

Effects of Esketamine on Postoperative Sleep Quality: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Jiacheng Zhao^{1,*}, Yanan Yan^{2,*}, Xiaohan Wang² , Chao Zhang¹, Jie Wang¹ 

¹Department of Anesthesiology, Suzhou Ninth Hospital Affiliated to Soochow University, Suzhou, 215200, People's Republic of China; ²School of Anesthesiology, Xuzhou Medical University, Xuzhou, Jiangsu, 221004, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jie Wang, Department of Anesthesiology, Suzhou Ninth Hospital Affiliated to Soochow University, 2666 Ludang Road, Wujiang District, Suzhou, Jiangsu, 215200, People's Republic of China, Email zwd7171@126.com

Purpose: Postoperative sleep disturbances are common and deleteriously affect patient recovery, yet effective pharmacologic interventions remain limited. Esketamine has demonstrated analgesic and antidepressant properties, but its effect on postoperative sleep quality is unclear. To assess the impact of perioperative esketamine on subjective sleep quality in adult surgical patients.

Patients and Methods: Randomized controlled trials (RCTs) comparing esketamine with placebo, standard care, or other sedatives were retrieved from PubMed, Embase, and the Cochrane Library up to September 1, 2025. The primary outcome was postoperative subjective sleep quality, measured by validated scales. Secondary outcomes included incidence of sleep disturbance, pain scores, anxiety, depression, and quality of recovery (QoR-15). Subgroup analyses were prespecified by dose, timing, and dexmedetomidine co-administration. Among 21 included RCTs, 15 studies with 6880 participants reported postoperative subjective sleep quality.

Results: The baseline sleep scores were comparable between esketamine and control groups. On postoperative day 1, esketamine significantly improved sleep quality (SMD = -0.40, 95% CI [-0.59, -0.20], $I^2 = 72\%$, $p < 0.0001$). Subgroup analyses indicated that higher doses (> 0.25 mg/kg) and intraoperative administration yielded larger effects. Esketamine also significantly decreased the incidence of postoperative sleep disturbance, reduced pain scores, and improved QoR-15. No significant effects were found for anxiety or depression outcomes.

Conclusion: Perioperative esketamine significantly enhances subjective sleep quality, reduces sleep disturbance incidence, and also confers analgesic and recovery benefits.

Systematic Review Registration: www.crd.york.ac.uk/PROSPERO/, identifier, CRD420251138011.

Keywords: esketamine, postoperative sleep quality, sleep disturbance, systematic review, meta-analysis

Introduction

Postoperative sleep disturbance (PSD) is a common but often underestimated complication following surgery. Epidemiological studies have shown that up to 60–80% of surgical patients experience varying degrees of sleep disruption during the first few postoperative nights, characterized by difficulty falling asleep, frequent awakenings, and reduced sleep efficiency.^{1,2} These disturbances have been linked to increased pain perception, heightened sympathetic activity, immune suppression, delayed wound healing, and a higher risk of postoperative neurocognitive disorders (PND).^{3–5} Sleep deprivation during the perioperative period also interferes with circadian regulation and hormonal secretion, particularly melatonin and cortisol rhythm.⁶ As perioperative medicine increasingly emphasizes enhanced recovery and holistic outcomes, the maintenance and restoration of sleep quality have become critical but underappreciated components of postoperative care.

Various pharmacologic and nonpharmacologic interventions have been investigated to mitigate PSD, including dexmedetomidine, melatonin, and cognitive-behavioral strategies.^{7–9} Among these, dexmedetomidine has shown sleep-promoting properties by mimicking non-rapid eye movement (NREM) sleep; however, its clinical application is limited

by bradycardia, hypotension, and dose-dependent sedation.¹⁰ Melatonin and its agonists exhibit variable efficacy across surgical types and patient populations.¹¹ Moreover, pharmacologic sleep aids often fail to address the multifactorial causes of perioperative sleep loss, including pain, inflammation, and psychological stress. Given these limitations, there is growing recognition that certain anesthetic and analgesic agents themselves may have therapeutic potential in regulating perioperative sleep. Anesthetic drugs that modulate NMDA or GABA receptors may influence sleep–wake homeostasis beyond their sedative properties, providing an innovative direction for improving sleep quality and enhancing postoperative recovery.

