, beyond merely identifying statistical significance. Therefore, SUCRA scores in the ranking of treatments offers significant implications for evidence-based practice.

Credibility Intervals (CrIs) play a crucial role in interpreting the results of Bayesian analysis, offering a range within which the true effect size is likely to lie within a certain probability, in our study, 95%. The width of the credibility interval is influenced by the sample size and the number of studies analyzed; larger samples tend to yield narrower intervals, indicating greater precision in effect estimation.

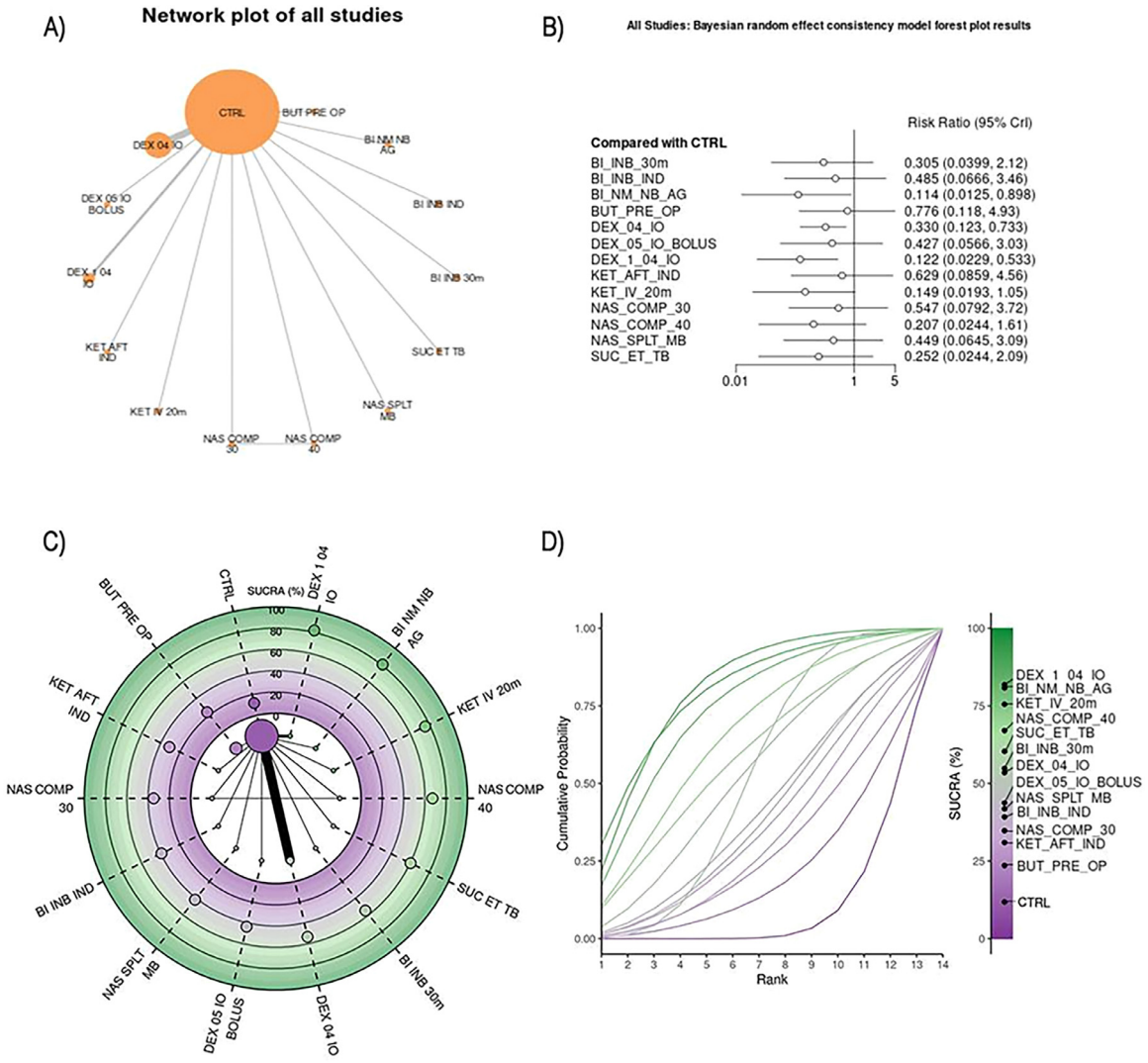

Figure 2 (A) A network plot of the studies included in the analysis that used inhalation agents for anesthesia maintenance. The number of studies that examined a treatment and compared two given treatments is represented by the size of the nodes and the thickness of the edges, respectively. (B) Bayesian random effect consistency model forest plot results. Forest plot for pairwise comparisons of included interventions versus placebo of the studies included in the analysis that used inhalation agents for anesthesia maintenance. The effect size is expressed as risk ratio. (C) Radial Surface Under the Cumulative Ranking Curve (SUCRA) plot of the studies included in the analysis that used inhalation agents for anesthesia maintenance. The treatments are ordered clockwise starting at "12 o'clock," with the SUCRA value of each treatment plotted radially. The more outward the representation of the intervention, the higher its relative efficacy. The radial SUCRA contains a network of interventions with node sizes proportional to the evidence supporting them. (D) Litmus Rank-O-Gram in relation to individual outcomes of the studies included in the analysis that used inhalation agents for anesthesia maintenance. It shows the cumulative probability for each guidance technique to be ranked as first, second, third and beyond alongside with the SUCRA values. The higher the bar, the greater the probability of ranking in that position. CTRL, Control (Saline, placebo, or procedure not performed); BI_INB_30m, Bilateral Infraorbital and Infratrochlear Nerve Block 30 min before surgery; BI_INB_IND, Bilateral Infraorbital and Infratrochlear Nerve Blocks before induction; BI_NM_NB_AG, Bilateral nasociliary and maxillary nerve block after general anesthesia; BUT_PRE_OP, Preoperative administration of butorphanol 20 mcg.kg^{-1}; DEX_04_IO, Intraoperative Dexmedetomidine infusion of 0.4 mcg.kg^{-1}.h^{-1}; DEX_05_IO_BOLUS, Intraoperative Dexmedetomidine bolus of 0.5 mcg.kg^{-1}; DEX_1_0.4_IO, Intraoperative Dexmedetomidine bolus of 1 mcg.kg^{-1} for 10 min followed by infusion of 0.4 mcg.kg^{-1}.h^{-1}; KET_AFT_IND, Ketamine bolus of 1 mg.kg^{-1} after induction; KET_IV_20m, Ketamine bolus of 0.5 mg kg^{-1} IV 20 min before end of the surgery; NAS_COMP_30, Nasal compression for 30 min before induction of anesthesia; NAS_COMP_40, Nasal compression for 40 min before induction of anesthesia; NAS_SPLT_MB, Nasal splinting and mouth breathing training before procedure; SUC_ET_TB, Suction above Cuff Endotracheal Tube.

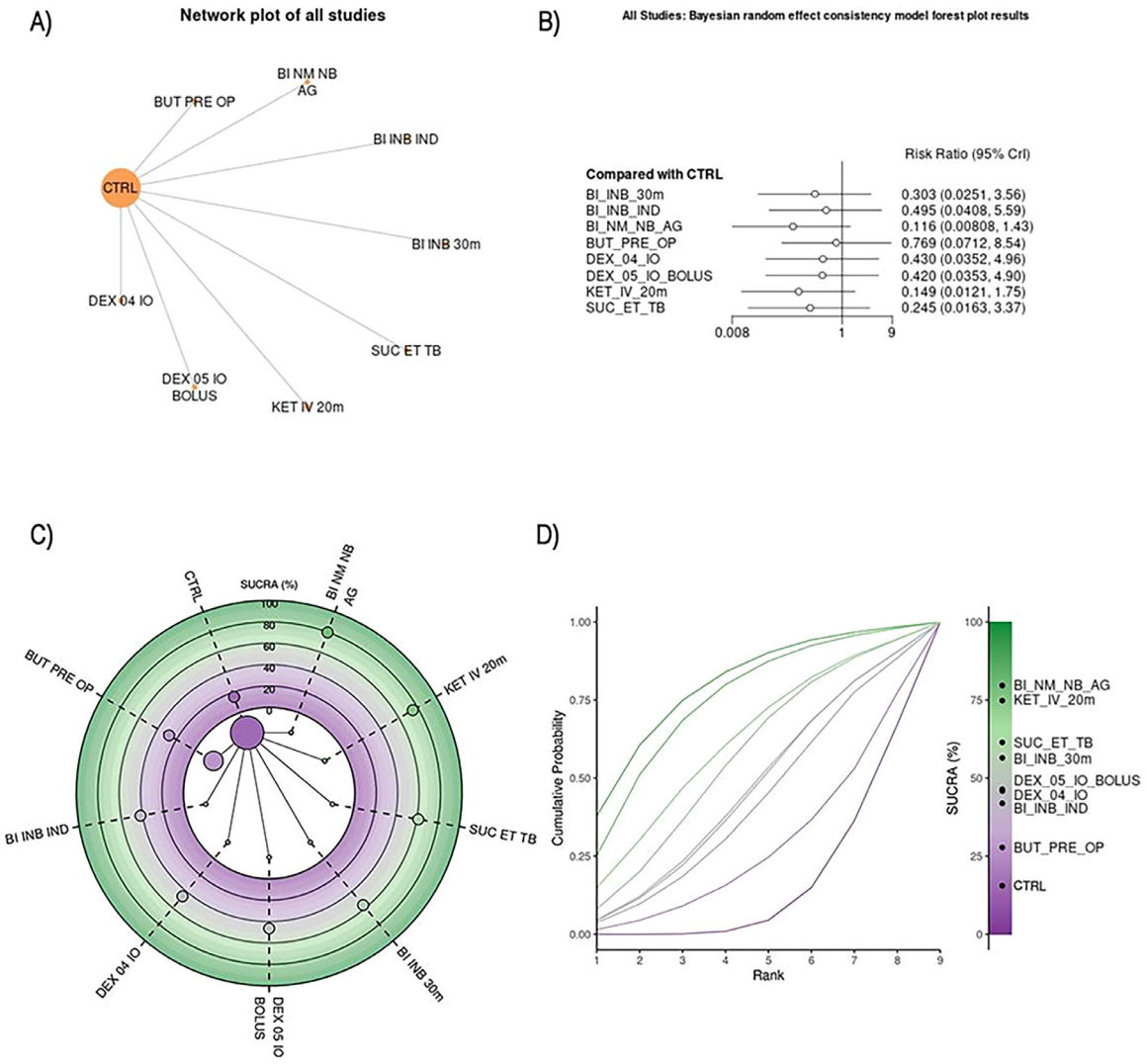

Figure 3 (A) A network plot of the studies included in the analysis that used non-sevoflurane inhalation agents for anesthesia maintenance. The number of studies that examined a treatment and compared two given treatments is represented by the size of the nodes and the thickness of the edges, respectively. (B) Bayesian random effect consistency model forest plot results. Forest plot for pairwise comparisons of included interventions versus placebo of the studies included in the analysis that used non-sevoflurane inhalation agents for anesthesia maintenance. The effect size is expressed as risk ratio. (C) Radial Surface Under the Cumulative Ranking Curve (SUCRA) plot of the studies included in the analysis that used non-sevoflurane inhalation agents for anesthesia maintenance. The treatments are ordered clockwise starting at "12 o'clock," with the SUCRA value of each treatment plotted radially. The more outward the representation of the intervention, the higher its relative efficacy. The radial SUCRA contains a network of interventions with node sizes proportional to the evidence supporting them. (D) Litmus Rank-O-Gram in relation to individual outcomes of the studies included in the analysis that used non-sevoflurane inhalation agents for anesthesia maintenance. It shows the cumulative probability for each guidance technique to be ranked as first, second, third and beyond alongside with the SUCRA values. The higher the bar, the greater the probability of ranking in that position. CTRL, Control (Saline, placebo, or procedure not performed); KET_IV_20m, ketamine bolus of 0.5 $mg.kg^{-1}$ IV 20 min before end of the surgery; DEX_04_IO, Intraoperative Dexmedetomidine Infusion of 0.4 $mcg.kg^{-1}.h^{-1}$; BI_INB_IND, Bilateral Infraorbital and Infratrochlear Nerve Blocks before induction; BI_NM_NB_AG, Bilateral nasociliary and maxillary nerve block after general anesthesia; DEX_05_IO_BOLUS, Intraoperative Dexmedetomidine bolus of 0.5 $mcg.kg^{-1}$; SUC_ET_TB, Suction above Cuff Endotracheal Tube; BUT_PRE_OP, Preoperative administration of butorphanol 20 $mcg.kg^{-1}$.

Narrow credibility intervals suggest that the estimated treatment effects are more reliable, whereas wider intervals indicate greater variability and uncertainty, suggesting that further research may be needed.

An intervention can be statistically significant within its confidence interval in a single study but not within its credibility interval when considering broader evidence due to the differences in how these intervals are constructed. Confidence intervals reflect the variability within the study's sample, indicating where the true effect is likely to fall in repeated sampling from the same population.

