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Effect of esketamine on postoperative delirium in general anesthesia patients undergoing elective surgery: a meta-analysis of randomized controlled trials

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Abstract

Background Postoperative delirium is a common neurological complication, especially in older patients undergoing surgery, which is closely related to the poor prognosis of patients. The objective was to investigate the effects of esketamine on postoperative delirium in patients with general anesthesia.

Methods The databases of PubMed, Embase, Cochrane Library and the Chinese National Knowledge Infrastructure were searched for all available randomised controlled trials on the effects of esketamine induction on postoperative delirium in patients undergoing elective general anesthesia from inception until April 21, 2024. We used RevMan5.4 software for data analysis. Dichotomous data was analyzed by risk ratios(RR) with a 95% confidence interval(CI), and continuous data by mean differences(MD). We also evaluated the risk of literature bias using the Cochrane Bias Risk Assessment tool.

Results We included a total of 17 randomized controlled trials, including 1286 patients undergoing elective general anesthesia. In 17 studies, esketamine significantly reduced the incidence of postoperative delirium (RR: 0.43; 95%CI: 0.33 ~ 0.57; $p < 0.001$). Five studies examined the incidence of postoperative adverse events (nausea, vomiting, dizziness and resporatory depression) and showed no statistically significant difference between the esketamine group and the control group (normal saline or dexmedetomidine) (RR: 0.82; 95%CI: 0.65 ~ 1.03; $p = 0.08$). In addition, this study found that the esketamine group had a lower incidence of hypotension (RR: 0.24; 95%CI: 0.12 ~ 0.48; $p < 0.001$) and a lower score on the visual analogue scale 24 h after surgery (MD: -0.44; 95%CI: -0.54 ~ -0.33; $p < 0.001$).

Conclusion According to our meta-analysis, the use of esketamine during anesthesia induction significantly reduced the incidence of postoperative delirium in patients undergoing elective general anesthesia without increasing the incidence of postoperative adverse reactions.

Keywords Esketamine, Postoperative delirium, Delayed neurocognitive recovery, Cognitive dysfunction, Postoperative cognitive complications, Neuropsychological tests, Delirium, Surgery, General anesthesia, Older patients

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Introduction

Delirium is a cognitive disturbance characterised by acute and fluctuating impairment in attention and awareness. Postoperative delirium (POD) usually arises between postoperative days 2–5 [1]. POD is more frequent with increasing age, occurring in up to 65% of older patients [2]. In addition, POD is considered a strong predictor of delayed neurocognitive recovery [3]. Postoperative delirium and delayed neurocognitive recovery have been associated with higher odds of mortality, postoperative complications, unplanned intensive care unit admissions, length of hospital stay, and increased healthcare resource expenditure [4, 5]. There are several factors that contribute to POD, including patient characteristics, anesthetic and operation factors, and postoperative factors. Advanced age, preoperative cognitive dysfunction, long-term use of multiple drugs, multiple co-existing diseases, long duration of anesthesia, postoperative infection, and respiratory problems are all considered as risk factors for POD [6].

Ketamine is an intravenous anesthetic with both sedative and analgesic effects. The nonanesthetic action of ketamine represents an innovative approach for its clinical application, but its use for POD prophylaxis remains disputed. Studies have demonstrated that the administration of sub-anesthetic dose of ketamine (0.2–0.5 mg/kg) during anesthesia induction can reduce the occurrence of neurocognitive disorders to some extent, although the preventative effect on POD is unknown [7]. Two recent systematic reviews have shown that intraoperative ketamine does not reduce the incidence of POD or neurocognitive disorders [8, 9]. As can be observed, the usefulness of intraoperative ketamine usage for avoiding POD or neurocognitive disorders requires more research.

Esketamine is an optically active isomers of ketamine [10]. Its action site is similar to ketamine, mainly N-methyl-D aspartic acid receptor, but it has an enhanced affinity than ketamine, a stronger analgesic effect, a higher clearance rate in vivo, and a lower incidence of side effects [11]. However, at present, the relevant clinical evidence of esketamine is limited, and the effect of esketamine on POD unclear. Therefore, we conducted this study to investigate the effects of esketamine on postoperative delirium in patients with general anesthesia.

Methods

The article was finished in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis Statement guidelines. The study protocol was registered in PROSPERO (CRD42024549036).

Search strategy

We systematically searched the databases of PubMed, Embase, Cochrane Central Registry of Controlled Trials and the Chinese National Knowledge Infrastructure for all relevant studies from inception to March 17, 2024. The search strategy in PubMed was as follows: ((("delirium"[MeSH Terms] OR "delirium"[All Fields] OR ("Postoperative Cognitive Complications"[MeSH Terms] OR "Postoperative Cognitive Complications"[All Fields])) AND ("esketamine"[MeSH Terms] OR "esketamine"[All Fields])). The search strategy was limited to randomized controlled trials (RCTs) and participants were restricted to adults.