Esketamine, the S-enantiomer of racemic ketamine, is a potent N-methyl-D-aspartate (NMDA) receptor antagonist with approximately twice the affinity of ketamine for the NMDA receptor and a more favorable pharmacokinetic profile.^{12,13} Clinically, esketamine has demonstrated rapid-acting antidepressant, anxiolytic, and analgesic effects, making it an attractive candidate for improving postoperative recovery beyond anesthesia and pain control.^{14,15} Over the past few years, multiple trials have examined its perioperative use, particularly in cesarean section and general surgical populations, suggesting potential benefits in mood stabilization and pain reduction. However, the evidence concerning its effect on sleep remains inconsistent and inconclusive.

Given the growing clinical and scientific interest in the relationship between anesthetic agents and perioperative sleep regulation, it remains unclear whether esketamine exerts a consistent and clinically meaningful effect on postoperative sleep quality. Although individual trials have explored perioperative esketamine use, postoperative sleep quality has often been reported as a secondary outcome, and no prior meta-analysis has specifically synthesized its effects on postoperative subjective sleep quality with consideration of dose and timing strategies. Therefore, this study aimed to systematically evaluate the impact of perioperative esketamine administration on postoperative sleep quality in adult surgical patients. In addition, secondary outcomes—including the incidence of sleep disturbance, postoperative pain, anxiety, depression, and the 15-item Quality of Recovery (QoR-15) score—were analyzed to provide a multidimensional understanding of postoperative recovery.

Methods and Materials

This systematic review and meta-analysis adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines¹⁶ ([Supplementary Material: Table S1](#)). The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD420251138011, dated September 1, 2025.

Inclusion and Exclusion Criteria

Studies were deemed eligible for inclusion when they fulfilled the following conditions as defined by the PICOS criteria: (1) population: adult individuals aged 18 years or older who underwent elective surgical procedures under any form of anesthesia; (2) intervention: administration of esketamine during the perioperative period, regardless of the route of administration, dosage, or dosing regimen; (3) comparison: placebo (normal saline), standard care, or other sedative agents administered as control interventions; (4) outcomes: postoperative subjective sleep quality, evaluated using validated and standardized scales (eg., PSQI, AIS, or other sleep quality assessment tools); (5) study design: only randomized controlled trials (RCTs) were included.

Studies were excluded if they satisfied any of the following conditions: (1) non-randomized or retrospective designs, including case reports, conference abstracts, reviews, animal experiments, or protocols without available data; (2) studies involving pediatric, obstetric, or non-surgical populations; (3) studies in which anesthetic techniques or anesthetic agents differed substantially between groups, potentially confounding postoperative sleep outcomes; (4) articles retracted after publication; (5) duplicate publications or studies with incomplete or unavailable outcome data even after contacting the authors. No language restriction was applied.

Search Strategy

A comprehensive literature search was conducted in PubMed, the Cochrane Library, and Embase to identify eligible studies published before March 1, 2026. To ensure a comprehensive and sensitive search, both Medical Subject Headings

(MeSH) terminology and free-text keywords were applied. The core search terms included “esketamine”, “sleep”, and “randomized controlled trial”. The search strategy was tailored to each database and combined using Boolean operators (“AND” and “OR”) as appropriate. Detailed search strategies for each database are outlined in [Supplementary Material: Table S2](#). Both reviewers (JCZ and YNY) worked independently, and disagreements were resolved by consensus or a third reviewer (XHW).