In contrast, credibility intervals incorporate prior knowledge, and the entire distribution of effect estimates across multiple studies. This means they account for more

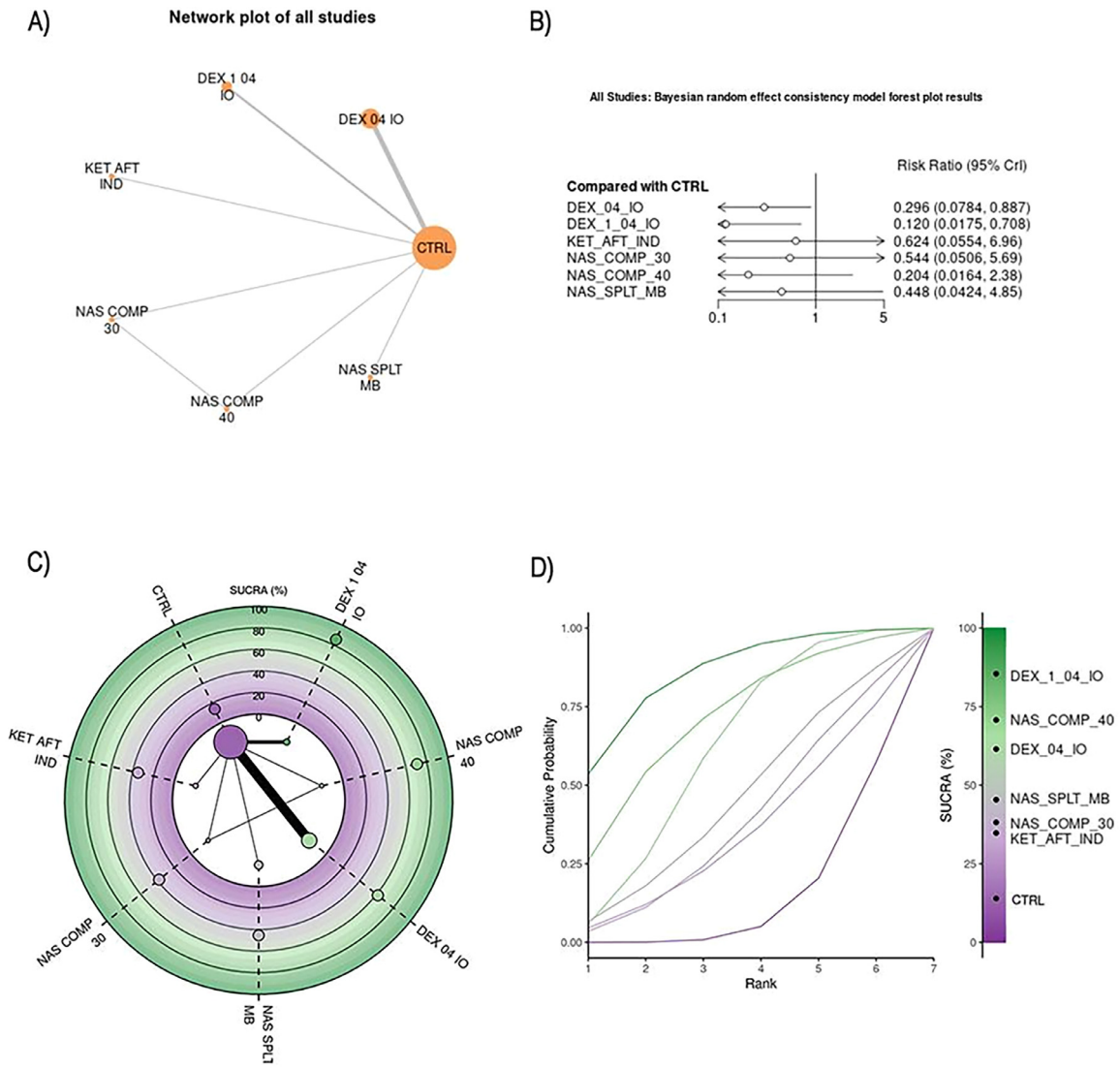

Figure 4 (A) A network plot of the studies included in the analysis that used sevoflurane for anesthesia maintenance. The number of studies that examined a treatment and compared two given treatments is represented by the size of the nodes and the thickness of the edges, respectively. (B) Bayesian random effect consistency model forest plot results. Forest plot for pairwise comparisons of included interventions versus placebo of the studies included in the analysis that used sevoflurane for anesthesia maintenance. The effect size is expressed as risk ratio. (C) Radial Surface Under the Cumulative Ranking Curve (SUCRA) plot of the studies included in the analysis that used sevoflurane for anesthesia maintenance. The treatments are ordered clockwise starting at "12 o'clock," with the SUCRA value of each treatment plotted radially. The more outward the representation of the intervention, the higher its relative efficacy. The radial SUCRA contains a network of interventions with node sizes proportional to the evidence supporting them. (D) Litmus Rank-O-Gram in relation to individual outcomes of the studies included in the analysis that used sevoflurane for anesthesia maintenance. It shows the cumulative probability for each guidance technique to be ranked as first, second, third and beyond alongside with the SUCRA values. The higher the bar, the greater the probability of ranking in that position. CTRL, Control (Saline, placebo, or procedure not performed); DEX_04_IO, Intraoperative Dexmedetomidine infusion of 0.4 mcg.kg^{-1}.h^{-1}; DEX_1_0.4_IO, Intraoperative Dexmedetomidine bolus of 1 mcg.kg^{-1} for 10 min followed by infusion of 0.4 mcg.kg^{-1}.h^{-1}; KET_AFT_IND, Ketamine bolus of 1 mg.kg^{-1} after induction; NAS_COMP_30, Nasal compression for 30 min before induction of anesthesia; NAS_COMP_40, Nasal compression for 40 min before induction of anesthesia; NAS_SPLT_MB, Nasal splinting and mouth breathing training before procedure.

sources of variability and uncertainty. If an intervention's CrI is wide or includes the possibility of no effect, it suggests that, when considering all available evidence and prior beliefs, there is more uncertainty about the true effect size.

Almost all interventions analyzed were statistically significant when compared individually to their respective control groups in their respective studies, with the only exception being the article by Abitağaoğlu et al.[6] The implication of an intervention being significant in its confidence intervals but not in its credibility intervals is that while the single study's result may be promising, the broader analysis incorporating more data and prior information indicates that the effect is less certain. This highlights the value of

considering the full body of evidence to make more reliable clinical decisions.

Intraoperative dexmedetomidine[30,34]

Dexmedetomidine administered intraoperatively as a 1 mcg.kg^{-1} bolus over 10 minutes followed by an infusion of 0.4 mcg.kg^{-1}.h^{-1} was ranked as the best intervention in both the overall analysis and the subgroup of non-sevoflurane inhalation anesthetics. This intervention showed a statistically significant effect in both the overall analysis (RR = 0.122, 95% CrIs: 0.0229 to 0.533) and the non-sevoflurane subgroup (RR = 0.120, 95% CrIs: 0.0175 to 0.708). The sevoflurane subgroup analysis could not be conducted due to the lack of studies evaluating dexmedetomidine in this specific context. The studies by Garg et al.[30] and Naqvi et al.[34] were reviewed, and no potential confounding factors affecting the estimated effect were identified.

Our analysis supports the evidence for using intraoperative dexmedetomidine infusion with a bolus for preventing emergence agitation in patients undergoing nasal surgery under inhalation anesthesia.

Bilateral nasociliary and maxillary nerve blocks[9]

Bilateral nasociliary and maxillary nerve block after general anesthesia was ranked as the second-best intervention for preventing emergence agitation in the overall analysis and the best intervention in the sevoflurane subgroup analysis. The intervention showed a statistically significant effect in the overall analysis (RR = 0.0114, 95% CrIs: 0.0125 to 0.898), but it was not statistically significant in the sevoflurane subgroup analysis (RR = 0.116, 95% CrIs: 0.00808 to 1.43). The non-sevoflurane subgroup analysis could not be conducted due to the absence of studies evaluating bilateral nasociliary and maxillary nerve blocks in this specific context. The study by Parthasarathy et al.[9] was reviewed, and no potential confounding factors affecting the estimated effect were identified.

Despite the lack of statistical significance in the subgroup analysis for the credibility interval, our overall analysis demonstrates significant evidence supporting bilateral nasociliary and maxillary nerve blocks for preventing emergence agitation in patients undergoing nasal surgery under inhalation anesthesia.

Intraoperative ketamine[7]

Ketamine 0.5 mg.kg^{-1} 20 minutes before the end of surgery was ranked as the third-best intervention for preventing emergence agitation in the overall analysis and the second-best intervention in the sevoflurane subgroup analysis. However, it was not statistically significant in either analysis (overall: RR = 0.149, 95% CrIs: 0.0193 to 1.05; sevoflurane: RR = 0.149, 95% CrIs: 0.0121 to 1.75). The non-sevoflurane subgroup analysis could not be performed due to the absence of studies involving intraoperative ketamine in that setting.

The study by Demir et al.[7] reported a statistically significant difference in anesthesia duration, with a longer anesthesia duration in the control group (113.62±9.80) compared to the intervention group (106.31±10.67). This discrepancy suggests a potential influence on the estimated effect of ketamine bolus 20 minutes before the end of surgery, possibly leading to an overestimation of its beneficial effects. Prolonged surgery durations have been identified as a risk factor for emergence agitation, raising the possibility that the higher incidence of emergence agitation could be attributed to extended exposure to anesthetics.[37]

Our analysis suggests that further research is needed to confirm the effectiveness of ketamine bolus 20 minutes before the end of surgery.

Nasal compression[14]

Nasal compression for 40 minutes before the induction of anesthesia was ranked as the fourth-best intervention for preventing emergence agitation in the overall analysis and the second-best intervention in the non-sevoflurane subgroup analysis. However, it was not statistically significant in either analysis (overall: RR = 0.207, 95% CrIs: 0.0244 to 1.61; non-sevoflurane: RR = 0.204, 95% CrIs: 0.0164 to 2.38). The sevoflurane subgroup analysis could not be performed due to the absence of studies evaluating nasal compression in that setting. The study by Kumari and Agrawal[14] was reviewed, and no potential confounding factors affecting the estimated effect were identified.

Our analysis suggests that further research is needed to confirm the effectiveness of nasal compression for preventing emergence agitation.

Suction above cuff endotracheal tube[12]

Suction above the cuff of the endotracheal tube was ranked as the fifth-best intervention for preventing emergence agitation in the overall analysis and the third-best in the sevoflurane subgroup analysis. However, it was not statistically significant in either analysis (overall: RR = 0.252, 95% CrIs: 0.0244 to 2.09; sevoflurane: RR = 0.245, 95% CrIs: 0.0163 to 3.37). The non-sevoflurane subgroup analysis could not be performed due to the absence of studies evaluating suction above the cuff of the endotracheal tube in that setting. The study by Yuzkat et al.[12] was reviewed, and no potential confounding factors affecting the estimated effect were identified.

Our analysis suggests that further research is needed to confirm the effectiveness of suction above the cuff endotracheal tube.

Sensitivity analysis

There were no zero-event arms to perform a sensitivity analysis or enough plots to perform a nodesplit analysis.

Risk of bias

The risk of bias of the randomized controlled trial was summarized in Figure 5. Of the 17 trials, eight were graded as having some concerns of bias and nine as having a low risk of bias.