Study selection

The inclusion criteria were: (1) studies examining the association between esketamine vs. control and delirium under general anesthesia; (2) studies must be a randomized controlled trial. (3) articles are journal articles. (4) articles were available in English and Chinese only. The exclusion criteria were: (1) the participants were children; (2) studies were spinal anesthesia; (3) the full text was not available. (4) dissertations were not included.

Study endpoints

The primary outcome was the incidence of POD, and the secondary outcomes were incidence of adverse reactions, blood pressure after induction, and visual analogue scale scores(VAS) 24 h after surgery. Adverse reactions included nausea, vomiting, dizziness, and respiratory depression.

Data extraction and quality assessment

Data extraction was done by two people. One evaluator completed the data extraction, while the other validated it independently. The main information of included studies was extracted, such as first author, year of publication, interventions, type of operation, sample size, age range, Grade of ASA, the administration of esketamine, outcome measures and the assessment methods for POD. The extracted literature information was shown in Table 1. We assessed the risk of bias using tools recommended in the Cochrane Manual, including randomization, assignment concealment, blind implementation, outcome data, selective reporting results, and other sources of bias. The risk deviation diagram of the included literature is shown in Fig. 2. Finally, publication bias was assessed by examining funnel plots (Fig. 9) and a sensitivity analysis was performed to evaluate the stability of the results (Fig. 10).

Table 1 The information and characteristics of studies

Study	Experimental	Control	Operative type	Number of patients	Age(years)	Grade of ASA	Strategy of esketamine	Outcome	Assessment
Cao 2022 [12]	Esketamine	NS	Gastrointestinal surgery	40/40	≥ 60	I-II	0.25 mg/kg esketamine intravenously injected before anesthesia induction	POD	CAM
Chen 2023 [13]	Esketamine	NS	Spinal operation	31/29	48–68	I-II	Before induction of anesthesia, esketamine 0.3 mg/kg was administered intravenously	POD	CAM-CR
Chen 2023(2) [14]	Esketamine	Blank	Thoracic sugery	40/40	60–75	Without	Esketamine hydrochloride injection was used for induction, the dose was controlled to be 0.3 mg/kg, and during the operation, the dosage should be 0.25 mg/kg continuous intravenous pump	POD	Without
Ding 2023 [15]	Esketamine	NS	Endoscopic sinus surgery	45/45	18–65	I-III	Esketamine was injected intravenously 0.25 mg /kg 10 min before anesthesia induction, and then pumped continuously at 0.25 mg / (kg·h) until the end of surgery	POD	CAM
Cheng 2024 [16]	Esketamine	NS	Abdominal surgery	46/46	65–85	II-III	Before induction, 0.25 mg/kg esketamine was injected intravenously, and 0.25 mg/(kg·h) esketamine was maintained by pump during the operation	POD	MMSE
Huang 2024 [17]	Esketamine	NS	Thoracic sugery	30/30	34–68	II-III	Esketamine hydrochloride injection 0.3 mg/kg was used for anesthesia induction before surgery, and fentanyl10μg/kg + esketamine 1.44 mg/kg + Ondansetron 8mgwas added into 100mLnormal saline for postoperative analgesia	POD	MMSE
Li 2021 [18]	Esketamine	NS	Breast cancer surgery	30/30	18–65	Without	A single intravenous injection of esketamine (0.2 mg/kg) was administered 5 min before the operation	POD	Without
Li 2022 [19]	Esketamine	NS	Unilateral total knee arthroplasty	40/40	65–85	II-III	Intravenously injected with 0.2-mg/kg esketamine	POD	CAM
Li 2023 [20]	Esketamine	NS	Gastrointestinal surgery	40/40	≥ 60	I-II	0.25 mg/kg esketamine was administered before induction of anesthesia	POD	CAM
Liu 2024 [21]	Esketamine	Blank	Gastrointestinal surgery	30/30	≥ 65	I-III	Intravenous esketamine 1 mg/kg	POD	CAM
Lu 2023 [22]	Esketamine	Dex	Thoracic surgery	47/47	60–85	I-III	Esketamine 0.5 mg/kg was given IV 20 min after induction of anesthesia was completed	POD	CAM, MMSE
Ma 2023 [23]	Esketamine	NS	Gastrointestinal surgery	31/31	≥ 65	I-III	0.25 mg/kg loading, 0.125 mg/kg/h infusion	POD	MMSE
Xiong 2024 [24]	Esketamine	NS	Cardiac surgery	56/56	≥ 18	II-III	Esketamine (0.25 mg/kg) was administered intravenously before anesthesia induction	POD	CAM, CAM-ICU
Sun 2022 [25]	Esketamine	NS	Cardiac surgery	40/40	51–71	II-III	0.5 mg/kg of esketamine intravenously during the induction period and0.5 mg/kg/h intravenously during the maintenance period, and the infusion was stopped at the end of the operation	POD	CAM-ICU