Data Extraction

Two reviewers (JCZ and YNY) independently extracted data using a predesigned and standardized form. The following baseline characteristics were collected from each included study: first author, year of publication, country, type of surgery, sample size, mean age, and sex distribution of the study population. Information regarding sleep quality assessment included the measurement tools (eg., PSQI, AIS, VAS, or other validated scales) and the specific time points of evaluation. In addition, data were extracted for secondary outcomes, if reported, including: (1) incidence of sleep disturbance; (2) pain score; (3) anxiety score; (4) depression score; and (5) 15-item Quality of Recovery (QoR-15) scale score. Detailed intervention characteristics were also recorded, including the type of anesthesia, route, timing, dosage, and frequency of esketamine administration, as well as any co-administered agents (eg., dexmedetomidine). For control groups, the type of comparator (placebo, standard care, or other sedative) was documented. Any disagreements between the two reviewers were settled through discussion or, if necessary, by consultation with a third investigator (XHW).

Risk of Bias Assessment and Quality Assessment

Two independent reviewers (JCZ and YNY) evaluated the methodological quality of the included randomized controlled trials using the Cochrane Collaboration’s Risk of Bias assessment tool.¹⁷ The following seven domains were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was judged as having a low, high, or unclear risk of bias. Discrepancies in assessments were resolved through discussion or, if necessary, by consultation with a third reviewer (XHW). A summary of the risk of bias evaluation was presented in both tabular and graphical formats. The certainty of evidence was assessed using the GRADE approach.

Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.3 and Stata version 17.0. For continuous outcomes, results were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs), in order to account for potential variations in measurement units across studies. For dichotomous outcomes, risk ratios (RRs) with corresponding 95% CIs were calculated. When continuous data were presented as median with interquartile range (IQR) or range, the values were converted to mean $\pm$ standard deviation (SD) using established methods proposed by Luo et al¹⁸ and Wan et al¹⁹. Between-study heterogeneity was assessed using the Cochrane Q test and I^2 statistic. An I^2 value $> 50\%$ or a p -value < 0.10 for the Q test was considered indicative of substantial heterogeneity, in which case a random-effects model was applied; otherwise, a fixed-effects model was used. Sensitivity analyses were conducted by sequentially omitting each study to assess the robustness of pooled results. Publication bias was evaluated through funnel plot inspection and Egger’s regression test when at least 10 studies were included in the analysis. A two-tailed p -value < 0.05 was considered statistically significant.

Subgroup Analysis

Prespecified subgroup analyses were conducted to explore potential sources of between-study heterogeneity in the primary outcome (postoperative subjective sleep quality on postoperative day 1).

Subgroups were defined based on clinically relevant and methodological variables, including esketamine dosage (≤ 0.25 mg/kg vs > 0.25 mg/kg), timing of administration (intraoperative only, postoperative only, or both), co-administration with dexmedetomidine (yes vs no), age (< 60 years vs ≥ 60 years), sex distribution (female-dominant vs mixed population), type of surgery (abdominal surgery, orthopedic surgery, or other), anesthesia modality (general anesthesia vs non-general anesthesia), and sleep assessment tool (AIS, PSQI, or other scales such as NRS, RCSQ, and

RCQS). The dose cut-point of 0.25 mg/kg was selected based on commonly used dosing regimens in the included studies and clinical practice.

Subgroup analyses were conducted only when sufficient data (at least two studies) were available for comparison.

Results

Study Selection

An initial search of the databases yielded 607 records in total, including 73 from PubMed, 335 from the Cochrane Library, and 199 from Embase. After the removal of duplicates, 345 studies remained for title and abstract screening. Subsequently, a total of 68 full-text articles were evaluated for eligibility, with 47 excluded for failing to meet the inclusion criteria, primarily because they were not randomized controlled trials ($n = 5$), involved racemic ketamine rather than esketamine ($n = 22$), included non-surgical patients ($n = 11$), did not report sleep-related outcomes ($n = 5$), had inaccessible data ($n = 2$), or had been retracted ($n = 2$). Ultimately, 21 randomized controlled trials satisfied the inclusion criteria and were incorporated into both the qualitative and quantitative analyses (Figure 1).

