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Impact of perioperative esketamine on the perioperative neurocognitive dysfunction: a systematic review and meta-analysis of randomised controlled studies

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ABSTRACT

Objectives The effect of esketamine on perioperative neurocognitive dysfunction (PND) remains controversial. This systematic review and meta-analysis aimed to evaluate the impact of perioperative esketamine administration on PND.

Design Systematic review and meta-analysis.

Data sources PubMed, EMBASE, Web of Science and Cochrane Library were searched from their inception to 25 April 2024.

Eligibility criteria for selecting studies We included the randomised controlled trials (RCTs) that compared single or continuous intravenous infusion of esketamine to saline among adult surgical patients without pre-existing neurocognitive disorders.

Data extraction and synthesis Two reviewers independently extracted pertinent information from the included studies. Risk of bias was assessed using Cochrane's risk of bias criteria. Risk ratios (RRs) and their corresponding 95% CIs were synthesised using a random-effects model. The overall evidence quality was appraised using the Grading of Recommendations Assessment, Development and Evaluation framework.

Results 10 RCTs were included in our meta-analysis, involving 854 surgical patients. Perioperative esketamine was associated with a reduced risk of postoperative delirium (POD) (relative risk (RR): 0.46, 95% CI: 0.30 to 0.71, p<0.001) and delayed neurocognitive recovery (dNCR) (RR: 0.41, 95% CI: 0.21 to 0.78, p<0.001). However, no statistically significant difference was found in the risk of postoperative neurocognitive disorder (post-NCD) at 3 months postsurgery between the esketamine and control groups (RR: 0.57, 95% CI: 0.19 to 1.73, p=0.40). Additionally, pain severity was reduced on postoperative day 1, with no difference in the risk of adverse events or length of hospital stay.

Conclusion Perioperative esketamine reduces the risk of short-term PND, including POD and dNCR, without significantly affecting the incidence of adverse events or length of hospital stay. However, no significant differences were observed in the risk of post-NCD at 3 months following surgery. This systematic review and meta-analysis offers valuable data for PND research and clinical drug intervention strategies.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study applied strict inclusion criteria, focusing only on studies reporting the standardised neuropsychological assessments.
⇒ The inclusion of only randomised controlled trials.
⇒ Various types of perioperative neurocognitive dysfunction, including postoperative delirium, delayed neurocognitive recovery and postoperative neurocognitive disorder, were included.
⇒ Most of the included studies were conducted in Chinese populations.
⇒ The limited number of studies and small sample sizes in some subgroup analyses.

PROSPERO registration number CRD42024538438.

INTRODUCTION

Neurocognitive disorder is a prevalent and well-documented complication following surgery and anaesthesia, particularly among the older adults. It is characterised by a discernible decline in memory, attention, orientation, information processing and social skills.[1] The Perioperative Cognition Nomenclature Working Group has designated these clinical manifestations as perioperative neurocognitive dysfunction (PND), encompassing postoperative delirium (POD), delayed neurocognitive recovery (dNCR), postoperative neurocognitive disorder (post-NCD) and both mild and major cognitive impairments.[2] The incidence of PND is acknowledged to vary based on the type of disorder, age, surgical procedure, anaesthesia type and additional factors. For example, a prior review synthesising various procedures and patient demographics reported POD incidence rates ranging from 13.2% to 41.7% and PND incidence rates from 8.9% to

46.1%.[3] Moreover, PND is more prevalent among older patients, with incidence rates increasing with age.[4] The rapid ageing of the general population, coupled with a higher number of surgeries performed on older patients, has thrust PND into the spotlight.[5] Importantly, previous research indicates that PND can deteriorate quality of life, prolong hospital stays and escalate morbidity and mortality rates.[6 7] Consequently, the identification and prevention of PND have become paramount concerns.[8–10]

Given its multifactorial aetiology,[8 9 11] recent studies have highlighted the significant involvement of the N-methyl-D-aspartate (NMDA) receptor—an essential mediator of learning, memory and synaptic plasticity[12 13]—in the development of PND.[14 15] Esketamine, the S-enantiomer of ketamine and an NMDA receptor antagonist, has been consistently confirmed in numerous studies for its antidepressant effects, particularly in alleviating postpartum depression.[16] A network meta-analysis comparing different anaesthetic drugs in reducing the incidence of PND for older adults undergoing non-cardiac surgery revealed that there was no significant difference in the ketamine group compared with placebo.[17] Contrastingly, preclinical studies in aged rats suggested that esketamine has an alleviating effect on neurocognitive impairment after surgery and anaesthesia.[18 19] These findings, when considered alongside prior research highlighting differences in adverse reactions (eg, hallucinations and nightmares) and anxiolytic properties between the two agents,[20 21] provide a compelling rationale to hypothesise divergent clinical efficacy in the prevention and management of PND. Consequently, ketamine and esketamine should not be conflated in evaluating their effects in prior studies, [22]and independent analyses of esketamine are warranted.

However, data from previous clinical studies on the efficacy of esketamine in reducing the risk of PND are currently disparate. Given the potential of these agents to revolutionise perioperative care, synthesising the available evidence and providing guidance for clinical practice is imperative.

To address this clinical controversy and explore the potential impact of perioperative esketamine on the incidence of PND, we conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) involving surgical patients, thereby providing a comprehensive and consolidated source of information for both clinical practitioners and researchers.

MATERIALS AND METHODS

The reporting of this meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[23] and adhered to a protocol registered with PROSPERO (CRD42024538438).