Table 1 (continued)

Study	Experimental	Control	Operative type	Number of patients	Age(years)	Grade of ASA	Strategy of esketamine	Outcome	Assessment
Ren 2023 [26]	Esketamine	NS	Hip arthroplasty	30/30	65–75	I-II	Intravenous injection of esketamine 0.2 mg/kg	POD	3D-CAM
Wu 2023 [27]	Esketamine	Blank	Thoracolumbar fracture surgery	25/25	≥ 60	Without	During the induction phase of anesthesia, esketamine was administered intravenously at 0.3 mg/kg, and during the maintenance phase, Esketamine was also administered at a pumping rate of 0.3 mg/(kg·h)	POD	Without
Xu 2023 [28]	Esketamine	NS	Breast cancer surgery	43/43	18–70	I-II	A subanesthetic dose of 0.2 mg/kg esketamine was administered 5 min before surgery by a single intravenous injection	POD	Without

Statistical analysis

For processing and analysis, RevMan5.4 statistical software was utilized. Relative hazard ratio (RR) and 95% confidence interval (CI) were used to calculate dichotomous variables. For the purpose of expressing continuous variables, the means difference (MD) and its 95% confidence interval (CI) are utilized. To ascertain the heterogeneity among the analyzed studies, the I^2 statistic and Q tests were implemented. Heterogeneity was graded according to Cochrane guidelines: $I^2 < 25\%$ was low heterogeneity, 25–50% was moderate heterogeneity, 50–75% was substantial heterogeneity, and > 75% was considerable heterogeneity. This determined whether we used a fixed effect model or a random effect model to analyze the data. When $P > 0.1$ or $I^2 \leq 50\%$, it was considered that no significant heterogeneity existed in each study, and fixed effect model was selected for analysis. Otherwise, when $P \leq 0.1$ and $I^2 > 50\%$, it was considered that there was significant heterogeneity among the studies, and we used the random effect model to conduct the analysis.

Results

Search results

The process of searching and including literature in the databases was illustrated in Fig. 1. We found 146 articles after searching various databases, and no articles found by other sources, and 100 of them were obtained after deleting duplicate entries. Following the abstract and title screens, 74 records were excluded. A total of 26 articles underwent a thorough full text review, but four articles were excluded because the full text could not be found, and five were excluded because no data was available. The PRISMA flow diagram of the included documents was shown in Fig. 1. Ultimately, 17 RCT studies were included, and the information and characteristics of the literature are presented in Table 1.

Characteristics of trials

The trials ultimately included in this meta-analysis were published between 2021 and 2024 and involved a total of 1286 patients (643 patients included in the esketamine group and 643 patients included in the control group). In our meta-analysis, 2 studies with 192 patients analyzed the effect of esketamine on postoperative delirium after cardiac surgery, and 15 studies containing of 1094 patients analyzed the association between esketamine and postoperative delirium in non-cardiac surgery patients. Table 1 provided a detailed description of the included trials.

Risk of bias in included studies

We evaluated 17 RCTS using the Cochrane risk-of-bias Tool [12–28]. Three trials were judged to be of "some concern", ten trials were judged to be of "low risk of bias", and four were judged to be of "high risk of bias" (Fig. 2A and B).

Meta-analysis for the studies of outcomes

POD

There were 17 studies with a total of 1286 patients with POD incidence, and there was no statistical heterogeneity among the studies ($P = 0.81$, $I^2 = 0\%$). The fixed-effect model was used for analysis, and it was found that the use of esketamine was significantly associated with the incidence of postoperative delirium compared with the control group (RR: 0.43; 95%CI: 0.33 ~ 0.57; $p < 0.001$) (Fig. 3). Correspondingly, the intraoperative administration of esketamine had a protective effect against postoperative delirium, reducing the risk of postoperative delirium by 57%.

Secondary outcomes

Five studies examined the incidence of postoperative adverse events [12, 16, 17, 20, 27], including nausea and vomiting, dizziness and respiratory depression. The results of our analysis showed no statistically significant difference in the incidence of adverse reactions between the esketamine group and the control group (RR: 0.80; 95%CI: 0.48 ~ 1.33; $p = 0.39$) (Fig. 4).

Five studies recorded blood pressure after induction [12, 16, 18, 22, 23], three of which recorded the incidence of induced hypotension, and the analysis showed that the incidence of hypotension was significantly lower in the esketamine group than in the control group (RR: 0.24; 95%CI: 0.12 ~ 0.48; $p < 0.001$) (Fig. 5). Mean arterial pressure after induction was recorded in two studies, and analysis showed that mean arterial pressure was significantly higher in the esketamine group than in the control group (MD:7.28; 95%CI: 3.67 ~ 10.89; $p < 0.001$) (Fig. 6).