Characteristics of the Included Studies

21 randomized controlled trials,^{20–40} all conducted in China, were included (Table 1). Per-arm sample sizes ranged from 23 to 195, and the overall age spanned approximately the third to eighth decades; sex distribution varied by procedure, with several female-only cohorts (eg., gynecologic and breast surgeries) and others including a majority of men. Sleep quality were evaluated using diverse scoring scales: AIS in 7 trials, PSQI in 6, NRS in 6, RCQS in 3, RCSQ in 1, and a 4-point sleep scale in 1 trial. Assessment time points most commonly included baseline and

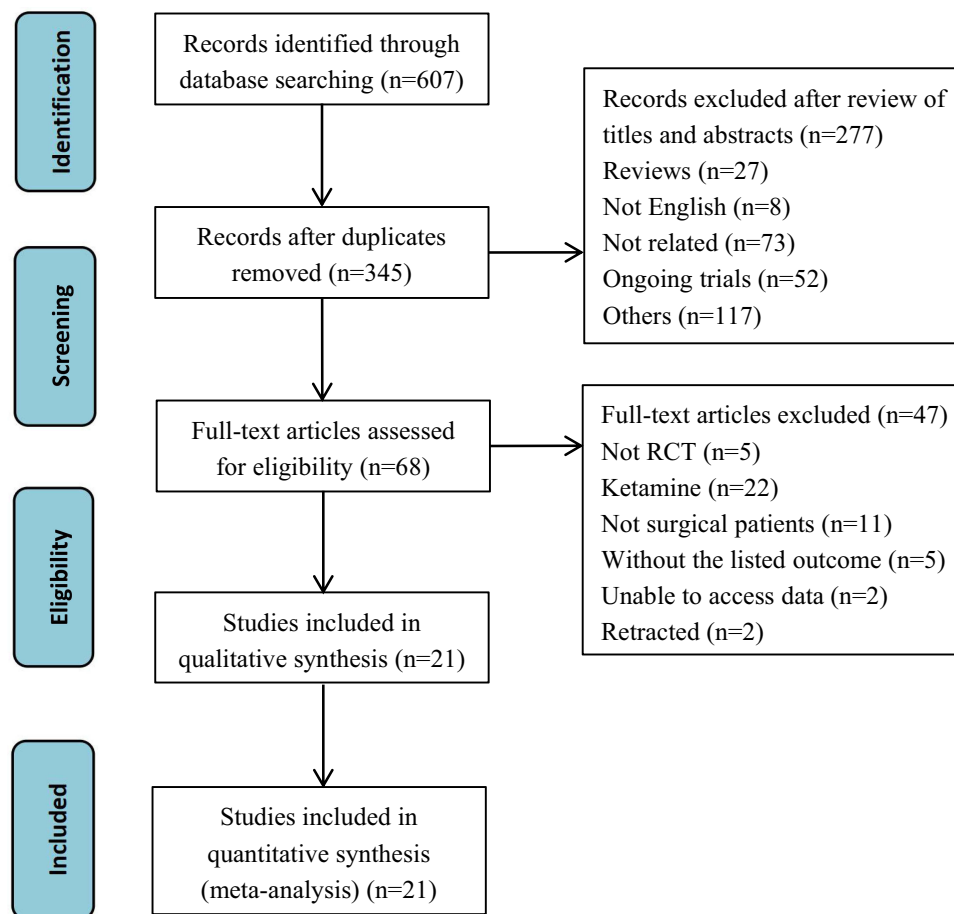


Figure 1 Flow diagram of the study selection.