Search strategy

XS and LC independently executed a thorough search across various online databases, including PubMed, EMBASE, Web of Science and the Cochrane Library, with a focus on English-language articles containing the keywords “esketamine” and “PND.” The restriction to English-language articles was based on practical constraints, the predominance of high-quality research published in English and the need to ensure consistency and accuracy in data extraction and analysis. The literature search was comprehensive, covering all available records from their inception up to 25 April 2024. Any differences encountered were addressed through discussions with ST to achieve consensus. Specific search terms used for each database are provided in online supplemental table 1.

Study selection

The references obtained from the search were exported to Endnote V.2022 and assessed by XS and YZ independently. The initial screening involved evaluating titles and abstracts, followed by a thorough review of full texts for potentially relevant studies. Eligible studies were required to fulfil the “Population, Intervention, Comparator, Outcome, and Study design” (PICOS) criteria: (1) Population: adult surgical patients (≥18 years old) without pre-existing neurocognitive disorders; (2) Intervention: single or continuous intravenous infusion of esketamine; (3) Comparator: saline or no treatment; (4) Outcome: risk estimates or incidence of PND at defined postoperative time points (eg, 3, 7 or 30 days), measured by standardised neuropsychological assessments such as Mini-Mental State Examination (MMSE), International Study on Post-Operative Cognitive Dysfunction, Confusion Assessment Method (CAM) and Confusion Assessment Method for the Intensive Care Unit; (5) Study design: RCT. Studies not meeting these criteria, including those with inadequate data, animal studies or abstracts, were excluded. Disagreements regarding study eligibility were resolved through discussions involving ST.

Quality assessment

The risk of bias in the included RCTs was independently assessed by CL and SL using Cochrane’s risk of bias criteria,[24] which covers aspects such as randomisation, allocation concealment, participant and personnel blinding, outcome assessment blinding, completeness of data, selective reporting and other biases. Each study was classified as having ‘low’, ‘high’ or ‘unclear’ risk. The overall evidence quality was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[25–28] Discrepancies in quality assessments were reconciled through discussions with ST.

Data extraction

XS and ZW independently extracted pertinent information from the studies, resolving any discrepancies through discussions with JZ, XY and ST. Extracted data included the following: (1) study characteristics: first author’s name, publication year, country and sample size; (2) participant characteristics: age, gender proportion

and type of surgeries; (3) esketamine administration route and dosage; (4) method and timing of neurocognitive assessments, along with types of PND (POD, dNCR or post-NCD); (5) number of PND cases and adverse events at least one postoperative time point. Furthermore, during the data extraction process, primary outcomes at long-term follow-up (postoperative 3 months) and secondary outcomes—including postoperative nausea and vomiting (PONV), cardiovascular adverse events, length of hospital stay and postoperative pain—were identified in several studies. These outcomes were subsequently analysed, where data sufficiency and clinical relevance permitted to provide a more comprehensive evaluation of esketamine's effects.

Statistical analysis

Statistical analyses were performed using Stata software V.18.0. For dichotomous data, relevant information included the total number of patients in each group and the count of those developing PND. Risk ratios (RRs) and their corresponding 95% CIs were synthesised and mean differences (MD) or Standardized Mean Difference (SMD) (when different scales are used) with 95% CIs for continuous outcomes using a random-effects model due to expected clinical and methodological diversity. The Cochran Q statistic was employed to assess heterogeneity, quantified using the I^2 metric (with significant heterogeneity defined as $I^2>50\%$ and $p<0.05$).[29] For outcomes involving more than 10 studies, publication bias was evaluated through funnel plots and Egger's tests.

Subgroup analyses were conducted to explore potential sources of heterogeneity and provide additional insights into the effects of esketamine. Specifically, subgroup analyses were performed based on the type of PND, timing of esketamine administration (before, during and after surgery) and patient age (older surgical patients vs non-older surgical patients). These subgroup analyses were conducted where data were available to assess whether the timing of esketamine administration or patient age influenced the risk of PND.

Patient and public involvement

None.

RESULTS

Search results and study characteristics

The initial search identified 338 articles, of which 10 RCTs[30–39] were included in our systematic review and one RCT[30] was excluded in our meta-analysis (figure 1). These studies included a total of 803 surgical patients, with a wide age range and diverse surgical procedures, such as cardiothoracic, abdominal, hip and knee surgeries. Most studies were conducted in Chinese populations, which may limit generalisability to other ethnic groups. Detailed study characteristics are presented in table 1 and online supplemental table 2. And the risk of bias assessment for the 10 RCTs is shown in online supplemental figure 1.

Effects of perioperative esketamine on the incidence of perioperative neurocognitive dysfunction

Two points need particular attention. First, to obtain more robust results, two pooled analyses were conducted based on the grouping settings of the included studies. In the first pooled analysis, we included RCTs grouped into two groups. In the second, we included RCTs grouped into three groups and artificially divided them into experimental and control groups based on whether esketamine was used or not, combining them with the original two-group RCTs. Second, in some included studies, neurocognitive assessment results were reported at multiple time points. We combined results from different time points within 7 days postoperatively from the same study for analysis, applying the same method for results beyond 7 days.

Primary outcome

Within 7 days postoperatively

Nine RCTs were included in our analysis to investigate the effect of perioperative esketamine on the incidence of PND. The pooled results from seven RCTs with two groups indicated that perioperative esketamine was associated with a significantly lower risk of developing PND (RR: 0.44, 95% CI: 0.31 to 0.63, p<0.001, GRADE: high, figure 2A). Sensitivity analyses further supported these findings (online supplemental figure 2), with no significant heterogeneity (I^2 = 0.00%, p=0.98). The pooled results from six two-group RCTs and two three-group RCTs also showed a statistically significant reduction in the risk of developing PND with perioperative esketamine (RR: 0.51, 95% CI: 0.38 to 0.70, p<0.001, GRADE: high, figure 2B). Sensitivity analyses supported these findings as well (online supplemental figure 3), with no significant heterogeneity (I^2 = 0.00%, p=0.93).