Discussion

Our findings suggest that the most effective interventions for preventing emergence agitation include intraoperative dexmedetomidine bolus followed by infusion with the doses of 1 mcg.kg^{-1} for 10 minutes followed by 0.4 mcg.kg^{-1}.h^{-1}, bilateral nasociliary and maxillary nerve blocks, ketamine

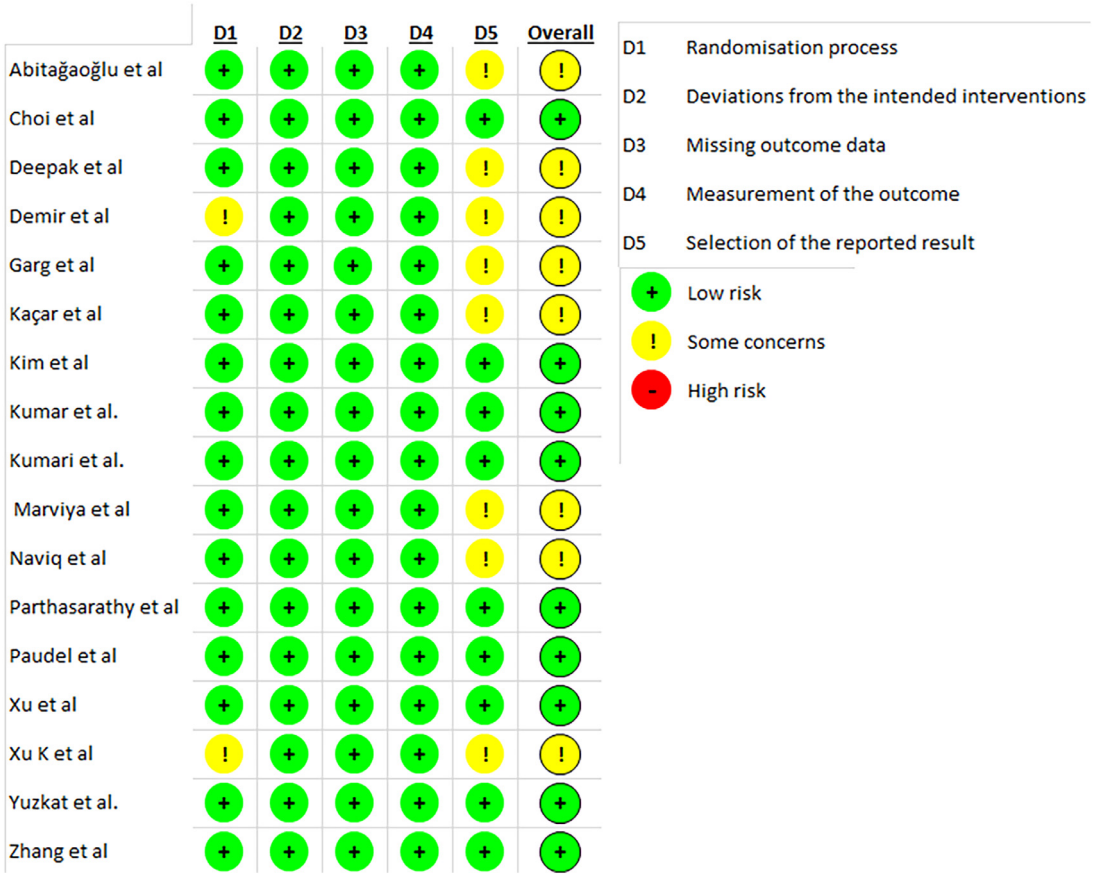

Figure 5 Risk of bias summary of included trials: evaluation of bias risk items for each included study. D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result. Green circle, low risk of bias; yellow circle, some concerns about bias; red circle, high risk of bias.

infusion at a dose of 0.5 $mg.kg^{-1}$ 20 minutes before the end of the procedure, and non-pharmacological interventions such as nasal compression for 40 minutes before surgery and suction above the cuff endotracheal tube.

Although suction above the cuff endotracheal tube and ketamine infusion at the end of the procedure were highly ranked, their effectiveness was not confirmed by the credibility interval. Additionally, dexmedetomidine infusion at 0.4 $mcg.kg^{-1}.h^{-1}$ was statistically significant and ranked second in the subgroup analysis using non-sevoflurane inhalation agents for anesthesia maintenance but ranked seventh in the overall analysis.

Thus, different doses of dexmedetomidine, various timings of ketamine administration, different types of regional anesthetic blocks, and a range of non-pharmacological interventions were analyzed, necessitating a discussion on the implications of our findings for these strategies.

Dexmedetomidine

Dexmedetomidine bolus followed by infusion was found to be the most effective intervention for preventing emergence agitation among the different methods of dexmedetomidine utilization. Studies employing similar doses of dexmedetomidine, whether through isolated bolus or infusion at the usual dose, yielded outcomes that were comparable to each other but inferior to the combined infusion and bolus administration. Future trials investigating the use of dexmedetomidine for emergence agitation prevention should consider this finding.

Ketamine

Administering ketamine at 0.5 $mg.kg^{-1}$ 20 minutes before the end of the procedure was ranked higher than administering ketamine at 1 $mg.kg^{-1}$ 10 minutes after anesthetic induction. This observation suggests that the enhanced effectiveness of ketamine is likely attributable to its pharmacological activity during the immediate postoperative period or at the point of anesthetic emergence.

Regional blocks

Performing nasociliary and maxillary nerve blocks after anesthesia induction was ranked higher than bilateral infraorbital and infratrochlear nerve blocks 30 minutes before surgery and preoperative bilateral infraoptic nerve and infratrochlear nerve blocks. It is unclear whether the superior effectiveness of nasociliary and maxillary nerve blocks is related to the type of regional blockade or to the timing of the blockade. Further studies should explore different regional block strategies and timings to optimize this intervention for emergence agitation prevention.

Non-pharmacological interventions

Two main forms of non-pharmacological interventions were evaluated: techniques to educate patients on breathing through the mouth to reduce the sensation of suffocation associated with nasal surgeries and interventions aimed at reducing secretion impact during extubation.

Nasal compression for 40 minutes before anesthesia induction was the highest-ranked intervention and the only statistically significant one in the first group. Suction above the cuff endotracheal tube was the only intervention evaluated in the second group, showing a favorable ranking but with non-statistically significant results. These non-pharmacological strategies are relevant for anesthetic practice, as they are low-cost and easily implementable.

Diagnosis of emergence agitation

The diagnosis of emergence agitation in our meta-analysis relied on the Riker Agitation-Sedation Scale (SAS) and the Richmond Agitation-Sedation Scale (RASS).[38-41] Both scales are standardized and validated clinical tools with high inter-rater reliability and reproducibility. The SAS employs a numerical scale ranging from unarousable (score of 1) to dangerous agitation (score of 7) to assess sedation levels, while the RASS is a 10-point scale spanning from unarousable (score of -5) to combative (score of +4). Despite some differences in scoring, both scales share similar descriptions, with scores of 5 on the SAS and +1 on the RASS indicating the initial onset of agitation or anxiety.

For the identification of emergence agitation, the selected studies utilized the criteria of SAS $\geq$ 5 or RASS $\geq$ +1. However, it is noteworthy that two studies employing the SAS criteria did not specify the cutoff value used.[12,34] Although previous research has demonstrated a high level of agreement between the two scales for assessing agitation,[42] our meta-analysis is vulnerable to the implications arising from disparities in assessment methodologies between the scales, thereby constituting a limitation of our study.

Limitations

Although our network meta-analysis has aggregated several valuable studies on the prevention of emergency agitation after nasal surgeries, its conclusions are subject to some limitations. Firstly, there was high heterogeneity among the included studies, and the number of patients undergoing each assessed intervention was restricted. Additionally, the included studies used two different scales for measuring emergency agitation; despite the scales demonstrating similar sensitivities and our exclusion of articles with excessively or insufficiently sensitive cutting points, there is a persistent possibility of bias in our results. Finally, even though the bias risk assessment for each included item has suggested a low or moderate risk, potential biases within the studies, along with the assumption of equivalence for different forms of control, may influence our findings.

Conclusion

The present network meta-analysis, which included 2122 patients across 17 randomized controlled trials, identified effective strategies for enhancing perioperative care in nasal surgeries. Specifically, intraoperative dexmedetomidine infusion with bolus, bilateral nasociliary and maxillary nerve blocks administered after general anesthesia, and nasal compression for 40 minutes prior to induction were associated with statistically significant reductions in the risk of emergence agitation. These findings provide robust evidence for tailoring perioperative management strategies based on emergence agitation outcomes. Implementing these measures could significantly improve patient outcomes and enhance overall perioperative care.

Authors' contributions

The authors confirm contribution to the paper as follows: study conception and design: Gustavo R. M. Wegner, Gilberto Tadeu Ferrugem de Oliveira; data collection: Gustavo R. M. Wegner, Henrik G. Oliveira; analysis and interpretation of results: Gustavo R. M. Wegner, Bruno F. M. Wegner, Luis A. Costa, Luigi W. Spagnol, Valentine W. Spagnol; draft manuscript preparation: Gustavo R. M. Wegner, Gilberto Tadeu Ferrugem de Oliveira, Bruno F. M. Wegner, Henrik G. Oliveira, Luis A. Costa, Luigi W. Spagnol, Valentine W. Spagnol. All authors reviewed the results and approved the final version of the manuscript.

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.2024.844565.

References

1. Kim HJ, Kim DK, Kim HY, Kim JK, Choi SW. Risk factors of emergence agitation in adults undergoing general anesthesia for nasal surgery. Clin Exp Otorhinolaryngol. 2015;8:46—51.
2. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic Deficiency Hypothesis in Delirium: A Synthesis of Current Evidence. J Gerontol Ser A. 2008;63:764—72.
3. The Cholinergic System and Inflammation: Common Pathways in Delirium Pathophysiology - Cerejeira - 2012 - Journal of the

American Geriatrics Society - Wiley Online Library [Internet]. [cited 2023 Dec 31]. Available from: https://agsjournals.onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2011.03883.x.
4. Flükiger J, Hollinger A, Speich B, Meier V, Tontsch J, Zehnder T, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. Ann Intensive Care. 2018;8:92.
5. Jacob Y, Schneider B, Spies C, et al. In a secondary analysis from a randomised, double-blind placebo-controlled trial Dexmedetomidine blocks cholinergic dysregulation in delirium pathogenesis in patients with major surgery. Sci Rep. 2023 Mar 9;13 (1):3971.
6. Abitağaoğlu S, Köksal C, Alagöz S, Karip CŞ, Arı DE. Effect of ketamine on emergence agitation following septoplasty: a randomized clinical trial. Braz J Anesthesiol. 2021;71:381—6.
7. Demir CY, Yuzkat N. Prevention of Emergence Agitation with Ketamine in Rhinoplasty. Aesthetic Plast Surg. 2018;42:847—53.
8. Zhang X, Qi S, Lin Z, et al. Pre-operative administration of butorphanol mitigates emergence agitation in patients undergoing functional endoscopic sinus surgery: A randomized controlled clinical trial. Front Psychiatry. 2023;13:1090149.
9. Parthasarathy S, Krishnapriyanka KJ, Saravanan B. Effectiveness of pre-emptive nerve block on opioid consumption in patients undergoing nasal surgery under general anaesthesia: A double-blinded randomised controlled study. Indian J Anaesth. 2022; 66:133—9.
10. Kaçar CK, Uzundere O, Salık F, Akgündüz M, Bıçak EA, Yektaş A. Effects of Adding a Combined Infraorbital and Infratrochlear Nerve Block to General Anaesthesia in Septorhinoplasty. J Pain Res. 2020;13:2599—607.
11. Choi H, Jung SH, Hong JM, Joo YH, Kim Y, Hong SH. Effects of Bilateral Infraorbital and Infratrochlear Nerve Block on Emergence Agitation after Septorhinoplasty: A Randomized Controlled Trial. J Clin Med. 2019;8:769.
12. Yuzkat N, Demir CY. Effect of using the Suction Above Cuff Endotracheal Tube (SACETT) on postoperative respiratory complications in rhinoplasty: a randomized prospective controlled trial. Ther Clin Risk Manag. 2019;15:571—7.
13. Xu H, Shen Z, Gu Y, et al. Nasal splinting and mouth breathing training reduce emergence delirium after endoscopic sinus surgery: a randomized controlled trial. BMC Anesthesiol. 2023; 23:302.
14. Kumari A, Agrawal A. Effect of Preoperative Preconditioning of Patients with External Nasal Compression for Different Time Intervals on Emergence Agitation After Nasal Surgeries: A Randomised Controlled Trial. J Clin Diagn Res [Internet]. 2023. [cited 2024 Jun 15]; Available from https://www.jcdr.net//article_fulltext.asp?issn=0973-709x&year=2023&volume=17&issue=8&page=UC57&issn=0973-709x&id=18371.
15. Watt J, Del Giovane C. Network Meta-Analysis. In: Evangelou E, Veroniki AA, editors. Meta-Research: Methods and Protocols [Internet]. New York, NY: Springer US; 2022 [cited 2024 Jan 1]. p. 187—201. (Methods in Molecular Biology). Available from: https://doi.org/10.1007/978-1-0716-1566-9_12.
16. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [cited 2023 Aug 29]. Available from: https://training.cochrane.org/handbook/current.
17. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162:777—84.
18. RoB 2: a revised tool for assessing risk of bias in randomised trials | The BMJ [Internet]. [cited 2023 Aug 29]. Available from: https://www.bmj.com/content/366/bmj.l4898.
19. Nevill CR, Cooper NJ, Sutton AJ. A multifaceted graphical display, including treatment ranking, was developed to aid interpretation of network meta-analysis. J Clin Epidemiol. 2023;157:83—91.
20. Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Res Synth Methods. 2019;10:569—81.
21. Balduzzi S, Rücker G, Nikolakopoulou A, Papakonstantinou T, Salanti G, Efthimiou O, et al. netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods. J Stat Softw. 2023;106:1—40.
22. gemtc: Network Meta-Analysis Using Bayesian Methods version 1.0-2 from CRAN [Internet]. [cited 2024 Jan 1]. Available from: https://rdrr.io/cran/gemtc/.
23. Béliveau A, Boyne DJ, Slater J, Brenner D, Arora P. BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. BMC Med Res Methodol. 2019;19:196.
24. rjags-package: Bayesian graphical models using MCMC in rjags: Bayesian Graphical Models using MCMC [Internet]. [cited 2024 Jan 1]. Available from: https://rdrr.io/cran/rjags/man/rjags-package.html.
25. Plummer M, Best N, Cowles K, Vines K. CODA: convergence diagnosis and output analysis for MCMC. R News. 2006;6:7—11.
26. Brooks SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. J Comput Graph Stat. 1998; 7:434—55.
27. Liu Z. [Analysis of risk factors for emergence agitation in adults undergoing general anesthesia for nasal surgery]. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi J Clin Otorhinolaryngol Head Neck Surg. 2015;29:1881—5.
28. Yang Y, Feng L, Ji C, Lu K, Chen Y, Chen B. Inhalational Versus Propofol-based Intravenous Maintenance of Anesthesia for Emergence Delirium in Adults: A Meta-analysis and Trial Sequential Analysis. J Neurosurg Anesthesiol. 2023;35:177—86.
29. Deepak BK, Kulkarni M, Sumanth MM, Kulkarni MM. Effect of intraoperative infusion of dexmedetomidine on emergence agitation among adults undergoing nasal surgeries-a prospective randomised double-blind study. Middle East J Anesthesiol. 2018;25:95—101.
30. Garg A, Kamal M, Mohammed S, Singariya G, Chouhan DS, Biyani G. Efficacy of dexmedetomidine for prevention of emergence agitation in patients posted for nasal surgery under desflurane anaesthesia: A prospective double-blinded randomised controlled trial. Indian J Anaesth. 2018;62:524—30.
31. Kim SY, Kim JM, Lee JH, Song BM, Koo BN. Efficacy of intraoperative dexmedetomidine infusion on emergence agitation and quality of recovery after nasal surgery. Br J Anaesth. 2013; 111:222—8.
32. RK N. Dexmedetomidine Infusion for Prevention of Emergence Agitation after Nasal Surgery. J Evol Med Dent Sci. 2020;9:844—50.
33. Jalja R, Lopa H, Sameer H. Role of dexmedetomidine infusion on post operative emergence agitation and quality of recovery after nasal surgery: A prospective randomized double blind controlled trial. Indian J Clin Anaesth. 2020;7:533—7.
34. Abbas Naqvi SA, Ahmad MS, Khan Z. Prevention of emergence agitation with dexmedetomidine in the patients undergoing nasal surgery under anesthesia with Desflurane. Med Forum Mon. 2021;32:24—8.
35. Paudel B, Gautam S, Bhandari D, Paudel S. To Evaluate the Effect of Intraoperative Dexmedetomidine on Emergence Agitation in Patient Undergoing Nasal and Pharyngeal Surgery. SSR Inst Int J Life Sci. 2024;10:3682—8.
36. Xu K, Pan Y, Zhu M. Effects of dexmedetomidine on the recovery profiles from general anesthesia in patients undergoing endoscopic sinus surgery. Int J Clin Exp Med. 2016;9:8405—10.
37. Lee SJ, Sung TY. Emergence agitation: current knowledge and unresolved questions. Korean J Anesthesiol. 2020;73 (6):471—85.
38. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive

care unit patients. Am J Respir Crit Care Med. 2002;166:1338—44.
39. Ely EW, Truman B, Shintani A, et al. Monitoring Sedation Status Over Time in ICU Patients: Reliability and Validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289:2983.
40. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med. 1999;27:1325—9.
41. Riker RR, Fraser GL, Simmons LE, Wilkins ML. Validating the Sedation-Agitation Scale with the Bispectral Index and Visual Analog Scale in adult ICU patients after cardiac surgery. Intensive Care Med. 2001;27:853—8.
42. Khan BA, Guzman O, Campbell NL, et al. Comparison and agreement between the Richmond Agitation-Sedation Scale and the Riker Sedation-Agitation Scale in evaluating patients' eligibility for delirium assessment in the ICU. Chest. 2012;142:48—54.

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REVIEW ARTICLE

The use of methylene blue in adult patients with septic shock: a systematic review and meta-analysis

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Systematic review

Abstract
Objectives: Methylene blue exerts its vasopressor properties by inhibiting nitric oxide-mediated vasodilation. Recent studies have advocated the use of methylene blue as a rescue therapy for patients with septic shock. The primary aim was to investigate the effect of methylene blue on the mean arterial pressure among adult patients with septic shock.
Methods: Databases of MEDLINE, EMBASE, and CENTRAL were searched from their inception date until October 2023. Randomized Clinical Trials (RCT) comparing methylene blue and placebo in adults with septic shock were included.
Results: Our systematic review included 5 studies (n = 257) for data analysis. As compared to the placebo, our pooled analysis showed that methylene blue significantly increased mean arterial pressure (MD: 1.34 mmHg, 95% CI 0.15 to 2.53, p = 0.03, level of evidence: very low). Patients who were given methylene blue were associated with statistically lower mortality rate (OR = 0.49, 95% CI 0.27 to 0.88, p = 0.02, level of evidence: low), reduced serum lactate levels (MD: -0.76 mmoL.L^{-1}, 95% CI -1.22 to -0.31, p = 0.0009, level of evidence: low), reduced length of hospital stay (MD: -1.94 days, 95% CI -3.79 to -0.08, p = 0.04, level of evidence: low), and increased PaO_2/FiO_2 (MD: 34.78, 95% CI 8.94 to 60.61, p = 0.008, level of evidence: low).
Conclusions: This meta-analysis demonstrated that methylene blue administration was associated with an increased in mean arterial pressure and PaO_2/FiO_2 ratio, along with a reduction in mortality rates, serum lactate levels, and length of hospital stay. However, substantial degree of heterogeneity and inadequate number of studies with low level of evidence warrant future adequately powered RCTs to affirm our results.
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Introduction

Sepsis is a life-threatening condition, resulting from a dysregulated host response to infection.[1] Septic shock is characterized by persistent hypotension and elevated lactate levels (> 2 mmoL.L^{-1}) that are unresponsive to fluid resuscitation.[1] It is classified as a vasodilatory shock, marked by reduced myocardial contractility, widespread vasodilatation, and diminished responsiveness to vasopressors.[2] Research has identified three primary mechanisms underlying vasopressor-resistant septic shock: vasopressin deficiency, activation of Adenosine Triphosphate (ATP)-sensitive potassium channels, and increased nitric oxide synthesis in vascular smooth muscle cells.[2]

According to the 2021 Surviving Sepsis Campaign guidelines, norepinephrine, epinephrine, or dopamine, and vasopressin are recommended as first-line, second-line and third-line therapies for treating septic shock, respectively.[3] Prolonged stimulation of adrenergic receptors by norepinephrine, epinephrine, and dopamine may result in receptor downregulation and desensitization, leading to diminished responsiveness to vasopressor therapy.[4] Additionally, studies have demonstrated that the use of catecholamines, dopamine, and vasopressin in septic shock can cause various adverse effects, including digital ischemia, mesenteric ischemia, and an increased incidence of arrhythmic events, respectively.[5,6] Given the risks of adverse effects associated with these vasopressor agents, there is a growing interest in vasopressor-sparing strategies. Non-adrenergic adjuncts, such as methylene blue are being explored as alternatives to increase Mean Arterial Pressure (MAP) and maintain organ perfusion.

Nitric Oxide Synthase (NOS) produces Nitric Oxide (NO) from its derivative L-arginine, which activates a second messenger (guanylate cyclase and cyclic guanosine monophosphate) to cause vasodilatation.[7] Nitric oxide synthase can be subdivided into two types, Namely Constitutive (cNOS) that is constantly active, also known as endothelial NOS (eNOS) and Inducible (iNOS) that is produced in large quantities upon activation by cytokines, endotoxin, and other inflammatory mediators.[7] Nitric oxide has both beneficial and harmful effects in septic shock. While it reduces vascular responsiveness to catecholamines, it concurrently enhances oxygen delivery, promotes free radical scavenging, and stimulates macrophage activity.[8] Given its varied impact, non-selective blockade of NOS inhibitors can be detrimental. A phase III clinical trial by Lopez et al. demonstrated that non-selective NOS inhibitors increased mortality and morbidity, including cardiac arrest and pulmonary hypertension, in patients with septic shock.[9] This finding underscores the importance of preserving the function of the constitutive isoform (cNOS) to maintain homeostasis, even in the context of sepsis. These results suggests that a more targeted approach to modulating nitric oxide synthase and its downstream pathways is warranted.

Methylene blue is one of the earliest synthetic drugs to be used in medicine, which was first employed to treat patients with septic shock in the 1990s.[10] It exhibits the potential of targeted inhibition on the iNOS, which demonstrated favourable hemodynamic effects with increased MAP and cardiac function.[11,12] Experimental studies showed that methylene blue normalized plasma concentrations of nitric oxide end-products, improved cardiopulmonary function, and reversed endotoxin-induced hypotension in animals with endotoxemia.[13,14] However, the inhibition of iNOS is associated with side effects on cardiovascular parameters and gas exchange.[15]

Current findings on the effects of methylene blue yielded mixed results. In a systematic literature review published in 2006, which included 14 studies, Kwok et al. highlighted that methylene blue increased systemic vascular resistance and MAP.[16] However, Porizka et al. showed that there are no significant differences between methylene blue administration and MAP among patients with refractory distributive shock.[17] In addition, studies have administered methylene blue in doses ranging from 1 mg.kg^{-1} to 7 mg.kg^{-1}.[16,18] Some studies employed bolus-only administration, while others utilized continuous infusion or a combination of bolus infusion followed by continuous infusion.[16,19] Consequently, there is no clear consensus on the optimal dosing strategy for administering methylene blue. To address this knowledge gap, a systematic review and meta-analysis assessing the efficacy and safety profile of methylene blue is timely and essential before making any recommendation for its use in patients with septic shock.

We hypothesized that methylene blue administration improves MAP in patients with septic shock. The primary objective of this systematic review and meta-analysis was to evaluate the clinical efficacy of methylene blue in improving MAP in septic shock patients. Secondary objectives included examining its effects on mortality rate, serum lactate levels, length of hospital stay, heart rate, and the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2).

Methods

This review was conducted according to the guidelines outlined by the Cochrane Handbook for Systematic Reviews and Interventions.[20] Our protocol was registered and published in the database of PROSPERO under CRD42023460671 prior to commencement of literature search. Review questions were formed based on the Population (adult patients with septic shock), Intervention (Methylene Blue), Comparison (control drugs), and Outcomes framework. The primary aim of the review is to examine the effect of methylene blue on MAP. Other secondary aims include mortality rate (all-cause mortality rate for the longest follow-up), serum lactate, length of hospital stay, heart rate and PaO_2/FiO_2.

Literature search and study identification

Databases of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from their inception until October 2023. Clinical trial registries were searched systematically for ongoing trials. The definition of septic shock was tabulated in Supplementary Table 1 whereas the search strategies and terms utilized in this review was shown in the Supplementary Table 2. In general, eligibility criteria were: 1) All Randomized Controlled Trials (RCT) comparing methylene blue versus control group were included. 2) All RCTs comparing methylene blue versus control group involving adults (> 18-years-old) with septic shock, regardless of reported outcomes were included.

No language restrictions were applied. From our search, we included non-English studies, in which these articles were translated to English with the help of certified translators. Observational studies, case series or reports, conference abstract were excluded. The references of the included RCTs were manually searched and cross referenced for further potential studies. Authors of relevant studies were contacted at least three times for any incomplete data.

Study selection and data extraction

The review was reported in accordance with the guideline from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement 2020.[21,22] Two authors (PK and WL) briefed by the principal author (KN) for the inclusion and exclusion criteria. Titles and abstracts were screened for eligibility criteria by two authors (PK and WL) independently. The final selection of all the included RCTs were discussed and agreed among all the authors (KN, PK, WL). Any disagreements were solved by the principal author (KN). The clinical characteristics of all included studies were recorded independently by two authors (PK and WL) using an online data extraction sheet. Our data extraction sheet included the following important data: author, publication year, type of control drug, dosage of control drug and methylene blue, mean age of both intervention and control group, mean weight of both groups, timing of administration of methylene blue, and sample sizes.

Risk of bias assessment

The included RCTs were assessed for their respective risk of bias according to the Cochrane Collaboration Risk of Bias Assessment Tool by 2 authors (PK and WL) independently.[23] Any disagreements were resolved via discussions with the principal author (KN). Summary of findings and the assessment on the level of evidence were conducted by 2 authors (PK and WL) independently. These assessments were evaluated using the GRADEpro software.[24] A third author (KN) was consulted to solve any conflicts.

Statistical analysis

Review Manager version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) was used to carry out statistical meta-analysis.[25] All p-values were two tailed, with statistical significance denoted as less than 0.05. With regards to dichotomous outcomes, Odd Ratios (OR) and 95% Confidence Interval (95% CI) were calculated. For continuous outcomes, Mean Difference (MD) and 95% Confidence Interval (95% CI) were utilized. The heterogeneity of pooled outcomes was evaluated by the I-square (I^2) test, where the values of $< 40\%$, 40%–60% and $> 60\%$ were indicated as low, moderate, and high heterogeneity, respectively. A fixed-effect model was used to calculate the estimates of the primary and secondary outcomes. However, if high heterogeneity ($I^2 > 60\%$) was observed, a random-effect model was used. When the values were reported as median or interquartile range, these values were converted to mean and standard deviation.[26] Publication bias was evaluated using funnel plots for any asymmetry.[27] Subgroup analysis was performed on specific time intervals on the primary outcome of MAP. Two specific time-intervals, namely immediate period after administration of methylene blue and 3-day after methylene blue administration, were chosen to study its immediate effects and its effects after being eliminated from the body.[28]

Results

PRISMA flow chart of the study selection was illustrated in Figure 1. After removing duplicates, 658 articles remained for title and abstract screening. A total of 26 articles were downloaded for full text screening. A total of 21 papers were excluded due to failure to fulfil the inclusion criteria. The list of excluded studies is shown in Supplementary Table 3. Five articles with 257 participants were eligible to be included in this review. The demographics of the included RCTs are illustrated in Table 1. Searching of trial registries found 1 ongoing study, which is shown in Supplementary Table 4.