Table 1 Characteristics of the Included Trials

First Author, Year	Country	Type of Surgery	Sample Size (E/C)	Age (E/C)	Male (E/C)(%)	Evaluation Scale	Evaluation Time	Other Outcomes
Chen H ³³ 2024	China	Liposuction	78/77	33.3/33.1	25.6/22.1	AIS	AB	③④
Chen Y, ²⁷ 2025	China	Modified radical mastectomy	72/73	48.30/49.60	0/0	RCQS	ABC	②
Geng X, ²⁴ 2025	China	Radical mastectomy	25/25	50.44/50.80	0/0	AIS	BD	①②
He Q, ³² 2024	China	Debridement or skin graft	28/27	40.5/40.1	71.4/66.7	PSQI	E	②④
Lin X, ³⁴ 2024	China	Laparoscopic resection of gastric carcinoma	62/62	64.30/66.81	72.58/69.35	RCQS	ABDE	②
Ma C ³⁰ 2024	China	Total hip or knee arthroplasty	130/130	69.0/68.6	29/25	AIS, NRS	ABCD	②
Qiu D ³⁹ 2022	China	Gynecological laparoscopy	92/91	43/45	0/0	AIS	ABD	①②③④
Shang Y, ²¹ 2025	China	Cesarean delivery	62/62	31.00/31.83	0/0	PSQI	ADE	②④
Song Z, ²⁰ 2025	China	Surgical abortion	102/102	30.5/32	0/0	AIS	ABCDE	①②③④⑤
Wang P, ³⁷ 2023	China	Thyroidectomy	30/30	45.1/42.4	13.3/16.7	4-point scale	AB	②
Wang H, ²⁶ 2025	China	Laparoscopic abdominal surgery	100/100	72.65 /73.02	67/56	NRS	BD	①②③④
Wang W, ²⁵ 2025	China	Laparoscopic major abdominal surgery	80/77	55/55	61.3/70.1	PSQI	AE	②
Wei Q, ³¹ 2024	China	Total hip replacement	38/34	54/51	71.1/70.1	PSQI	ABC	②
Wu Y, ²² 2025	China	Laparoscopic cholecystectomy	43/43	47.9/49.7	53.5/48.8	PSQI,AIS	ABCD	①②
Yuan J, ⁴⁰ 2022	China	Thoracic surgery	29/23	56/53	21/30	NRS	BC	②
Zhang T, ²⁹ 2023	China	Gynecological abdominal surgery	33/31	53.6/54.3	0/0	RCQS	ABC	②
Zhang Y, ³⁵ 2023	China	Scoliosis correction surgery	99/100	35/35	62.6/70	NRS	ABCDE	②
Zhao Y, ²⁸ 2025	China	Total hip or knee arthroplasty	57/55	70/70	31.6/27.2	AIS	ABCDE	①②③④⑤
Zhou R, ³⁶ 2023	China	Video-assisted thoracoscopic surgical lung lesion resection	195/192	52.08/50.74	36.9/43.2	PSQI, RCSQ	ABD	②③
Zhou Y ²³ 2025	China	Gynecological laparoscopy	49/49	31/31	0/0	NRS	ABDE	①②③
Zhu M, ³⁸ 2022	China	Modified radical mastectomy	33/33	54.1/51.6	0/0	NRS	B	②⑤

Notes: A: baseline; B: on postoperative day 1; C: on postoperative day 2; D: on postoperative day 3; E: within one month after surgery. ①: incidence of sleep disturbance; ②: pain score; ③: anxiety score; ④: depression score; ⑤: 15-item quality of recovery (QoR-15) scale score. 4-point scale: 1, slept well; 2, disturbed sleep; 3, sleep with much dream; 4, sleepless.

Abbreviations: E, esketamine group; C, control group; NR, not reported; AIS, Athens insomnia scale; PSQI, Pittsburgh sleep quality index; NRS, numerical rating scale; RCQS, Richards-Campbell Sleep Questionnaire.

postoperative days 1–3, with several studies additionally assessing within one month after surgery. Besides subjective sleep quality, many trials also reported incidence of sleep disturbance, pain, anxiety, depression, and QoR-15 outcomes.