Subgroup analysis by type of PND (POD and dNCR) further supported these findings (figure 2A,B). Removing two studies that failed to distinguish the older patients undergoing surgery, subgroup analysis based on older patients (≥65 or 60 years) showed that esketamine also reduced the risk of PND (online supplemental figures 4 and 5). Subgroup analyses of esketamine use showed consistent results both before (for induction of anaesthesia) and during surgery (induction+maintenance of anaesthesia) (online supplemental figures 6 and 7).

Regarding different time points within 7 days postoperatively, neurocognitive assessment results at 24, 48 and 72 hours after surgery were reported in three, one and seven articles, respectively. Perioperative esketamine was not associated with the risk of PND at 24 hours postoperatively (figure 3A); subgroup analyses of PND types, older surgical patients and esketamine use all showed the same results (online supplemental figures 8 and 9). However, the small number of articles included in each subgroup limited the confidence of the results. At 48 hours postoperatively, Ma *et al* found no significant difference between groups with and without esketamine. Perioperative esketamine was associated with a reduced risk at 72 hours (figure 3B). Surprisingly, subgroup analyses

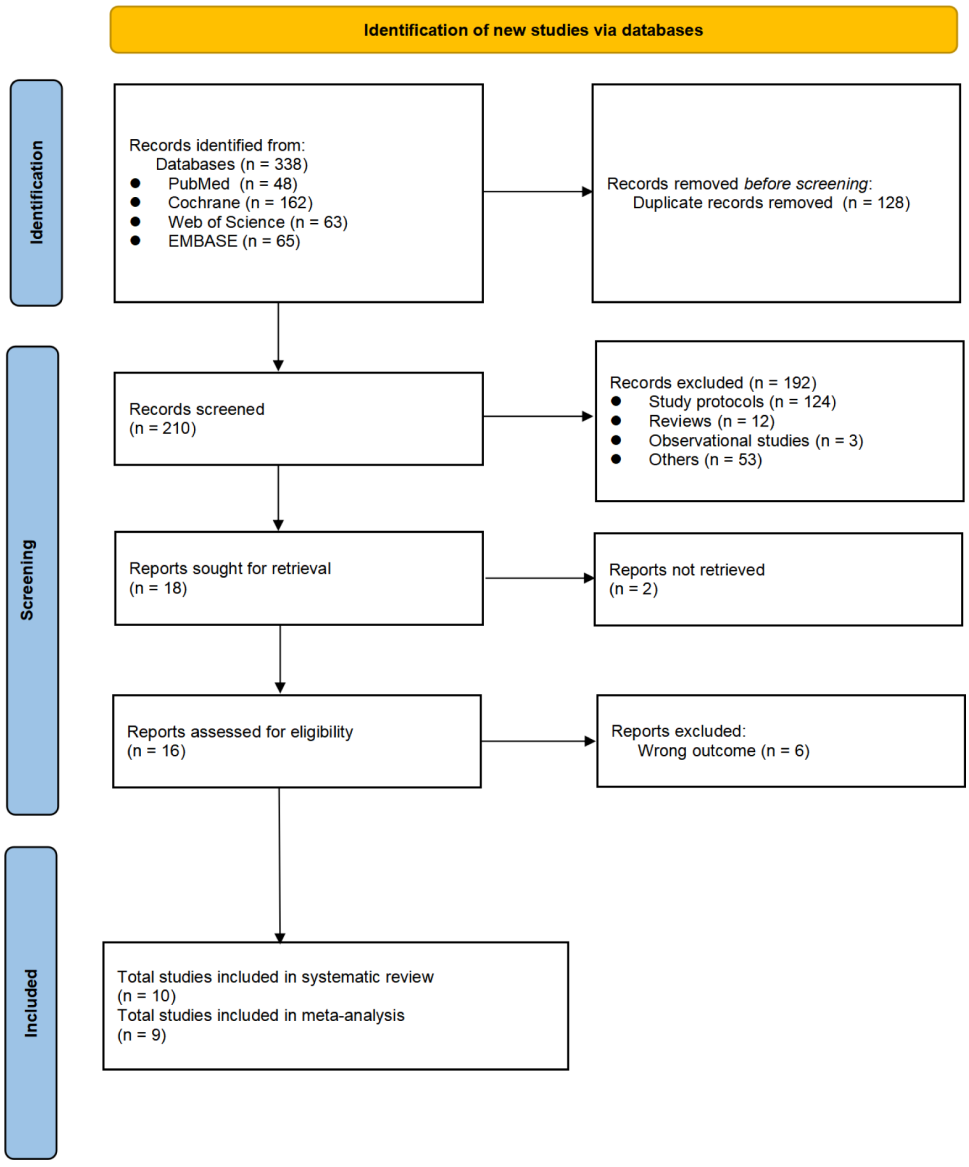

Figure 1 Flow diagram of study selection.

showed inconsistent effects of esketamine on POD and dNCR within 72 hours after surgery, that is, it reduced the risk of POD (RR: 0.51, 95% CI: 0.38 to 0.70) but did not significantly change the risk of dNCR (RR: 0.63, 95% CI: 0.31 to 1.27). Subgroup analysis of older patients showed a reduced risk of PND (online supplemental figure 10). And subgroup analyses of esketamine use showed an inconsistent result between induction and induction+-maintenance, but caution should be expressed as to whether only a small number of studies were included in each subgroup (online supplemental figure 11).