The control drugs varied among the included studies. Three studies used normal saline as the control drug,[29-31] whilst others employed glucose or alternative fluid resuscitation treatments.[32] The range of mean age of the control group is 23.8 to 76.0 years old whereas the range of mean age of the methylene blue group is 33.8 to 75.0 years old, respectively. The mean body mass index of the control group is 22.2 to 28.4 $kg.m^{-2}$ whereas the mean body mass index of the methylene blue group is 22.1 to 27.6 $kg.m^{-2}$. Of all, the year of publication ranged from 2001 to 2023 with sample sizes of each group varied from 10 to 46. Data analysis of primary and secondary outcomes is illustrated in Table 2. Summary of findings and certainty of evidence is shown accordingly in Table 3.

Overall, two of the included RCTs have a low risk of bias[30,32] whereas the other 3 studies were evaluated as unclear or high risk of bias[29-31] due to lack of blinding of participants and personnel, and lack of blinding of outcomes (Supplementary Table 5). The review was conducted with the aid of PRISMA checklist, as shown in Supplementary Table 6.

Primary outcome: mean arterial pressure

Three randomized-controlled trials examined the impact of methylene blue on MAP.[29,30,33] Methylene blue significantly increased MAP in patients randomized to receiving methylene blue (n = 203, MD = 1.34 mmHg, 95% CI 0.15 to 2.53, p = 0.03, level of evidence: very low) (Figure 2). However, there is a high degree of heterogeneity for this measured outcome (I^2 = 99%) and the funnel plot for MAP were asymmetrical, suggesting risk of publication bias. Subgroup analysis of specific time intervals revealed that methylene blue significantly increased MAP of patients in the immediate period after methylene blue infusion (studies = 4, n = 203, MD = 3.25, 95% CI 0.24 to 6.27, p = 0.03) (Supplementary Fig. 1).

Secondary outcome: mortality rate, serum lactate, PaO_2/FiO_2, length of hospital stay, heart rate

Based on the combined data from 3 RCTs, patients who received methylene blue had statistically lower mortality

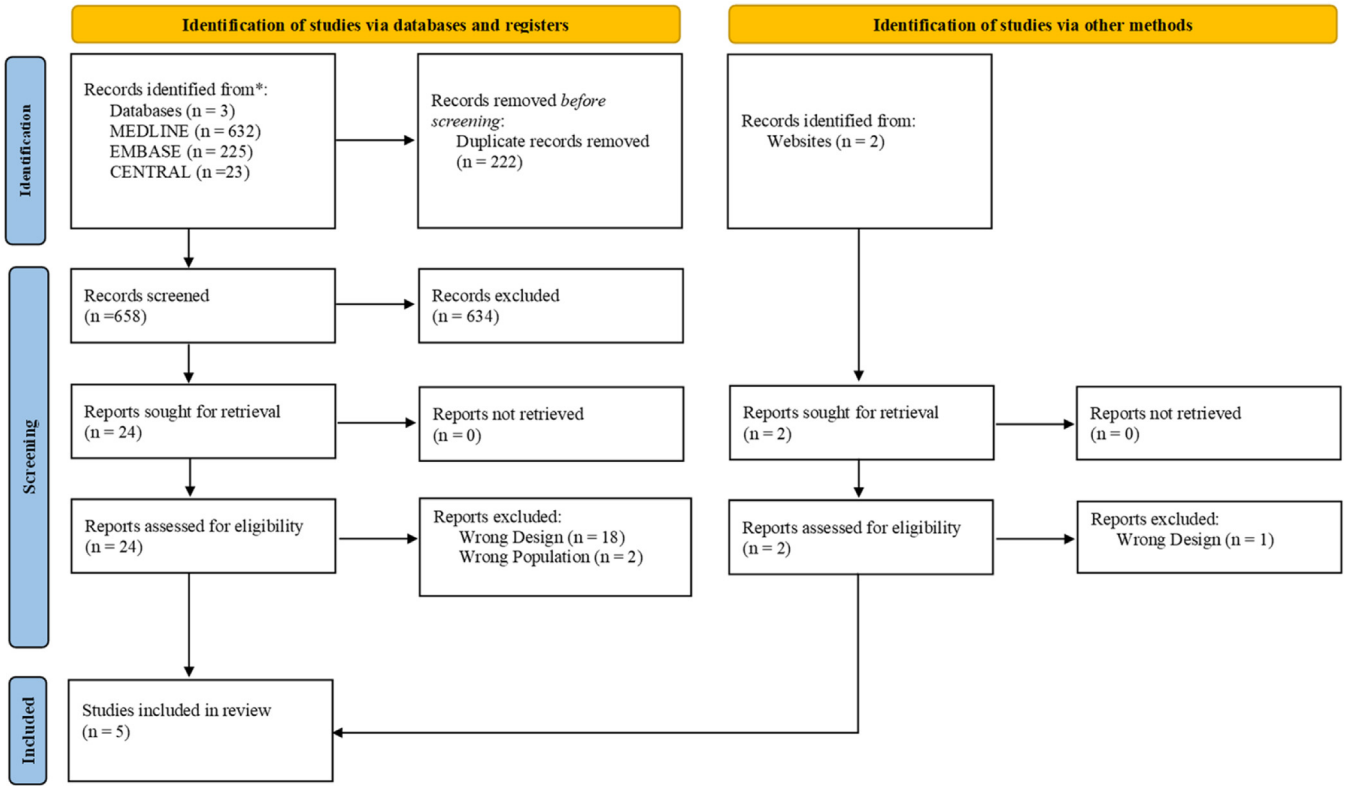

Figure 1 Prisma diagram. A total of 5 studies were included in this systematic review.

rate (n = 205, OR = 0.49, 95% CI 0.27 to 0.88, p = 0.02, level of evidence: low) (Figure 3).[30-32] Low statistical heterogeneity was denoted across included studies (I^2 = 0%). Pooled mean difference from 3 included studies showed that administration of methylene blue was associated with lower serum lactate levels compared to placebo (MD = -0.76 mmoL.L^{-1}, 95% CI -1.22 to -0.31, p = 0.0009, level of evidence: low) (Figure 3).[30,31,33] However, a moderate degree of heterogeneity was assessed in the pooled effect (I^2 = 45%).

There was a significant increase in PaO_2/FiO_2 in the methylene blue group than the control group (MD = 34.78, 95% CI 8.94 to 60.61, p = 0.008, level of evidence: low) (Figure 3).[29,30] A total of 2 studies (n = 111) measured the length of hospital stay. Patients who received methylene blue had a statistically shorter length of hospital stay as compared with the placebo group (MD = -1.94, 95% CI -3.79 to -0.88, p = 0.04, I^2 = 0%, level of evidence: low) (Figure 3).[29,30]

Three studies (n = 106 patients) indicated showed that there was no significant difference between the methylene blue and the control group on the heart rate (MD = -2.31, 95% CI -5.88 to 1.27, p = 0.21, level of evidence: low) (Supplementary Fig. 2). The test for statistical heterogeneity was low (I^2 = 0%).[29-31]

Discussions

Our meta-analysis revealed that the methylene blue administration in patients with septic shock is associated with an increase in MAP over a short-term period following its use, although the results show considerable variability. Additionally, methylene blue is likely associated with improvement in the PaO_2/FiO_2 ratio, as well as reductions in mortality rate, serum lactate levels, and length of hospital stay.

A previous systematic review completed by Kwok et al. included 2 randomized-controlled trials and 11 case reports/series.[16] Another systematic review by Paciullo et al. included 2 randomized-controlled trials and 8 prospective observational studies.[19] However, the inclusion of non-RCTs would have downgraded the quality of evidence for the measured outcomes.[34] Previously, no quantitative meta-analysis of the data could be performed due to the limited number of RCTs focusing on patients with septic shock. Given that more RCTs have been published, our team decided to perform an updated and comprehensive review and meta-analysis on the use of methylene blue in the adult population with septic shock.

Prompt treatment of hypotension is imperative in septic shock.[3] Observational studies of methylene blue in septic shock patients have generally shown short term improvements in hemodynamic parameters.[12,15,16,35] It is believed that methylene blue increases blood pressure via the inhibition of iNOS vasodilation, instead of vasoconstriction in catecholamines.[30] Memis et al. reported that methylene blue statistically increased MAP in patients with severe sepsis.[36] Similarly, our pooled analysis reported a statistical increase of MAP in the methylene blue group compared to the control group. However, the increase in MAP observed after 24 hours was not statistically significant in our findings. This suggests that the hemodynamic effects of methylene blue may be short-lived and transient. While methylene blue has long

Table 1 Clinical characteristics of included studies.

Author, Year	Methylene blue dose regimes	Control Group	Sample Size	Main Findings
Kirov et al., 2001	Intravenous bolus injection (2 mg.kg^{-1}) methylene blue, followed 2 hours later by infusion at stepwise increasing rates of 0.25, 0.5, 1, and 2 mg.kg^{-1}. hour^{-1} that were maintained for 1 hour each	Normal Saline	20	Methylene blue reduced the requirement for norepinephrine, epinephrine, and dopamine by as much as 87%, 81%, and 40%, respectively. Mean arterial pressure was significantly increased at the 6-hour and 24-hour after drug administration in the methylene blue group compared to the control group.
Arzapalo et al., 2016	2 mg.kg^{-1} methylene blue in 100 mL of 5% glucose solution infused over 1 hour	Glucose	60	Methylene blue group (22%) was associated with an increase mean arterial pressure than the control group (9.2%). Noradrenaline dose at the 6-hour was significantly reduced in the methylene blue group (86%) as compared to the control group (56%).
Lu et al., 2018	2 mg.kg^{-1} methylene blue (diluted with 50 mL of 0.9% sodium chloride injection) into a single intravenous pump. After 20 minutes, continue administering methylene blue at 2 mL/hour for 24 hours	Normal Saline	32	Mean arterial pressure after day 1 of drug administration was significantly higher in the methylene blue group than the control group. Perfusion index at day 1 to day 5 after drug administration was significantly higher in the methylene blue group than the control group. Oxygenation index at day 2 to day 5 after drug administration was significantly higher in the methylene blue group than the control group.
Lu et al., 2019	Group 1: Bolus Infusion (2 mg.kg^{-1} of methylene blue added into 50 mL of normal saline infused over 20 mins, and then continuous infusion of 50 mL of normal saline over 24 hours) Group 2: Continuous Infusion (2 mg.kg^{-1} of methylene blue added into 50 mL of normal saline infused over 20 mins, and then continuous infusion of methylene blue diluted with 50 mL of normal saline over 24 hours)	Normal Saline	54	Norepinephrine dosage at day 1 was significantly lower in the methylene blue group than the control group. Methylene Blue significantly increased perfusion index at day 1 to day 7 compared to the control group.
Ibarra-Estrada et al., 2023	100 mg of methylene blue in 500 mL of 0.9% sodium chloride solution over 6 hours once daily for a total of 3 doses	Normal Saline	91	The methylene blue group had a significantly shorter time to vasopressor discontinuation, a shorter ICU length of stay by 1.5 days and shorter hospital length of stay by 2.7 days as compared to the control group.

Data are presented as mean ± standard deviation. RCT, Randomised Controlled Trials.

Table 2 Data analysis of primary and secondary outcomes.