Four studies recorded VAS scores 24 h after surgery [13, 17, 22, 27] and found that the esketamine group had significantly lower VAS scores than the control group (MD: -0.44; 95%CI: -0.54 ~ -0.33; $P < 0.001$) (Fig. 7).

Subgroup analysis

The studies on the incidence of POD were divided into two subgroups based on the age of patients. Ten studies were conducted with patients aged 60 years or older and four studies were tested with patients aged 18 years or older, and assessed the effect on POD. Notably, esketamine significantly reduced the POD prevalence regardless of age (Fig. 8).

Publication bias and sensitivity analysis

We included a total of 17 studies, and funnel plots revealed a symmetrical distribution of these studies,

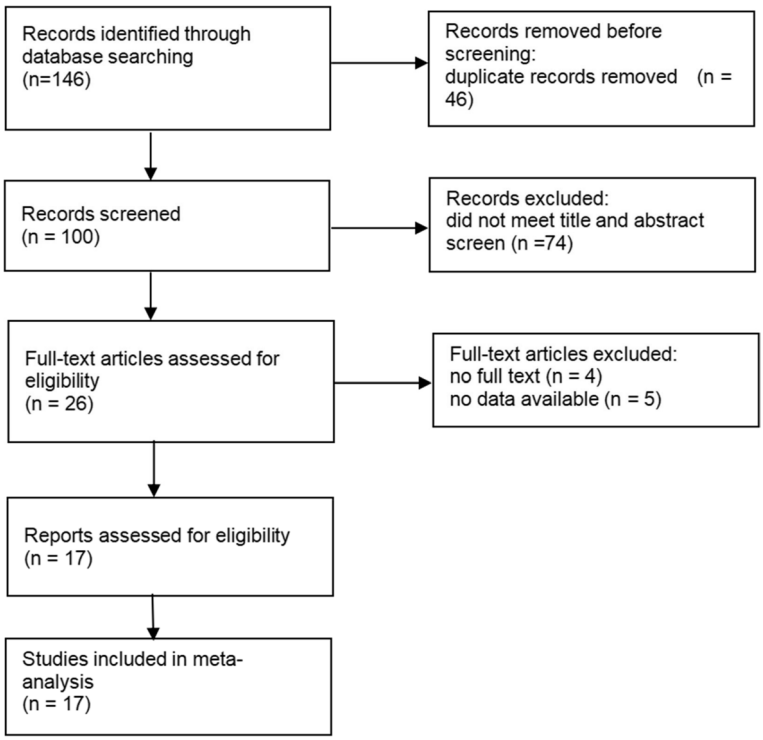


Fig. 1 PRISMA flow diagram

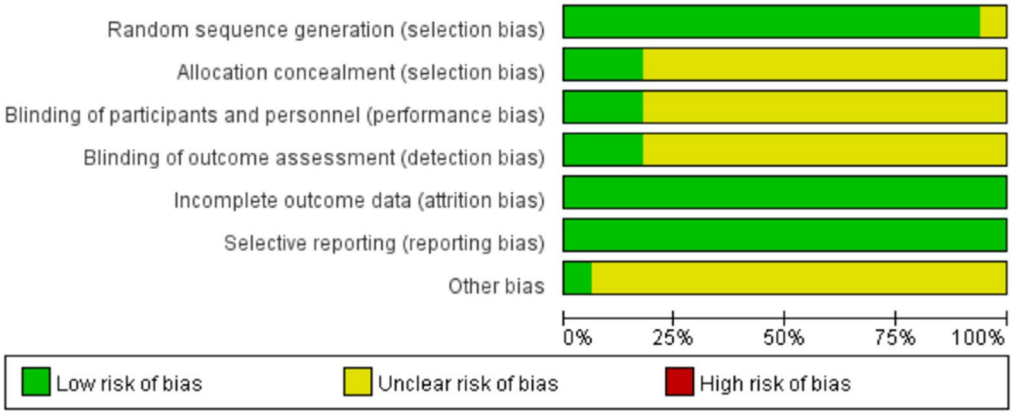
indicating no publication bias (Fig. 9). In addition, we performed a sensitivity analysis and found that the results of the meta-analysis did not change significantly with changes in the number of studies, indicating that the overall outcome regarding POD remained robust (Fig. 10).