3-month postoperatively

Two RCTs reported the incidence of post-NCD at 3 months postoperatively. The pooled result indicated that perioperative esketamine did not significantly reduce the risk of developing PND (RR: 0.57, 95% CI: 0.19 to 1.73, p=0.40, GRADE: moderate), with no significant heterogeneity (I^2 = 0.00%, p=0.57). The pooled results of two articles are shown in figure 3C.

Effects of perioperative esketamine on the scores of neurocognitive assessments

Four articles reported neurocognitive scores assessed by Intensive Care Delirium Screening Checklist (ICDSC), Montreal Cognitive Assessment (MoCA) and MMSE. Due to differing scoring scales between assessment methods and the fact that all RCTs had three groups, we did not perform a pooled analysis of these scores. The results were inconsistent. Luo *et al* found that neither the 0.2 mg kg^{-1} nor 0.5 mg kg^{-1} dose of esketamine during induction improved CAM and MMSE scores at 1 and 3 days post-surgery compared with placebo. Chen *et al* found no improvement in MMSE scores at 1 day and 3 months post-operatively with a bolus of 0.3 mg kg^{-1} followed by an infusion of 0.2 mg kg^{-1} h^{-1} until 30 min before the end of the

Table 1 Study characteristics

Study	Country	Age (years old)		N	Intervention (dose and route)	Surgery	Time	Scale
		Esketamine group	Control group					
Helmar, 2016*	Austria	62.2 (9.8), 58.4 (8.1)†	61.0 (12.4) †	57	Low-dose group: 0.25 mg kg^{-1} intravenous+0.125 mg kg^{-1} h^{-1} ivgtt; minimal-dose group: a 0.9% saline intravenous+0.015 mg kg^{-1} h^{-1} ivgtt	Elective major open abdominal surgery	48 hours	ICDSC
Xiaodan, 2022‡	China	57.14 (5.94)†	56.46 (6.07), 58.81 (5.58)†	110	0.3 mg kg^{-1} intravenous+0.2 mg kg^{-1} h^{-1} ivgtt	Video-assisted thoracoscopic surgery	24 hours+3 months	MMSE
Juan, 2021	China	68.8 (3.6)†	69.2 (5.4)†	80	0.2 mg kg^{-1} intravenous	Unilateral total knee replacement	24 hours+3 days	CAM
Chao, 2023	China	70.60 (7.63)†	70.00 (6.25)†	67	0.15 mg kg^{-1} intravenous	Gastrointestinal surgery	7 days+3 months	ISPOCD
Jiamin, 2023	China	69.45 (4.35)†	70.55 (4.24)†	62	0.25 mg kg^{-1} intravenous+0.125 mg kg^{-1} h^{-1} ivgtt	Elective major abdominal surgery for gastrointestinal tumours	3 days	CAM-ICU+MMSE
Zhaojun, 2024	China	69.20 (6.22)†	71.47 (6.18)†	87	0.25 mg kg^{-1} intravenous+0.1 mg kg^{-1} h^{-1} ivgtt	Laparoscopic gastrointestinal tumour surgery	3 days	CAM
Jing, 2024	China	NA	NA	60	1 mg kg^{-1} diluted to 100 mL with normal saline for PCIA	Gastrointestinal surgery	24 hours+3 days	CAM
Tianyuan, 2024*	China	55.95 (9.08), 55.20 (9.23)†	55.86 (10.60)†	129	Low-dose group: 0.2 mg kg^{-1} intravenous; high-dose group: 0.5 mg kg^{-1} intravenous	Elective non-cardiac thoracic surgery	24 hours+3 days	MMSE
Xinglong, 2023	China	52.5 (44.0–57.0)§	51.5 (47.2–56.0)§	112	0.25 mg kg^{-1} intravenous	Cardiac valve surgery with cardiopulmonary bypass	7 days	CAM or CAM-ICU
Tiantian, 2023	China	46.25 (6.77)†	44.37 (9.74)†	39	0.125 mg kg^{-1} intravenous	Elective laparoscopic gynaecological surgery	7 days	CAM-ICU

*Presented as the study was designed for two groups using esketamine, but with two different doses.
†Means (SD).
‡Presented as the study was designed for two groups without esketamine.
§Median (IQR).
CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICDSC, Intensive Care Delirium Screening Checklist; ISPOCD, International Study on Postoperative Cognitive Dysfunction; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NA, not reported; PCIA, patient-controlled intravenous analgesia.