Outcomes	Trials	n	I^2 (%)	MD/OR (95% CI)	p-value
Mean Arterial Pressure (Main Analysis) (mmHg)	6	286	99	1.34 [0.15, 2.53]	0.03
Mean Arterial Pressure (Subgroup Analysis) (mmHg)					
Time-points after MB Infusion					
a) Immediate period after MB Infusion	3	203	99	3.25 [0.24, 6.27]	0.03
b) 3-day after MB Infusion	3	183	29	0.22 [-0.30, 0.73]	0.42
Risk of Bias					
a) Low Risk of Bias	4	302	100	0.95 [-0.25, 2.15]	0.12
b) High/Unclear Risk of Bias	4	84	25	9.95 [3.51, 16.40]	0.002
Mortality Rate (Main Analysis)	4	259	0	0.49 [0.27, 0.88]	0.02
Mortality Rate (Subgroup Analysis)					
Time-points after MB Infusion					
a) 7-day	2	114	0	0.38 [0.13, 1.10]	0.08
b) 28-day	2	145	0	0.54 [0.26, 1.12]	0.10
Serum Lactate (Main Analysis) ($mmoL.L^{-1}$)	6	413	45	-0.76 [-1.22, -0.31]	0.0009
Serum Lactate (Subgroup Analysis) ($mmoL.L^{-1}$)					
Time-points after MB Infusion					
a) 1-hr after MB Infusion	2	77	0	0.00 [-0.94, 0.94]	1.00
b) 24-hr after MB Infusion	2	168	0	-1.06 [-1.32, -0.81]	<0.00001
c) 72-hr after MB Infusion	2	168	69	-1.04 [-2.26, 0.18]	0.09
d) PaO_2/FiO_2 (Main Analysis)	3	131	0	34.78 [8.94, 60.61]	0.008
PaO_2/FiO_2. (Subgroup Analysis)					
Time-points after MB Infusion					
a) Immediate Period After MB Infusion	2	111	0	34.37 [7.55, 61.19]	0.01
b) 24-hr after MB Infusion	1	20	N/A	40.00 [-56.51, 136.51]	0.42
Length of Hospital Stay (days)	2	111	0	-1.94 [-3.79, -0.08]	0.04
Heart Rate (Main Analysis) (bpm)	13	470	0	-2.31 [-5.88, 1.27]	0.21
Heart Rate (bpm)					
a) After MB Infusion	3	106	0	2.62 [-5.02, 10.25]	0.50
b) 24-hr after MB Infusion	3	106	10	-3.27 [-11.75, 5.22]	0.45
c) 72-hr after MB Infusion	2	86	0	-3.24 [-12.00, 5.52]	0.47
d) 5-day after MB Infusion	2	86	0	-3.26 [-11.34, 4.82]	0.43
e) 7-day after MB Infusion	3	86	0	-4.95 [-12.61, 2.70]	0.20

Values are Mean Difference (MD)/Odds Ratio (OR) and 95% Confidence Interval.
MB, Methylene Blue; PaO_2/FiO_2, Ratio of arterial oxygen partial pressure to fractional inspired oxygen; n, Sample Size; N/A, Not Applicable.

been established as the treatment of methemoglobinemia with dosages of 1–2 $mg.kg^{-1}$,[37] the optimal dosing strategy for methylene blue in septic patients is still not well defined. A study on seven healthy individuals where 100 mg of IV methylene blue was administered demonstrated that the estimated terminal half-life is 5.25 hours.[38] Three dosing strategies were identified in our study – single bolus, continuous infusion, and bolus dose followed by infusion. Doses based on weight ranged from 0.5 $mg.kg^{-1}.h^{-1}$ to 2.0 $mg.kg^{-1}.h^{-1}$. The most commonly used regimen, observed in four out of five included studies, was continuous infusion.[29,31-33] Ibarra-Estrada et al. was the only study to administer methylene blue for more than 24 hours, using repeated doses once daily for a total of three days.[30] Juffermans et al. demonstrated that the hemodynamic effects of methylene blue are dose-dependent, with an infusion of 1–3 $mg.kg^{-1}$ being sufficient to increase MAP.[18] This study also highlighted that the effects of a single infusion are transient, lasting approximately two hours.[18] These findings align with our study, which showed a statistically significant increase in MAP immediately after methylene blue infusion but no significant effect 24 hours post-infusion. Therefore, repeated boluses or continuous infusion may be considered to mitigate this limitation. A significant degree of heterogeneity was observed in the primary outcome, likely due to factors such as variability in baseline patient characteristics, differing dosing regimens, timing of drug administration, and types of control drugs used. As such, future randomized controlled trials in a more homogenous clinical setting are necessary to accurately assess the impact of methylene blue on MAP in adult patients with septic shock.

In the setting of sepsis, inflammatory cytokines have been theorized to suppress cortisol response or compete with intracellular glucocorticoid receptors, resulting in peripheral tissue resistance and eventual vascular collapse.[39,40] The utility of steroids was not explicitly described in all the included studies, except for Ibarra-Estrada et al.[30] This study was the only RCT that administered intravenous hydrocortisone at 200 mg/day by continuous infusion as part of the resuscitation protocol.[30] Hydrocortisone is one of the most commonly used corticosteroids in the management of septic shock patients due to its mineralocorticoid and

Table 3 Level of Evidence. Author(s): Ka Ting Ng, Pei En Kwok, Wei En Lim, Mohd Shahnaz Bin Hasan, Rafidah Atan, Nor' Azim Bin Mohammed Yunus, Mohd Fitry Zainal Abidin.
Question: Methylene Blue compared to Placebo for Septic Shock in Adults. **Setting:** Septic Shock Adult Patients.

Certainty assessment							N° of patients		Effect			
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylene Blue	Placebo	Relative (95% CI)	Absolute (95%CI)	Certainty	Importance
Mean Arterial Pressure (mmHg)												
4	Randomized trials	Serious[a]	Serious[b]	Not serious	Serious[c]	None	142	144	–	MD **2.94 higher** (1.52 higher t o 4.36 higher)	⊕○○○ Very low	
Mortality Rate												
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	27/147 (18.4%)	39/112 (34.8%)	**OR 0.49** (0.27 to 0.88)	**141 fewer per 1,000** (from 222 fewer to 28 fewer)	⊕⊕○○ Low	
Serum Lactate (mmoL.L^{-1})												
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	228	185	–	MD **0.76 lower** (1.22 lower to 0.31 lower)	⊕⊕○○ Low	
PaO_2/FiO_2 (ratio of arterial oxygen partial pressure to fractional inspired oxygen)												
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	65	66	–	MD **34.78 higher** (8.94 higher to 60.61 higher)	⊕⊕○○ Low	
Heart Rate (bpm)												
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	280	190	–	MD **2.31 lower** (5.88 lower to 1.27 higher)	⊕⊕○○ Low	
Length of Hospital Stay (days)												
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	55	56	–	MD **1.94 lower** (3.79 lower to 0.08 lower)	⊕⊕○○ Low	

CI, Confidence Interval; MD, Mean Difference; OR, Odds Ratio.
Explanations:
[a] Half of the included studies possess high or unclear risk of bias.
[b] High degree of heterogeneity.
[c] Sample size of each arm < 400.

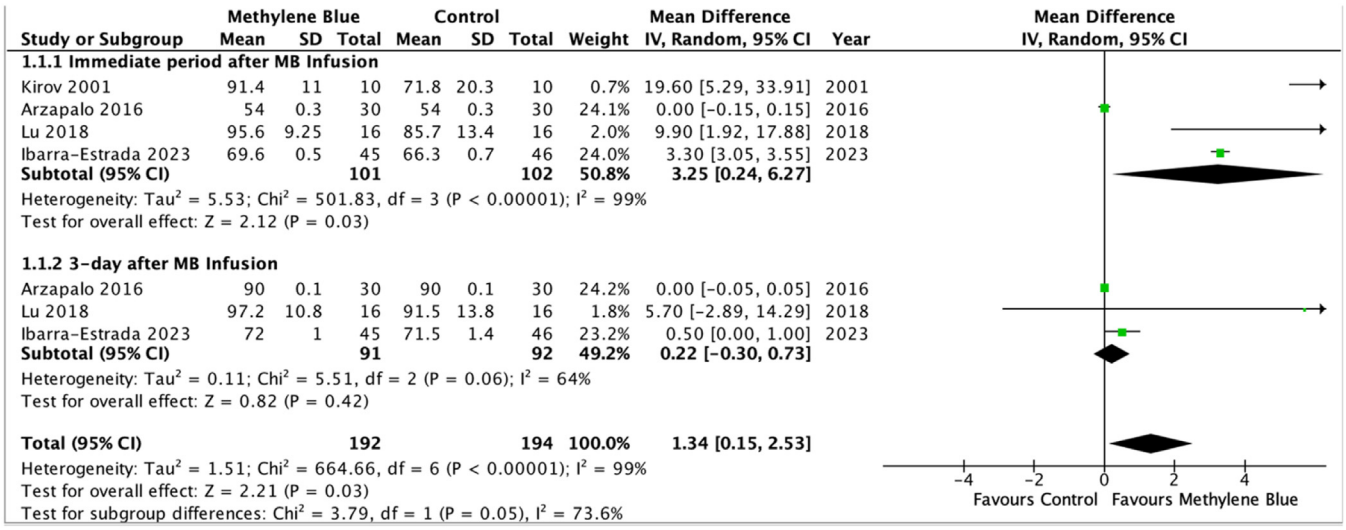

Figure 2 Forest plot of mean arterial pressure (mmHg) – Methylene blue is associated with a significant increase in mean arterial pressure compared to the control group.

glucocorticoid activity. Given these properties, hydrocortisone stimulates the release of aldosterone, promoting the reabsorption of salt and water and enhancing the vascular contractile response to pressor agents, thereby increasing blood pressure in septic shock patients. However, its use may introduce potential confounding in the measurement of MAP. Therefore, future randomized controlled trials are necessary to determine whether the combined administration of corticosteroids and methylene blue would positively influence MAP and to assess the extent of their respective effects.

Quantitative analysis of the three studies reporting mortality demonstrated a statistically significant reduction in the overall mortality rate among patients receiving methylene blue.[30,31,33] However, the total sample size (n = 205) was very small. Hence, it is unpowered to detect any clinically meaningful outcomes for mortality rate and the pooled findings should be interpreted with caution. Future adequately powered studies are required to examine the impact of methylene blue on the mortality rate in septic shock patients. Serum lactate has been included in the recent definition of septic shock as it is considered an important biomarker of cellular stress in a refractory hypotension.[1] Current guidelines recommend using lactate levels as biochemical indicators to guide resuscitation in early phases of septic shock.[3] Our finding demonstrated that methylene blue was associated with significantly lower serum lactate levels.[30,31,33] This suggests that methylene blue may exert favourable effects on tissue perfusion and anaerobic metabolism.[41-43] However, the interpretation of lactate levels should be approached cautiously and considered alongside other hemodynamic parameters.

The time factor remains a critical element in the management of septic shock and early intervention is crucial to improving outcome.[3] In our included studies, the timing of methylene blue administration and vasopressor titration varied across all the included studies. The majority of studies administered methylene blue within 24 hours after the initiation of vasopressors.[29,31-33] It is hard to determine if there are possible delays between the onset of septic shock and the administration of methylene blue. It has been proposed that there is a 'window of opportunity' and time-sensitive for methylene blue to restore vascular resistance in septic shock effectively.[44] A sepsis model in mice demonstrated that there exists a dynamic guanylate cyclase activity in three 8-hour windows.[44] An increase in guanylate cyclase and iNOS is observed in the first 8-hour window, followed by an absence of guanylate cyclase expression and down-regulation of iNOS in the second 8-hour window.[45] Then, there is an upregulation of guanylate cyclase and iNOS in the third 8-hour window.[45] This suggests that the use of methylene blue as a last rescue therapeutic option may not act (second window) or act too late (third window) when the shock is irreversible with profound tissue hypoxia and intractable metabolic acidosis.[46] In the current literature, methylene blue has been administered as a late rescue treatment during septic shock, and the impact of earlier administration as an adjunct is yet to be established.

There are some concerns that the use of methylene blue causes ventilation-perfusion mismatch and vasoconstriction via the inhibition of cGMP.[47] Previous studies demonstrated a significant reduction in the PaO_2/FiO_2 ratio in the methylene blue group.[15,36] Weingartner and colleagues specifically reported a decrease in the PaO_2/FiO_2 ratio from 168 (131–215) mmHg to 132 (109–156) mmHg following methylene blue administration ($p < 0.05$).[35] However, it is worth noting that all the included patients in this study had acute lung injury, and seven of the ten included patients fulfilled the criteria for ARDS.[35] Hence, the observed respiratory dysfunction may be attributed to septic shock secondary to respiratory pathology rather than the adverse effect of methylene blue. Our pooled results support this hypothesis by showing that methylene blue increases PaO_2/FiO_2 compared to the control group.[29,30] Methylene blue is a safe drug when used in therapeutic doses of < 2 mg.kg^{-1}.[38] All our included studies used the dose of methylene blue < 2 mg.kg^{-1} and no significant adverse events were reported. There was an increase in the level of methaemoglobin in one of the included studies albeit not clinically significant.[29] Other common side effects include blue skin and urine discoloration that are transient