Characteristics of Intervention

Intervention characteristics were depicted in [Table 2](#). Across the included trials, esketamine was administered intravenously under a variety of anesthetic techniques, most commonly general anesthesia. Timing of administration covered induction, maintenance, and postoperative PCIA, with many trials dosing during maintenance alone, and others using combinations schedules. Bolus doses at induction or PCIA ranged from 0.2–0.5 mg/kg, with fixed-dose PCIA regimens such as 50 mg or 100 mg, and a weight-based PCIA dose of 0.72 mg/kg in one trial. Maintenance infusions most often ranged from 0.1–0.5 mg/kg/h, though higher rates (eg., 1 mg/kg/h) were reported in individual studies. 3 trials co-administered dexmedetomidine with esketamine, while 2 specified that dexmedetomidine was provided to both groups. Control conditions were predominantly placebo (normal saline), with several studies using standard-of-care comparators.

Risk of Bias and GRADE Quality Assessment

A total of 21 randomized controlled trials were included in the risk of bias assessment. As shown in [Figures 2 and 3](#), 3 studies^{31,32,38} did not report the method of allocation concealment, and one study²⁹ had incomplete outcome data that could not be fully accounted for. Moreover, 3 studies^{21,32,33} explicitly acknowledged potential design-related biases in their limitation sections, which were therefore judged as high risk. These included potential confounding bias, lack of detailed stratification by surgical characteristics (eg., variation in liposuction sites without subgroup differentiation), restriction of participants without preoperative depressive history, and baseline imbalances between groups. Overall, only a few studies exhibited high-risk judgments, and the methodological quality of the included trials was considered acceptable. According to the GRADE assessment ([Supplementary Material: Table S3](#)), the certainty of evidence ranged from low to moderate across outcomes.

Publication Bias Assessment

Potential publication bias for the analysis of subjective sleep quality scores on the first postoperative day was assessed using both funnel plot inspection ([Supplementary Material: Figure S1](#)) and Egger's linear regression test. The funnel plot appeared generally symmetrical, and Egger's test ($p = 0.825$) showed no statistically significant evidence of publication bias. For postoperative pain scores at rest on postoperative day 1, publication bias was also evaluated because more than 10 studies were included in this analysis. Visual inspection of the funnel plot suggested a degree of asymmetry ([Supplementary Material: Figure S2](#)). Egger's regression test indicated potential publication bias ($p = 0.022$). Therefore, the pooled estimate for this outcome should be interpreted with caution.

Primary Outcome Assessment

Subjective Sleep Quality Score

A total of 15 studies involving 6880 patients (3450 in the esketamine group and 3425 in the control group) reported subjective sleep quality scores. At the preoperative baseline, there was no significant difference between groups (SMD = -0.01 , 95% CI [-0.10 , 0.08], $I^2 = 0\%$, $p = 0.88$), indicating comparable sleep quality before intervention. On postoperative day 1, esketamine significantly improved subjective sleep quality (SMD = -0.40 , 95% CI [-0.59 , -0.20], $I^2 = 72\%$, $p < 0.0001$). The corresponding prediction interval ranged from -1.02 to 0.22 . The effect persisted on day 2 (SMD = -0.47 , 95% CI [-0.85 , -0.10], $I^2 = 87\%$, $p = 0.01$), though heterogeneity remained high. By day 3, the difference narrowed and did not reach statistical significance (SMD = -0.24 , 95% CI [-0.50 , 0.01], $I^2 = 81\%$, $p = 0.06$). Within one month after surgery, sleep quality remained significantly better in the esketamine group compared with control (SMD = -0.31 , 95% CI [-0.57 , -0.06], $I^2 = 76\%$, $p = 0.01$) ([Figure 4](#)). Because lower scores on the included sleep scales indicate better sleep quality, negative SMD values favor the esketamine group.