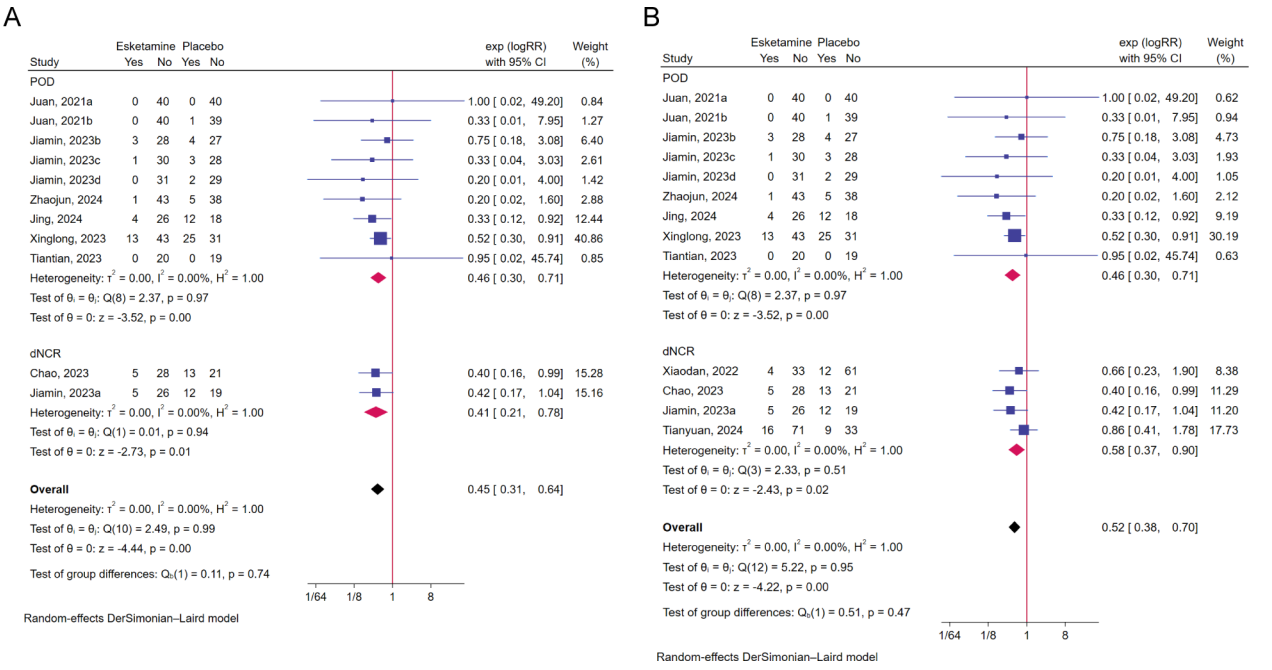

Figure 2 (A) Forest plot showing the effect of perioperative esketamine on the perioperative neurocognitive dysfunction (PND) and subgroup analysis of postoperative delirium (POD) and delayed neurocognitive recovery (dNCR) within 7 days postoperatively. The relative risk (RR) was calculated by pooling six randomised controlled trials (RCTs) compared with two groups. (B) Forest plot showing the effect of perioperative esketamine on the PND and subgroup of POD and dNCR within 7 days postoperatively. The RR was calculated by pooling six RCTs compared with two groups and two RCTs compared with three groups.

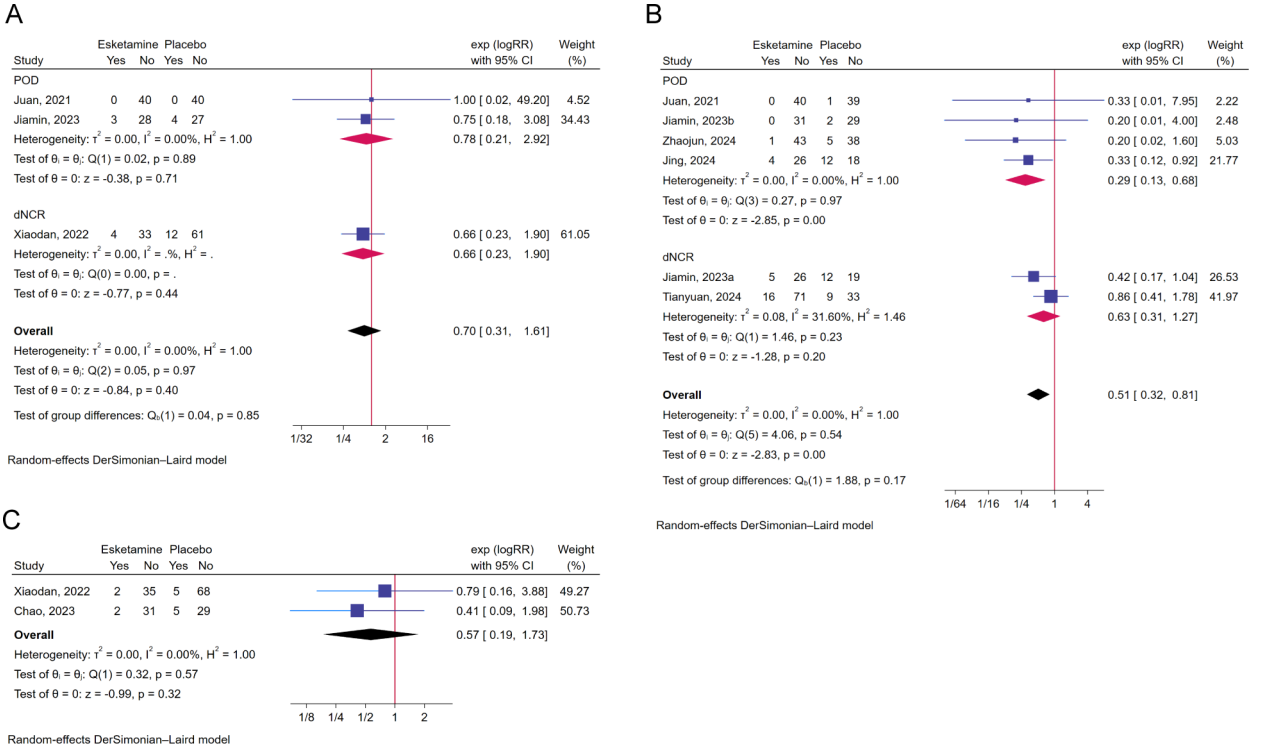

Figure 3 (A) Forest plot showing the effect of perioperative esketamine on the perioperative neurocognitive dysfunction (PND) and subgroup of postoperative delirium (POD) and delayed neurocognitive recovery (dNCR) at 24 hours postoperatively. (B) Forest plot showing the effect of perioperative esketamine on the PND and subgroup of POD and dNCR at 72 hours postoperatively. (C) Forest plot showing the effect of perioperative esketamine on the postoperative neurocognitive disorder (post-NCD) at 3 months postoperatively.