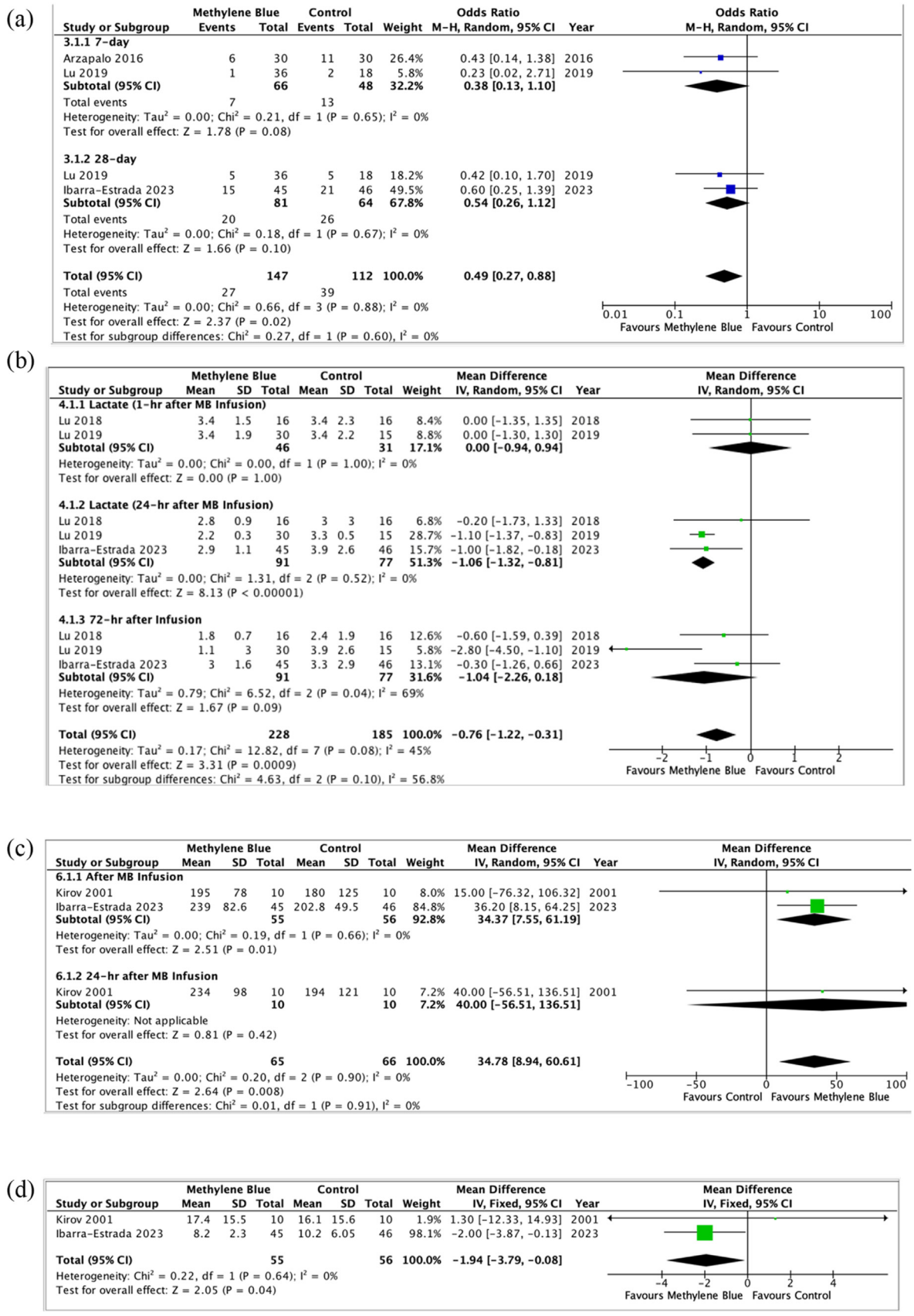

Figure 3 Comparison of mortality rate (a), serum lactate levels (b), PaO_2/FiO_2 ratio (c), and length of hospital stay (d), between the methylene blue group and the control group.

and benign.[38] Clinicians should also be conscientious of the interference in pulse oximeter readings caused by methylene blue as it absorbs most light emitted by the pulse oximeter.[47] This may be interpreted as a false reduction in circulating oxyhaemoglobin and reduced oxygen saturation.[48] Furthermore, a study by Juffermans et al. demonstrated that high doses (> 7 $mg.kg^{-1}$) of methylene blue may compromise splanchnic perfusion despite global haemodynamic enhancement.[39] The usage of methylene blue is contraindicated in patients with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency as it increases the risk of haemolytic anaemia.[49] Moreover, methylene blue also inhibits the monoamine oxidase enzyme, which may result in the manifestation of serotonin syndrome when used with monoamine oxidase inhibitors, such as antidepressant medications.[50]

Catecholamine-resistant shocked patients with high renin levels may benefit from early commencement of angiotensin II.[51] Measurement of the metabolites of the nitric oxide pathway in the form of nitrite and nitrate may suggest early initiation of methylene blue. Markers to predict specific vasopressor responsiveness may be the ideal approach to managing hypotension in septic shock. Physiologically, diastolic arterial pressure and dynamic arterial elastance may be useful parameters to guide patients who will benefit from early vasopressors.[52,53] Analysis of the kinetics of norepinephrine dose increment and the response to vasopressin treatment may suggest the need for early initiation of other vasopressors with different mechanisms of action.[54] According to Kram et al., who studied patients with vasoplegic syndrome, the minimum methylene blue required to reduce norepinephrine needs was 1.4 $mg.kg^{-1}$.[55] For each incremental dose increase of 0.5 $mg.kg^{-1}$, there is a 2.25 $mg.kg^{-1}$ decrease in norepinephrine dosage.[55] However, we have to be careful with the dose of methylene blue due to its side effects such as blue skin and urine discolouration.[38] Hence, future studies on the pharmacokinetics and pharmacodynamics of methylene blue are warranted to gauge the optimal dose of methylene blue.

Our study has several limitations. Variations in methylene blue administration regimens and vasopressors titration protocols may have contributed to the substantial heterogeneity observed in our primary outcome. Additionally, all the included studies had small sample size and were underpowered to detect the primary outcome of MAP, as well as secondary outcomes such as mortality rate and other clinical parameters. The lack of blinding of participants and outcome assessors (researchers) introduces a risk of overestimating the treatment effects of methylene blue. Study participants and clinicians, aware of the intervention, may have influenced subjective outcomes such as hospital discharge timing, potentially biasing the length of hospital stay. Furthermore, the follow-up periods were short and heterogeneous across most RCTs, increasing the likelihood of underreporting adverse outcomes. Another limitation is that the causes of septic shock were not consistently reported across the included studies, which could introduce bias to our findings. The transient urine discoloration commonly associated with methylene blue administration may have unintentionally unblind clinicians, further increasing the risk of bias. None of the studies measured nitrite or nitrate levels, making it unclear whether the observed effects of MAP could be directly attributed to methylene blue. Finally, there is a risk of publication bias due to the limited number of studies published on the effects of methylene blue in septic shock patients. These limitations highlight the need for more robust, adequately powered, and methodologically sound randomized controlled trials to better assess the efficacy and safety of methylene blue in this context.

This meta-analysis demonstrated that methylene blue shows promise in the management of patients with septic shock. However, due to the limited sample size and the low quality of evidence in the included studies, its use requires further validation through larger, well-designed clinical trials. Future adequately powered randomized controlled trials are necessary to determine the optimal dosing and timing of methylene blue, as well as its effect on hemodynamic and clinical outcomes, before its routine implementation in clinical practice.

Human ethics and consent to participate declarations

None.

Previous presentation in conferences

RCoA Anaesthesia Research.

Awards

RCoA Anaesthesia Research Presentation Award.

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Supplementary materials

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References

1. Singer M, Deutschman CS, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801.
2. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med. 2001;345:588—95.
3. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021;49:E1063—143.
4. Tsujimoto G, Honda K, Hoffman BB, Hashimoto K. Desensitization of postjunctional alpha 1- and alpha 2-adrenergic receptor-mediated vasopressor responses in rat harboring pheochromocytoma. Circ Res. 1987;61:86—98.

5. Nagendran M, Russell JA, Walley KR, et al. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. Intensive Care Med. 2019;45:844–55.
6. De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis. Crit Care Med. 2012;40:725–30.
7. Green SJ, Scheller F, Marietta MA, et al. Nitric Oxide: Cytokine-regulation of nitric oxide in host resistance to intracellular pathogens. Immunol Lett. 1994;43:87–94.
8. Tripathi P, Tripathi P, Kashyap L, Singh V. The role of nitric oxide in inflammatory reactions. Nitric oxide: control of immune response. FEMS Immunol Med Microbiol. 2007;51(3):443–52.
9. López A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. Crit Care Med;. 2004;32:21–30.
10. Brown G, Frankl D, Phang T. Continuous infusion of methylene blue for septic shock. Postgrad Med J. 1996;72:612–4.
11. Mayer B, Brunner F, Schmidt K. Inhibition of nitric oxide synthesis by methylene blue. Biochem Pharmacol. 1993;45:367–74.
12. Preiser JC, Lejeune P, Roman A, et al. Methylene blue administration in septic shock: A clinical trial. Crit Care Med. 1995;23:259–64.
13. Paya D, Gray GA, Stoclet JC. Effects of methylene blue on blood pressure and reactivity to norepinephrine in endotoxemic rats. J Cardiovasc Pharmacol. 1993;21:926–30.
14. Zhang H, Rogiers P, Preiser JC, et al. Effects of methylene blue on oxygen availability and regional blood flow during endotoxic shock. Crit Care Med. 1995;23:1711–21.
15. Gachot B, Bedos JP, Veber B, Wolff M, Regnier B. Short-term effects of methylene blue on hemodynamics and gas exchange in humans with septic shock. Intensive Care Med. 1995;21:1027–31.
16. Kwok ESH, Howes D. Use of methylene blue in sepsis: a systematic review. J Intensive Care Med. 2006;21:359–63.
17. Porizka M, Kopecky P, Dvorakova H, et al. Methylene blue administration in patients with refractory distributive shock – a retrospective study. Sci Rep. 2020;10:1828.
18. Juffermans NP, Vervloet MG, Daemen-Gubbels CRG, et al. A dose-finding study of methylene blue to inhibit nitric oxide actions in the hemodynamics of human septic shock. Nitric Oxide. 2010;22:275–80.
19. Paciullo CA, Horner DMM, Hatton KW, Flynn JD. Methylene Blue for the Treatment of Septic Shock. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2010;30:702–15.
20. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training [Internet]. London: Cochrane Training; 2020. Available from https://training.cochrane.org/handbook/current.
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372372:n71.
22. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst Rev. 2022;18:e1230.
23. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
24. GRADEproGDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2023. Accessed 9 September 2023. Available from gradepro.org.
25. Review Manager (RevMan) [Computer program]. Version 5.4. Accessed 9 September 2023.
26. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
27. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol. 2008;61:991–6.
28. Howland MA. Methylene Blue. In: Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS, eds. Goldfrank's Toxicologic Emergencies, 11e [Internet], New York, NY: McGraw-Hill Education; 2019. Available from: accessemergencymedicine.mhmedical.com/content.aspx?aid=1163003951.
29. Kirov MY, Evgenov OV, Evgenov NV, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. Crit Care Med. 2001;29:1860–7.
30. Ibarra-Estrada M, Kattan E, Aguilera-Gonzalez P, et al. Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial. Crit Care. 2023;27:110.
31. Lu Y, Yu H, Liu Q, Yao M, Zhu J. Therapeutic Effects of Intravenous Infusion of Methylene Blue on Patients with Septic Shock. National Medical J China. 2019;99:868–71.
32. Arzapalo MFA, Avendano VGL, Castillo AE, Mukul JJG, Herrera BF, Camara MAC. Efficacy of methylene blue as an adjuvant in the treatment of patients with septic shock. Medicina Crítica. 2016;30:102–10.
33. Lu Y, Liu Q, Yu H. Effect of methylene blue on arterial blood gas value and perfusion index in patients with septic shock. Zhejiang Medicine. 2019;41:575–8.
34. Reeves BC, Deeks JJ, Higgins JPT, Shea B, Tugwell P, Wells GA. Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023), Cochrane; 2023. Accessed 9 September 2023. Available from www.training.cochrane.org/handbook.
35. Weingartner R, Oliveira E, Oliveira ES, et al. Blockade of the action of nitric oxide in human septic shock increases systemic vascular resistance and has detrimental effects on pulmonary function after a short infusion of methylene blue. Braz J Med Biol Res. 1999;32:1505–13.
36. Memis D, Karamanlioglu B, Yuksel M, Gemlik I, Pamukcu Z. The Influence of Methylene Blue Infusion on Cytokine Levels During Severe Sepsis. Anaesth Intensive Care. 2002;30:755–62.
37. Ginimuge PR, Jyothi SD. Methylene Blue: Revisited. J Anaesthesiol Clin Pharmacol. 2010;26:517–20.
38. Peter C, Hongwan D, Küpfer A, Lauterburg BH. Pharmacokinetics and organ distribution of intravenous and oral methylene blue. Eur J Clin Pharmacol. 2000;56:247–50.
39. Huang ZH, Gao H, Xu RB. Study on glucocorticoid receptors during intestinal ischemia shock and septic shock. Circ Shock. 1987;23:27–36.
40. Molijn GJ, Spek JJ, van Uffelen JC, et al. Differential adaptation of glucocorticoid sensitivity of peripheral blood mononuclear leukocytes in patients with sepsis or septic shock. J Clin Endocrinol Metab. 1995;80:1799–803.
41. O'Conor E, Fraser JF. The interpretation of perioperative lactate abnormalities in patients undergoing cardiac surgery. Anaesth Intensive Care. 2012;40:98–603.
42. Evora PRB. Methylene blue does not have to be considered only as rescue therapy for distributive shock. J Med Toxicol. 2013;9:426.
43. Luis-Silva F, Menegueti MG, Sato L, et al. Effect of methylene blue on hemodynamic response in the early phase of septic shock: A case series. Medicine (Baltimore). 2023;102:e32743.
44. Fernandes D, Da Silva-Santos JE, Duma D, Villela CG, Barja-Fidalgo C, Assreuy J. Nitric oxide-dependent reduction in soluble guanylate cyclase functionality accounts for early