Discussion

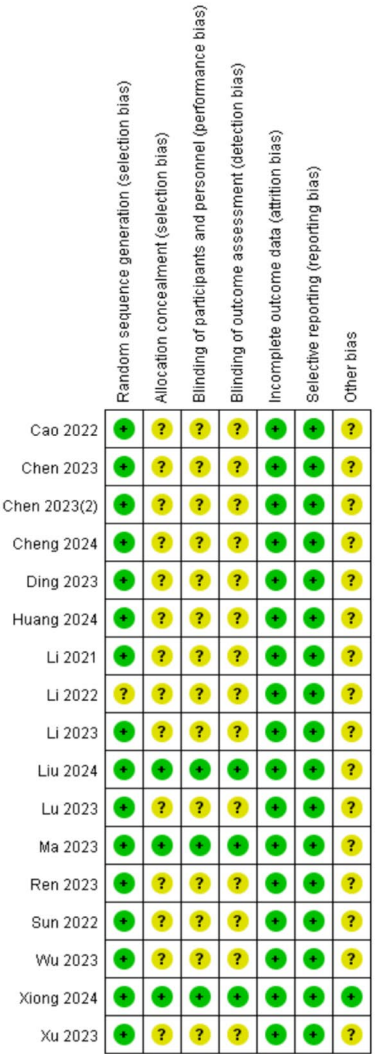
This study provides new evidence by conducting a comprehensive meta-analysis of published papers to determine the effect of esketamine on postoperative delirium. The results of this study demonstrated that esketamine can reduce the incidence of postoperative delirium in patients undergoing elective general anesthesia without increasing the incidence of postoperative adverse reactions. In addition, this study found that esketamine administration reduced the incidence of hypotension and VAS scores at 24 h after surgery.

The incidence of POD is 2–3% in the general surgery population, but it has been reported to occur in up to 50% to 70% of high-risk patient groups [29, 30]. POD has become an important issue in clinical practice because it has adverse effects on both early and long-term prognosis for patients. Therefore, the most critical method to reduce POD is prevention. Previous studies have shown that the use of preventive strategies can reduce the incidence of delirium by 40% in patients [31], however, these preventive strategies were non-drug preventive methods. Despite the lack of conclusive evidence for the application of medications to prevent POD, a number of medications have been investigated in clinical trials to observe their effects on POD, and esketamine is one of them.

Esketamine has multiple targets and exerts anesthetic and analgesic effects mainly through non-competitive antagonism of NMDA receptors. It also interacts with opioid and M-choline receptors, monoamine receptors, adenosine receptors, and other purine receptors [32]. Esketamine is widely used in clinic because of its many advantages, such as mild respiratory depression, anti-hyperalgesia, anti-inflammatory, reducing stress response, and activating cardiovascular system [33]. Among them, anti-inflammatory and anti-stress effects may be related to reducing delirium. Two studies on hip fracture surgery and gastrointestinal surgery have shown that esketamine may reduce delirium by lowering levels of interleukin-6 (IL-6), IL-8, IL-10, and tumor necrosis factor (TNF), and reducing neuroinflammatory responses in surgical patients [21, 26]. In addition, two studies by Chen, Wu and colleagues on esketamine in older thoracic surgery and older thoracolumbar fracture surgery found that esketamine can inhibit the activation of the hypothalamic–pituitary–adrenal cortex system, reduce the body's stress response, and reduce the risk of delirium [14, 27].



A: The Risk of bias in included studies



B: The Risk of bias in included studies

Fig. 2 **A** The Risk of bias in included studies. **B** Quality assessment of each study included in the meta-analysis