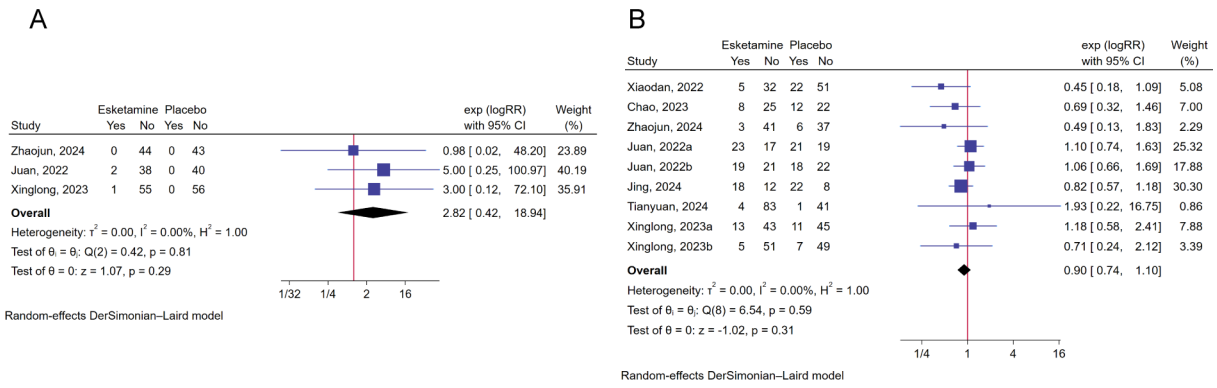

Figure 4 (A) Forest plot showing the effect of perioperative esketamine on the postoperative nightmare. (B) Forest plot showing the effect of perioperative esketamine on the PONV.

surgical procedure. Conversely, Helmar *et al* found that a 0.25 mg kg^{-1} intravenous bolus after induction followed by a 0.125 mg kg^{-1} h^{-1} continuous intravenous infusion improved ICDSC scores at 48 hours postsurgery. Zhao *et al* found that 0.5 mg kg^{-1} esketamine at induction and 2 or 4 µg kg^{-1} min^{-1} during maintenance improved MoCA scores 24 hours postsurgery compared with placebo.

Secondary outcomes

This meta-analysis found that perioperative esketamine was not associated with the risk of postoperative adverse events, including nightmare (RR: 2.82, 95% CI: 0.42 to 18.94, p=0.29, I^2=0%, GRADE: high, figure 4A), PONV (RR: 0.90, 95% CI: 0.74 to 1.10, p=0.59, I^2=0%, GRADE: high, figure 4B), postoperative cardiovascular adverse events (such as hypotension, hypertension, tachycardia and bradycardia) (RR: 1.03, 95% CI: 0.60 to 1.74, p=0.30, I^2=59.13%, GRADE: low, figure 5A) and hallucination (RR: 1.65, 95% CI: 0.22 to 12.43, p=0.63, I^2=0%, GRADE: moderate, figure 5B). Meanwhile, esketamine had no significant effect on length of hospital stay through pooling only two articles (SMD: −0.46, 95% CI: −0.93 to 0.02, p=0.06, I^2=68.98%, GRADE: moderate, figure 5C).

Regarding the postoperative pain, patients who received esketamine had lower pain severity on postoperative day