Table 2 Characteristics of the Interventions in the Included Studies

First Author, Year	Type of Anesthesia	Time of Administration	Dosage	Combined Medication	Control Group
Chen H, ³³ 2024	TLA+IVA	AB	0.3 mg/kg/h (A)+0.15 mg/kg/h (B)	None*	Placebo (saline)
Chen Y, ²⁷ 2025	TIVA	B	0.2 mg/kg loading dose, followed by 0.1 mg/kg/h infusion (B)	None	Placebo (saline)
Geng X, ²⁴ 2025	GA	B	0.3 mg/kg/h (B)	Dexmedetomidine	Placebo (saline)
He Q, ³² 2024	GA	AC	0.5 mg/kg (A)+1.5 mg/kg (C)	None	Placebo (saline)
Lin X, ³⁴ 2024	GA	AC	0.5 mg/kg (A)+1 mg/kg (C)	None	Placebo (saline)
Ma C, ³⁰ 2024	GA	ABC	0.20 mg/kg (A)+0.125 mg/kg/h (B)+0.5 mg/kg (C)	None	Placebo (saline)
Qiu D, ³⁹ 2022	GA	B	0.3 mg/kg/h (B)	None	Placebo (saline)
Shang Y, ²¹ 2025	CSEA	BC	0.25 mg/kg (B)+1.5 µg/kg (C)	None	Placebo (saline)
Song Z, ²⁰ 2025	GA	B	0.2 mg/kg (B)	None	Placebo (saline)
Wang P, ³⁷ 2023	GA	B	0.5 mg/kg loading dose, followed by 0.24 mg/kg/h infusion (B)	None	Placebo (saline)
Wang H, ²⁶ 2025	GA	B	0.3 mg/kg/h (B)	None	Placebo (saline)
Wang W, ²⁵ 2025	GA	B	0.2–0.5 mg/kg/h (B)	Dexmedetomidine	Standard-of-care
Wei Q, ³¹ 2024	GA+NBA	C	100 mg (C)	None*	Standard-of-care
Wu Y, ²² 2025	GA+LIA	B	0.5 mg/kg/h (B)	None	Placebo (saline)
Yuan J, ⁴⁰ 2022	TIVA	B	0.25 mg/kg/h (B)	None	Placebo (saline)
Zhang T, ²⁹ 2023	GA	BC	0.2 mg/kg/h (B)+50mg (C)	None	Placebo (saline)
Zhang Y, ³⁵ 2023	GA	C	50 mg (C)	Dexmedetomidine	Placebo (saline)
Zhao Y, ²⁸ 2025	GA+NBA	C	0.72 mg/kg (C)	None	Placebo (saline)
Zhou R, ³⁶ 2023	GA+NBA	A	0.5 mg/kg (A)	None	Placebo (saline)
Zhou Y, ²³ 2025	GA	B	1 mg/kg/h (B)	None	Placebo (saline)
Zhu M, ³⁸ 2022	GA	B	0.5mg/kg loading, followed by 4 µg/kg/h infusion (B)	None	Placebo (saline)

Notes: A: Induction of anaesthesia; B: Maintenance of anesthesia; C: PCIA. *: Both the experimental and control groups received dexmedetomidine.

Abbreviations: TLA, tumescent local anesthesia; IVA, intravenous anesthesia; TIVA, total intravenous anesthesia; GA, general anesthesia; CSEA, combined spinal-epidural anesthesia; NBA, nerve block anesthesia; LIA, local infiltration anesthesia.

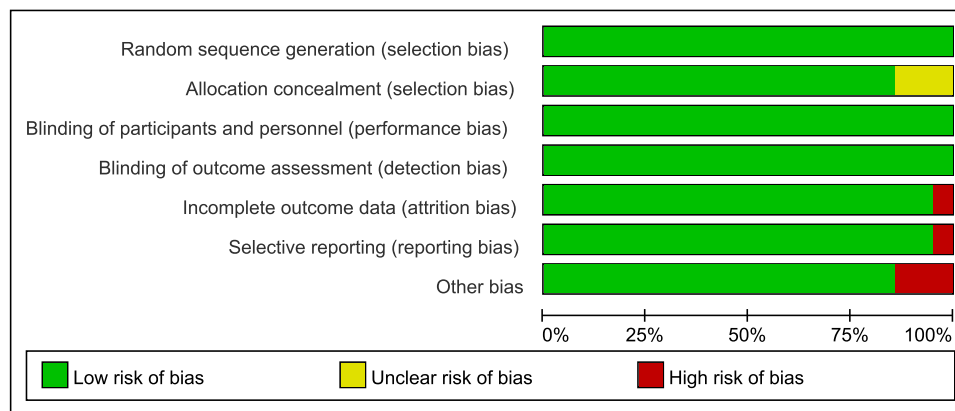


Figure 2 Risk of bias graph.