lipopolysaccharide-induced changes in vascular reactivity. Mol Pharmacol. 2006;69:983—90.
45. Evora PRB, Ribeiro PJF, Vicente VA, et al. Methylene blue for vasoplegic syndrome treatment in heart surgery: fifteen years of questions, answers, doubts and certainties. Rev Bras Cir Cardiovasc. 2009;24:279—88.
46. Grayling M, Deakin CD. Methylene blue during cardiopulmonary bypass to treat refractory hypotension in septic endocarditis. J Thorac Cardiovasc Surg. 2003;125:426—7.
47. Al-Halawani R, Charlton PH, Qassem M, Kyriacou PA. A review of the effect of skin pigmentation on pulse oximeter accuracy. Physiol Meas. 2023;144:05TR01.
48. Clifton J, Leikin JB. Methylene blue. Am J Ther. 2003;10:289—91.
49. McDonagh EM, Bautista JM, Youngster I, Altman RB, Klein TE. PharmGKB summary: methylene blue pathway. Pharmacogenet Genomics. 2013;23:498.
50. Ramsay RR, Dunford C, Gillman PK. Methylene blue and serotonin toxicity: inhibition of monoamine oxidase A (MAO A) confirms a theoretical prediction. Br J Pharmacol. 2007;152: 946—51.
51. Bellomo R, Forni LG, Busse LW, et al. Renin and survival in patients given angiotensin II for catecholamine-resistant vasodilatory shock. A clinical trial. Am J Respir Crit Care Med. 2020;202:1253—61.
52. Hamzaoui O, Teboul JL. Importance of diastolic arterial pressure in septic shock: PRO. J Crit Care. 2019;51:238—40.
53. Monge García MI, Pinsky MR, Cecconi M. Predicting vasopressor needs using dynamic parameters. Intensive Care Med. 2017;43: 1841—3.
54. Guerci P, Belveyre T, Mongardon N, Novy E. When to start vasopressin in septic shock: the strategy we propose. Crit Care. 2022;26:125.
55. Kram SJ, Kram BL, Cook JC, Ohman KL, Ghadimi K. Hydroxocobalamin or Methylene Blue for Vasoplegic Syndrome in Adult Cardiothoracic Surgery. J Cardiothorac Vasc Anesth. 2022;36: 469—76.

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LETTER TO THE EDITOR

Comparison of propofol-ketamine and propofol-fentanyl combinations for sedation in patients undergoing gastrointestinal endoscopy: a randomized clinical trial

Dear Editor,

Colonoscopy is a globally performed procedure, playing a crucial role in diagnosing and treating colon diseases, and significantly reducing colorectal cancer risk in symptomatic patients and those undergoing screening. Pain during colonoscopy arises from mesenteric traction maneuvers and distension of the colonic lumen, making adequate sedation and analgesia essential. Regarding the ketamine-propofol combination, the synergistic effects of these drugs can counterbalance their individual disadvantages; ketamine's sympathomimetic properties mitigate the hypotension and respiratory depression caused by propofol, while propofol reduces ketamine's adverse gastrointestinal effects.[1]

This randomized, double-blind clinical trial carried out between May 2022 and February 2023, conducted at Hospital São Domingos, São Luís, Maranhão, Brazil, aimed to evaluate the sedative efficacy by two different sedation regimens (Propofol + Ketamine vs. Propofol + Fentanyl) in patients undergoing elective Colonoscopy or Colonoscopy + Endoscopy. The study received ethical approval from the Research Ethics Committee (CAAE: 58003522.0.0000.5085) and was registered in the Brazilian Registry of Clinical Trials (REBEC) (RBR-4mvny8s).

Patients aged 18 to 65 years, classified as American Society of Anesthesiologists (ASA) physical status I or II, and scheduled for elective Colonoscopy (CLN) or bidirectional endoscopy (colonoscopy and upper endoscopy) were included. The sample size was calculated with a difference of at least 30% between the two groups regarding patient dropout or complications, considering an alpha error of 5% and a statistical power of 80%, 40 patients were allocated to each group. The primary objective was to assess sedation safety and effectiveness in achieving hemodynamic stability, with secondary objectives being the analysis of procedure duration, propofol doses, and satisfaction levels of both patients and anesthesiologists. Data analysis was performed using SPSS V.26. Categorical data were presented in absolute and relative frequency, and numerical data in mean and standard deviation or median and range. The Chi-Square, in categorical variables, *t*-test or Mann-Whitney in continuous variables, according to normality, verified by Shapiro-Wilk, were used to compare groups.

In the PF group (Propofol + Fentanyl), sedation and analgesia were performed with propofol 1 $mg.kg^{-1}$ and fentanyl 0.25 $\mu g.kg^{-1}$, and in the PK group (Propofol + Ketamine), sedation and analgesia were performed with propofol 1 $mg.kg^{-1}$ and ketamine 0.25 $mg.kg^{-1}$.

Demographic, clinical and anthropometry data were collected before the procedure. Heart Rate (HR), Respiratory Rate (RR), Peripheral O_2 Saturation (SpO_2), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were collected at the beginning and at 5, 10, 15, 20 and 30 minutes throughout the procedure. Procedure duration, sedation-related complications (including Systolic Blood Pressure [SBP < 85 mmHg] or Diastolic Blood Pressure [DBP < 50 mmHg], Mean Arterial Pressure [MAP > 20 mmHg], Heart Rate [HR < 55 bpm], anesthetic recovery (period after the end of the procedure until a score of 2 in the Ramsay Sedation Scale is reached), Ramsay Sedation Scale (RSS), hospital discharge and Visual Analog Scale of Satisfaction (1 to 10, 10 being the best satisfaction rate) were also recorded after the procedure.

The PK group included 40 patients, and 40 in the PF group. The social and clinical profiles showed no statistical difference. A statistically significant higher incidence of cardiovascular complications was observed in the PF group (62.5%, $p = 0.025$). The PK group had a significantly shorter discharge time (30.0 $\pm$ 8.7 minutes, $p = 0.019$) (Table 1).

Heart Rate (HR) was significantly lower in the PF group at 5, 10, and 15 minutes during the procedure and at 5 and 10 minutes in the recovery room ($p = 0.012$; $p = 0.003$; $p = 0.026$; $p = 0.008$; and $p = 0.009$, respectively), additionally the Respiratory Rate (RR) was significantly lower in the PF group at 5, 10, 15, 20, and 30 minutes during the procedure ($p = 0.001$; $p = 0.003$; $p = 0.024$; $p = 0.019$; and $p = 0.029$, respectively). There was no statistically significant difference in respiratory rate in the recovery room (Material Supp. 1).

SBP was significantly lower in the PF group in all evaluated intervals during the procedure ($p < 0.05$), and DBP was statistically significant at moments 5, 10, 15, 25, and 30 minutes during the procedure ($p < 0.05$), with lower values found in the PF group (Material Supp. 2).

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Table 1 Social and clinical profile of patients undergoing elective colonoscopy or Colonoscopy + Endoscopy procedures with sedation performed with Propofol-Fentanyl (n = 40) or Propofol-Ketamine (n = 40).

Variables	PF	PK	*p*-value
Social and clinical profile			
Age range (years) — Md ± Sd	52.0 ± 12.3	53.7 ± 9.8	0.508[a]
Gender — n (%)			
Male	10 (25.0)	15 (37.5)	0.228[b]
Female	30 (75.0)	25 (62.5)	
Comorbidities			
Yes	31 (77.5)	28 (70.0)	0.446[b]
No	9 (22.5)	12 (30.0)	
Anthropometry			
Weight (kg) — Md ± Sd	70.5±11.5	73.3±13.4	0.319[a]
BMI ($kg.m^{-2}$) — Md ± Sd	26.8±3.9	27.6±4.1	0.337[a]
Reason — n (%)			
Screening	19 (47.5)	16 (40.0)	0.499[b]
Diagnosis	21 (52.5)	24 (60.0)	
Procedure — n (%)			
CLN	18 (45.0)	26 (65.0)	0.072[b]
Bidirectional endoscopy	22 (55.0)	14 (35.0)	
Perioperative data			
Cardiovascular complications — n (%)			
Yes	25 (62.5)	15 (37.5)	***0.025***[b]
No	15 (37.5)	25 (62.5)	
SBP < 85, DBP < 50 or Δ da MAP > 20 — n (%)			
Yes	23 (57.5)	15 (37.5)	0.0732[b]
No	17 (42.5)	25 (62.5)	
Procedure duration (min) — Median (Min–Max)	31 (8–59)	27.5 (9–52)	0.470[c]
Recovery duration to hospital discharge (min) — Md ± Dp	34.8±9.1	30.0±8.7	***0.019***[a]
Initial dose of propofol (mg) — Md ± Sd	73.3±13.0	70.5±11.5	0.316[a]
Additional dose of propofol (mg) — Md ± Sd	138.6±88	117.2±102.5	0.319[a]
Recovery time (until RSS2) — Median (Min–Max)	10 (10–20)	10 (10–20)	0.628[c]
Patient satisfaction — Md ± Sd	10.0±0.0	10.0±0.0	1.000[a]
Anesthesiologist satisfaction — Md ± Sd	9.2±1.3	9.1±1.2	0.721[a]

PF, Propofol + Fentanyl; PK, Propofol + ketamine; CLN, Colonoscopy; Comorbidities: Obesity, Hypertension, Diabetes mellitus, Hypothyroidism; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; RSS, Ramsay Sedation Scale; Md ± Sd, Mean ± Standard deviation.

[a] Student's *t*-test.

[b] Chi-Square.

[c] Mann-Whitney.

Comparing moments 5, 10, 15, 25, and 30 minutes during the procedure, the PK group had significantly higher MAP values (p = 0.001; p = 0.000; p = 0.000; p = 0.016; and p = 0.026, respectively). There was no statistical significance between the groups when comparing baseline MAP and recovery period. There was no SBP and DBP baseline statistical significance in the recovery room. Baseline peripheral oxygen saturation (SpO_2) was significantly lower in the PF group (p = 0.029); however, during the procedure and the recovery period, there was no statistical significance (p > 0.05) (Material Supp. 3).

The higher incidence of cardiovascular complications in the PF group is consistent with the study by Vettorello et al.,[2] who found that there is activation of the cardiovagal reflex after administration of low doses of fentanyl.

Consistent with our results, Goh et al[1] found higher heart rate and higher systolic and mean arterial pressures in the ketamine-propofol group compared to the fentanyl-propofol or propofol alone groups in laryngeal mask insertion procedures in adults.

Hemodynamic stability in the PK group during and after the procedure was consistent with the study by Aydoghan et al,[3] who found that a propofol and ketamine combination generates improved hemodynamic stability and higher satisfaction compared to propofol alone.

In a study by Goel et al,[4] the authors demonstrated a significant decrease in SBP when propofol was used alone for induction compared to a propofol and ketamine combination during laryngeal mask insertion in children.

We observed higher respiratory rates in the PK group compared to the PF group, as Mortero et al[5] demonstrated an increase in the final expiratory $PaCO_2$ in patients who received the Propofol + Fentanyl combination and when ketamine was added, the final expiratory $PaCO_2$ did not increase.

In conclusion, the propofol-ketamine combination was found to be safe and effective in achieving hemodynamic stability with fewer complications compared to the propofol-fentanyl combination during colonoscopy and bidirectional endoscopy.

Conflicts of interest

The authors declare no conflicts of interest.

Ethics statement

The study was conducted following the guidelines of the Declaration of Helsinki, approved by the Ethics Committee of the Federal University of Maranhão (CAAE: 58003522.0.0000.5085/Opinion n° 5.426.295), and registered in the Brazilian Registry of Clinical Trials (REBEC) (RBR-4mvny8s).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844561.

References

1. Goh PK, Chiu CL, Wang CY, Chan YK, Loo PL. Randomised double-blind comparison of ketaminepropofol, fentanyl-propofol and propofol-saline on haemodynamics and laryngeal mask airway insertion conditions. Anaesth Intens Care. 2005;33. 223—22.
2. Vettorello M, Colombo R, De Grandis CE, et al. Effect of fentanyl on heart-rate variability during spontaneous and paced breathing in healthy volunteers. Acta Anaesthesiol Scand. 2008;52:1064—70.
3. Aydogan H, Aydogan T, Uyankoglu A, et al. Propofol-ketamine combination has shorter recovery times with similar hemodynamics compared to propofol alone in upper gastrointestinal endoscopy in adults: A randomized trial. Acta Med Okayama. 2012;29:259—64.
4. Goel S, Bhardwaj N, Jain K. Efficacy of ketamine and midazolam as co-induction agents with propofol for laryngeal mask insertion in children. Pediatric Anaesth. 2008;18:628—34.
5. Mortero RF, Clark LD, Tolan MM, et al. The effects of small-dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. Anesth Analg. 2001;92:1465—9.

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