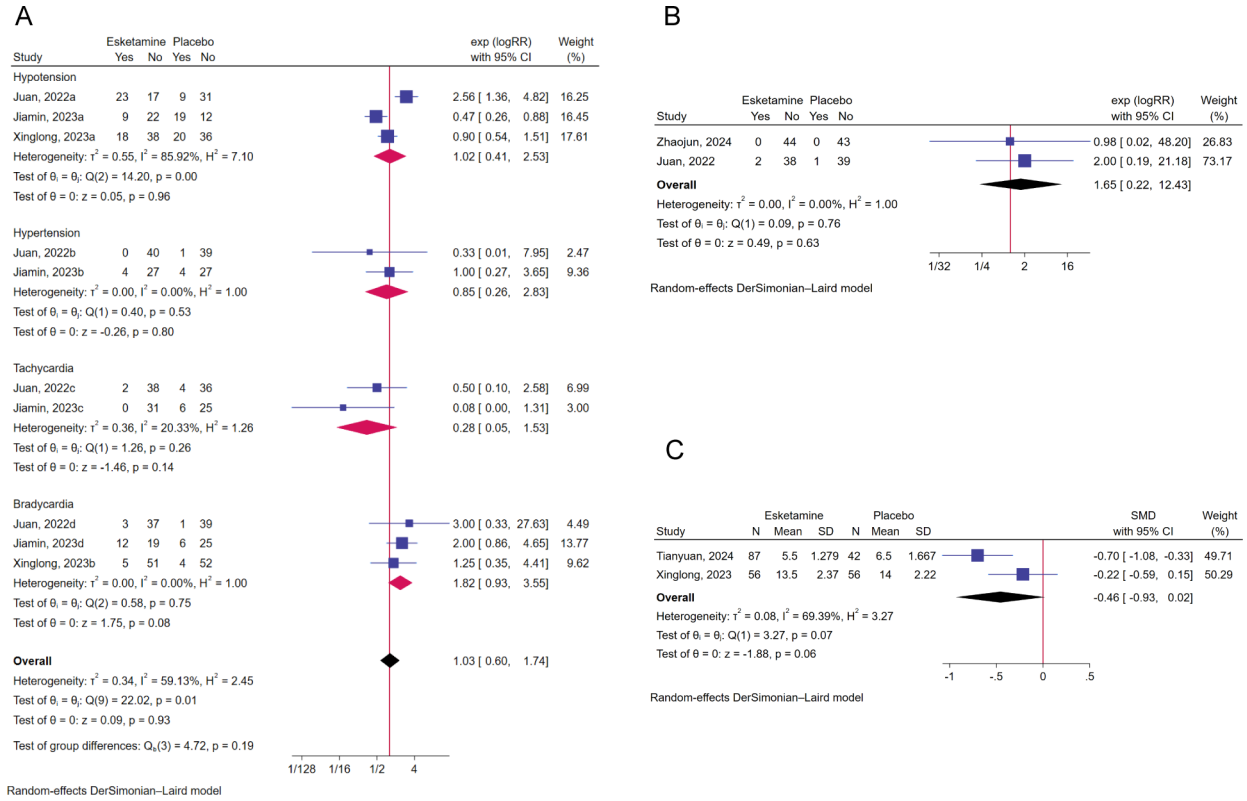

Figure 5 (A) Forest plot showing the effect of perioperative esketamine on the postoperative cardiovascular adverse events and subgroup. Analysis of hypotension, hypertension, tachycardia and bradycardia. (B) Forest plot showing the effect of perioperative esketamine on hallucination. (C) Forest plot showing the effect of perioperative esketamine on length of hospital stay.

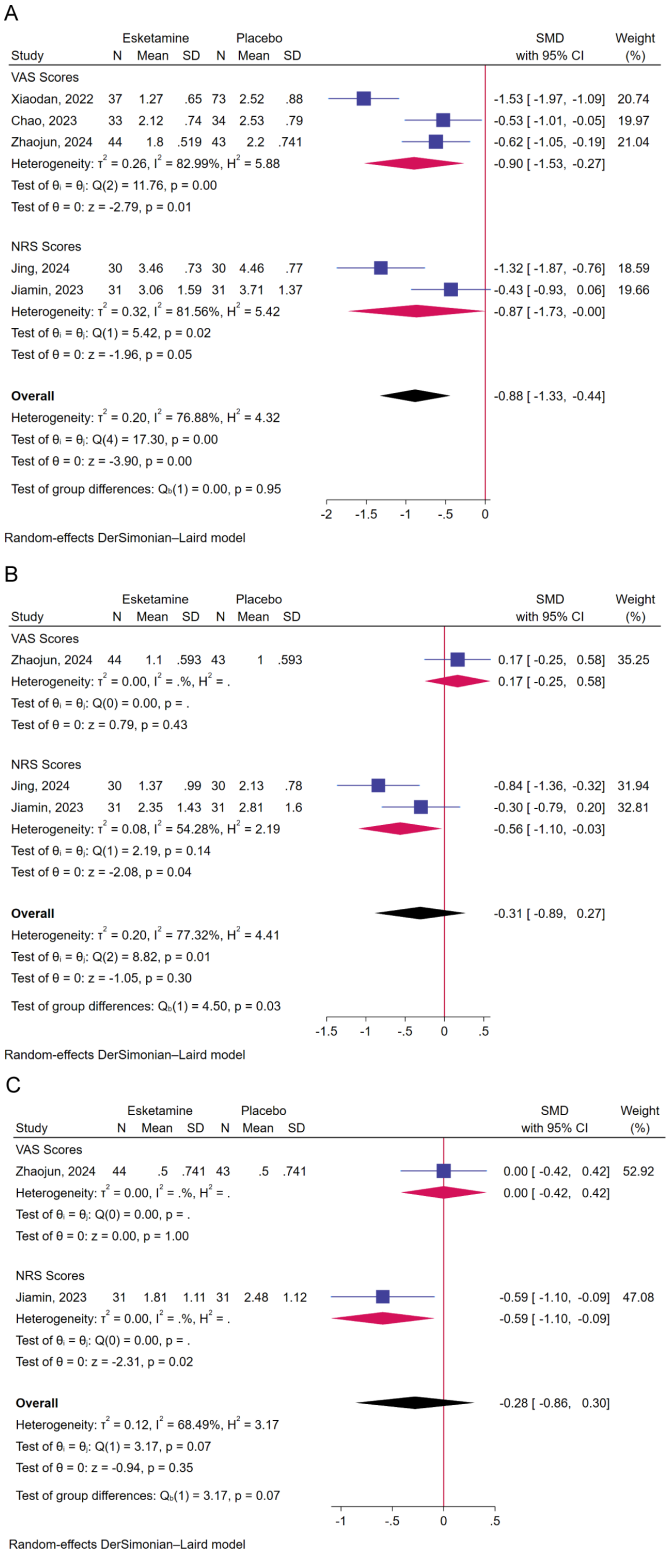

Figure 6 Forest plot showing the effect of perioperative esketamine on the postoperative pain and subgroup analysis of Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) scales. (A) At postoperative day 1. (B) At postoperative day 2. (C) At postoperative day 3.

1 than those who did not, regardless of the method of pain assessment (SMD: −0.88, 95% CI: −1.33 to −0.44, p<0.001, I^2=76.34%, GRADE: moderate, figure 6A). However, esketamine use could not relieve pain on the second and third days after surgery (SMD: −0.31, 95% CI: −0.88 to 0.27, p=0.30, I^2=76.76%, GRADE: low; SMD: −0.28, 95% CI: −0.86 to 0.30, p=0.35, I^2=67.75%, GRADE: low; figure 6B,C), through pooling two and three articles.