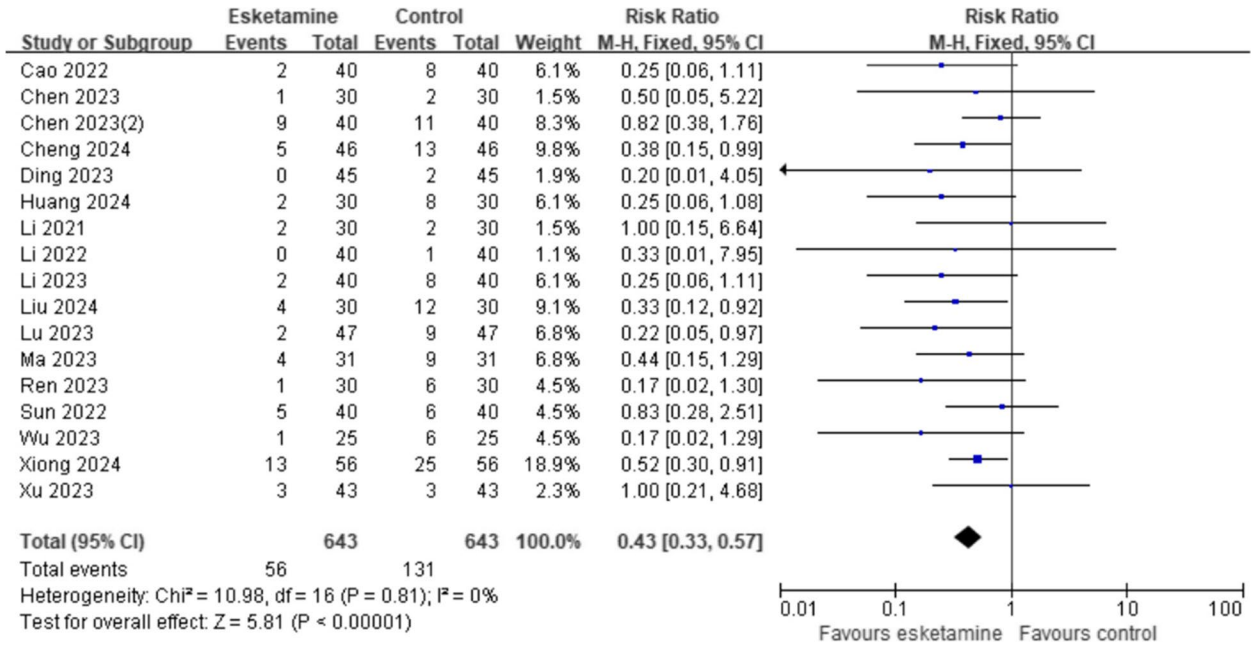


Fig. 3 Esketamine versus control group for postoperative delirium

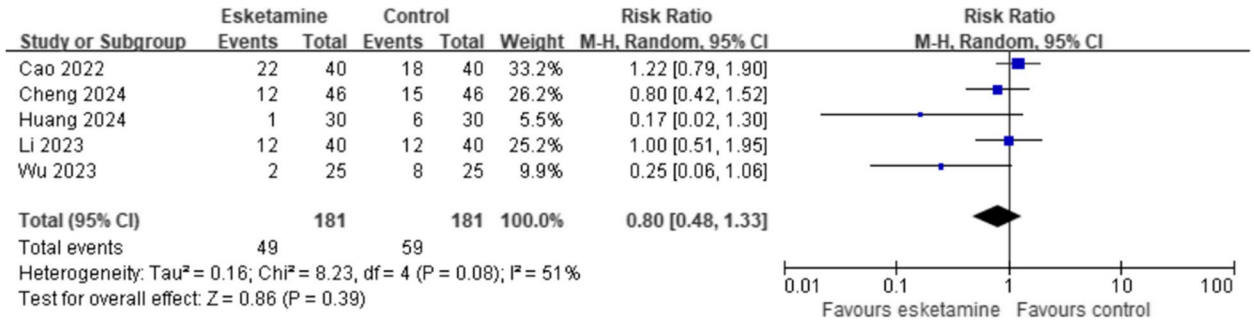


Fig. 4 Esketamine versus control group for adverse events

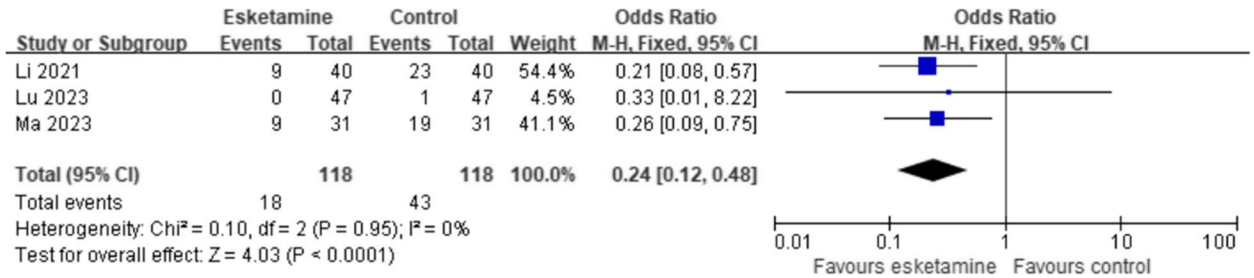


Fig. 5 Esketamine versus control group for the incidence of hypotension

With regard to secondary outcomes, our results suggested that esketamine can maintain hemodynamic stability after induction, such as reducing the incidence of postinduction hypotension and increasing the mean arterial pressure(MAP) after induction, attributable to the fact that it can stimulate the sympathetic nervous system, resulting in increased heart rate and blood pressure [34]. A recent randomized clinical trial of hysteroscopic surgery also found that esketamine reduced intraoperative hemodynamic fluctuations and the use