The summary of evidence certainty

The level of certainty regarding the evidence for each outcome is presented in online supplemental table 3. The overall certainty of the evidence was considered high to low for the risk of PND within 7 days and 3 months postoperatively. For the secondary outcomes, including the effects on nightmares, PONV, postoperative cardiovascular adverse events, hallucination, length of hospital stay and pain, the overall certainty was considered high to low. And the primary factors for downgrading include inconsistency and imprecision.

DISCUSSION

This meta-analysis revealed that perioperative esketamine use is associated with a reduced risk of POD and dNCR within 7 days after surgery. No significant differences were observed in the risk of PND at 3 months after surgery, based on the pooling of only two RCTs. No differences were observed in the risk of adverse events, including nightmares, PONV, cardiovascular adverse events and length of hospital stay between the groups. Evaluation of postoperative pain domains revealed that perioperative esketamine use reduced pain levels during the first 24 hours after surgery, whereas there was no positive effect during the 48 and 72 hours after surgery.

Several factors contribute to the novelty of this systematic review and meta-analysis: first, there are few previous clinical studies on esketamine, and second, most studies focus on its effects on negative emotions, depressive disorders and other mental health conditions. Recently, Zhou *et al* evaluated the effect of intraoperative subanesthetic doses of ketamine/esketamine versus no intervention in adults undergoing general anaesthesia on the incidence of PND.[22] However, they found no statistically significant difference in the incidence of PND within 7 days when comparing the intraoperative subanesthetic dose of ketamine/esketamine with the control group, which contrasts with our findings. Only two of the nine RCTs in the previous meta-analysis examined esketamine, likely contributing to the discrepancy.

NMDA receptors, ionotropic glutamate receptors primarily located on neurons, consist of essential Glutamate Ionotropic Receptor NMDA Type Subunit 1 (GluN1) paired with GluN2 and/or GluN3.[13 40] The relationship between NMDA receptors and PND is complex and not fully elucidated. Most studies have demonstrated that NMDA receptor function is bidirectional for PND[15]: physiological activation promotes neuron survival,[41] while dysregulation through underactivation or overactivation may induce oxidative stress and cell death, contributing to cognitive deficits in various neuropsychiatric and

neurodegenerative disorders.[42] The results of this meta-analysis, showing a reduction in the risk of short-term neurocognitive impairment postsurgery with esketamine use, align with theoretical speculations and preclinical findings. Various perioperative stressors, such as local tissue hypoxia,[43] pain[14] and inflammation,[11 44] can induce NMDA receptor overactivation, leading to PND. As an NMDA receptor antagonist, esketamine could theoretically mitigate PND by regulating this overactivation.[15] Furthermore, animal studies have demonstrated that targeting NMDA receptor overactivation can improve neurocognitive impairment.[45 46]

In addition, esketamine may work by reducing neuroinflammation, which is a major cause of PND. Surgical trauma and anaesthesia may trigger inflammation throughout the body, which can lead to neuroinflammation and subsequent cognitive decline. Previous studies have shown that esketamine can inhibit the M1 polarisation of microglia, improve the Brain-derived Neurotrophic Factor-Tropomyosin Receptor Kinase B (BDNF-TrkB) signal dysfunction caused by surgical anaesthesia stimulation, and reverse postoperative behavioural abnormalities and cognitive decline in older rats.[47]

However, our results show that perioperative esketamine use has a differential effect on POD occurrence at 24, 48 and 72 hours after surgery. First, the results are weak due to the small number of studies included in the analysis, especially for dNCR. Second, the possible reasons for this result are as follows: previous studies have confirmed that there are many postoperative factors that can cause or aggravate POD, such as inflammation caused by surgery, pain, intraoperative anaesthesia drugs and postoperative analgesics.[48–50] It can be observed that these risk factors gradually decrease with the extension of postoperative time or the gradual withdrawal of drugs. Previous observational studies have shown that the incidence of PND gradually decreases with the extension of postoperative time, which also supports this speculation.[51–53] Therefore, esketamine may not be effective in the 24 or 48 hours after surgery when there are more risk factors and higher levels.

In addition, our analysis indicated that perioperative esketamine did not improve the post-NCD of 3 months postoperatively, a finding based on only two studies, warranting further investigation. Although this is a weak result, the risk of postoperative long-term neurocognitive performance is related to more factors compared with early onset, such as postoperative complication, home nursing, work, living habits after discharge and compliance with medical instructions, and esketamine use is only a point-in-time intervention, and it is theoretically hard to envisage how the choice of a single point can affect long-term outcomes.

This meta-analysis has several limitations. First, the wide age range of participants could influence outcomes, given varying neurocognitive levels across different age groups. Second, the diversity of surgical procedures, including cardiothoracic, abdominal, hip and knee surgery, introduces heterogeneity that might impact neurocognitive outcomes differently. Thirdly, most of these studies were conducted on the Chinese population, so these results need to be carefully generalised to all ethnic groups. Additionally, the dose of single injection and continuous infusion of esketamine differed between studies, which may have influenced the analysis results. Very few studies have investigated the clinical effects of different doses of esketamine, but there appears to be no difference in postoperative neurocognitive prevention between high and low doses of esketamine. However, the effect of esketamine dosage on the prevention of PND and the optimal dose need to be further explored.

CONCLUSION

Perioperative esketamine use is associated with a reduced risk of PND within 7 days after surgery, including POD and dNCR. However, no significant differences were observed in the risk of PND at 3 months after surgery based on the pooling of only two RCTs. And no differences were observed in the risk of adverse events, including nightmares, PONV, cardiovascular adverse events and length of hospital stay. This systematic review and meta-analysis provides reference data for PND research and clinical drug intervention strategies.

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