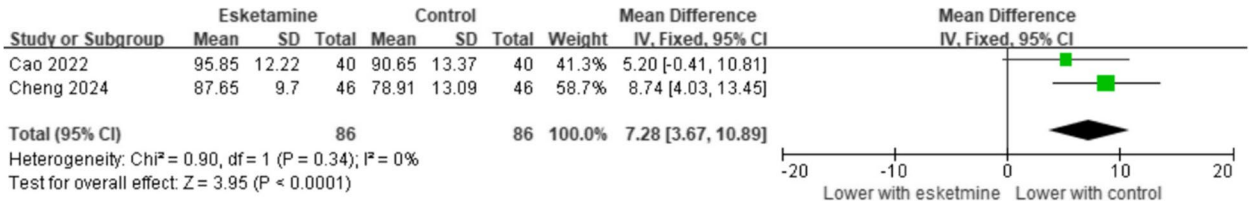


Fig. 6 Esketamine versus control group for MAP

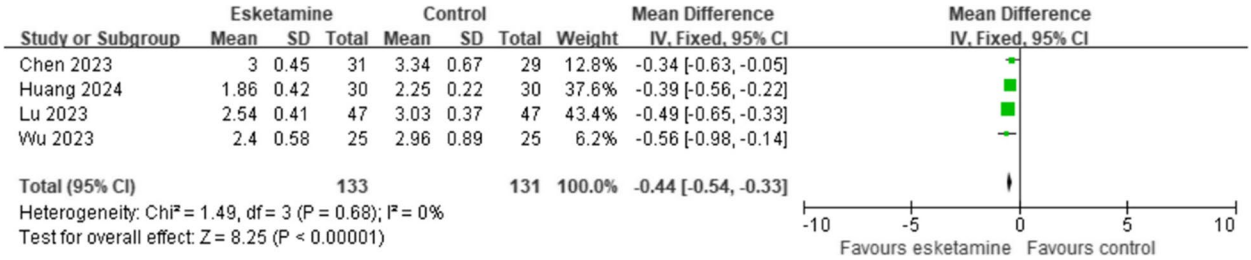


Fig. 7 Esketamine versus control group for VAS

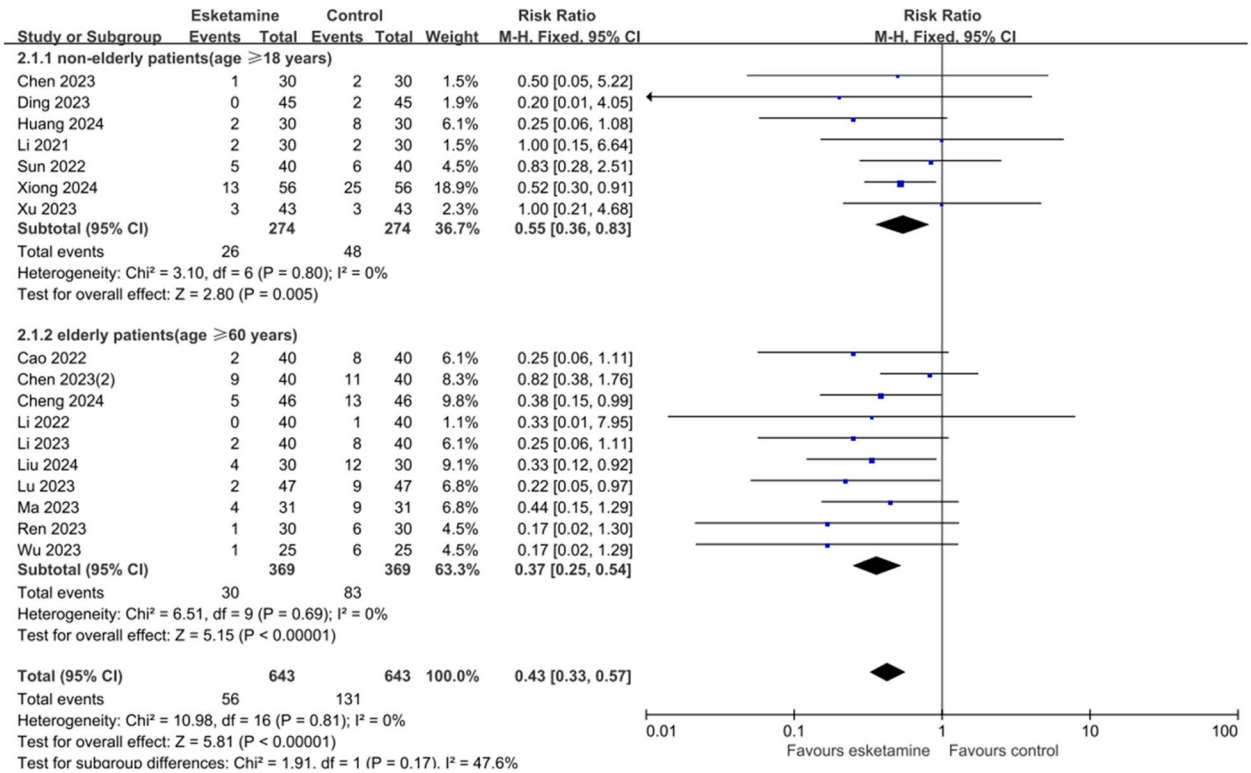


Fig. 8 Esketamine versus control group for subgroup analysis

of vasoactive medications [35]. Besides, esketamine reduced postoperative VAS scores 24 h after surgery to alleviate postoperative pain, which is consistent with the conclusions of a previous meta-analysis of the effect of esketamine on postoperative abdominal pain in adults [36]. Finally, compared with the control group, esketamine did not increase the incidence of postoperative adverse reactions (nausea, vomiting, dizziness, respiratory depression). Similarly, the results of Tu et al. 's study showed that esketamine combined with propofol

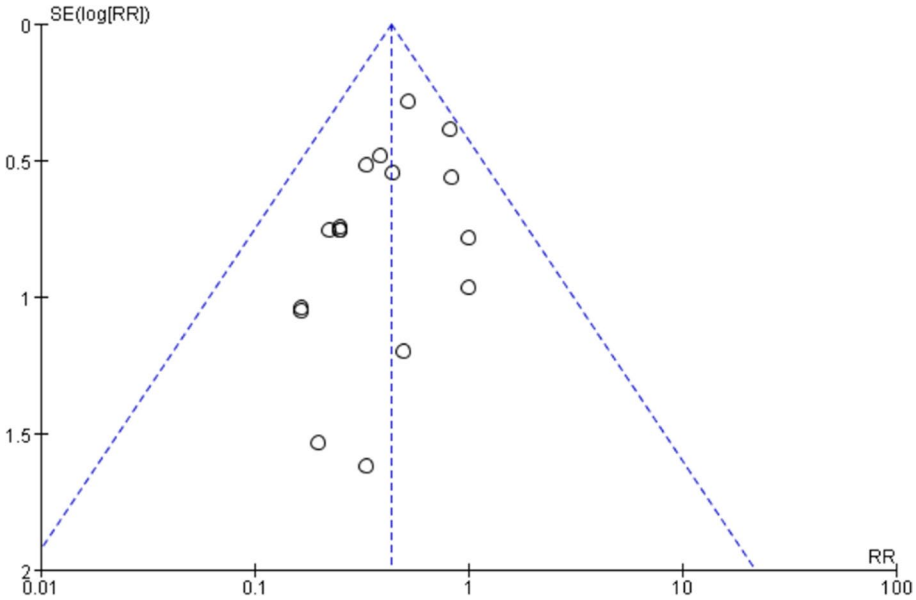


Fig. 9 Funnel plot

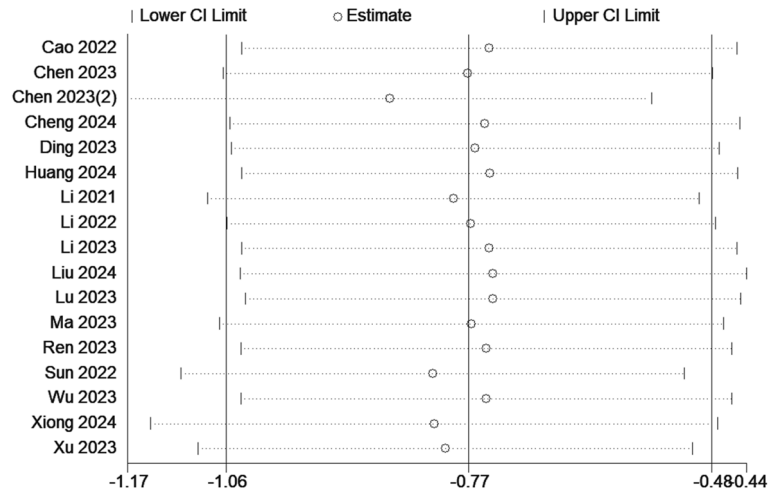


Fig. 10 Sensitivity analysis

for anesthesia induction in older patients did not increase the incidence of adverse reactions such as nausea and vomiting, respiratory depression, and delayed recovery [37]. However, a randomized controlled trial of esketamine on postoperative nausea and vomiting in patients undergoing thoracoscopic surgery proved that perioperative infusion of esketamine reduced the incidence of postoperative nausea and vomiting [38]. The difference in results may be due to the timing and dose of esketamine administration, so more studies of esketamine on adverse effects are needed in the future.

This study also conducted subgroup analyses based on older patients, and the results revealed that the application of esketamine reduced the incidence of delirium in older patients. Therefore, esketamine may be potentially beneficial in preventing postoperative delirium in older patients, but more high-quality studies are needed in the future.

The present meta-analysis had several limitations and shortcomings. Firstly, it should be emphasized that there was considerable heterogeneity in the timing and dosage of esketamine in the studies included in the analysis.

Secondly, medications in the control group and methods of assessment for POD were not identical, and there may be heterogeneity between some studies. Thirdly, the included studies had small sample sizes and were all conducted in China. Therefore, more large-sample, high-quality randomized controlled studies exploring different countries and different populations are needed in the future.

Conclusion

According to our meta-analysis, the use of esketamine significantly reduced the incidence of POD in patients undergoing elective general anesthesia without increasing the incidence of adverse reactions.

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Not applicable.

Author's contributions
Wenhui Zhang, Congjie Bi and Di Wang participated in the design, collection of data, statistical analysis and completion of the manuscript. Yutao Chen and Siru Li assisted in data collection and statistical analysis. All the authors have read and approved the final draft.

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Data availability
All data generated or analyzed during this study are included in the manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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