Subgroup Analysis

To explore potential sources of heterogeneity, prespecified subgroup analyses were performed for sleep quality on the first postoperative day based on dosage, timing of administration, co-administration with dexmedetomidine, age, sex distribution, surgical type, anesthesia modality, and sleep assessment tools (Table 3).

Studies using ≤ 0.25 mg/kg of esketamine showed a modest improvement in subjective sleep quality (SMD = -0.20 , 95% CI [-0.39 , -0.02], $I^2 = 30\%$, $p = 0.03$), whereas those using > 0.25 mg/kg demonstrated a larger and more significant benefit (SMD = -0.56 , 95% CI [-0.72 , -0.40], $I^2 = 0\%$, $p < 0.00001$) (Supplementary Material: Figure S3).

Esketamine administered only intraoperatively significantly improved postoperative sleep quality (SMD = -0.44 , 95% CI [-0.57 , -0.30], $I^2 = 0\%$, $p < 0.00001$). However, when administered only postoperatively, no significant difference was found (SMD = -0.38 , 95% CI [-1.09 , 0.32], $I^2 = 91\%$, $p = 0.29$). Similarly, combined intraoperative and postoperative administration did not result in a statistically significant improvement (SMD = -0.20 , 95% CI [-0.64 , 0.23], $I^2 = 76\%$, $p = 0.36$) (Supplementary Material: Figure S4).

In the co-administration subgroup analysis, both regimens were associated with improved postoperative sleep quality and the heterogeneity did not decrease. This finding suggests that the observed improvement was primarily attributable to esketamine itself rather than a synergistic interaction with dexmedetomidine (Supplementary Material: Figure S5).

For age, a significant effect was observed in patients aged < 60 years (SMD = -0.42 , 95% CI [-0.65 , -0.19], $I^2 = 70\%$), whereas the effect was not statistically significant in patients aged ≥ 60 years (SMD = -0.34 , 95% CI [-0.75 , 0.06], $I^2 = 79\%$).

In the sex subgroup, both female-dominant populations (SMD = -0.42 , 95% CI [-0.62 , -0.22], $I^2 = 21\%$) and mixed populations (SMD = -0.39 , 95% CI [-0.67 , -0.10], $I^2 = 80\%$) showed improvements, although heterogeneity was higher in mixed populations.

For surgical type, a significant effect was observed in abdominal surgery (SMD = -0.56 , 95% CI [-0.75 , -0.38], $I^2 = 0\%$) and other procedures (SMD = -0.31 , 95% CI [-0.49 , -0.12], $I^2 = 0\%$), whereas no significant effect was found in orthopedic surgery (SMD = -0.29 , 95% CI [-0.83 , 0.26], $I^2 = 91\%$).

In terms of anesthesia modality, a significant effect was observed in studies using general anesthesia (SMD = -0.42 , 95% CI [-0.65 , -0.20], $I^2 = 71\%$), while no significant difference was found in non-general anesthesia (SMD = -0.34 , 95% CI [-0.79 , 0.11], $I^2 = 80\%$).

Finally, in the sleep assessment tool subgroup, studies using the AIS demonstrated a consistent improvement with low heterogeneity (SMD = -0.47 , 95% CI [-0.63 , -0.30], $I^2 = 24\%$). Studies using other scales also showed a significant effect but with higher heterogeneity (SMD = -0.44 , 95% CI [-0.79 , -0.09], $I^2 = 81\%$). The PSQI subgroup included only one study and did not show a statistically significant difference.

The p values for subgroup interaction were as follows: dosage ($p = 0.0007$), timing of administration ($p = 0.60$), co-administration ($p = 0.26$), age ($p = 0.74$), sex ($p = 0.85$), surgical type ($p = 0.12$), anesthesia type ($p = 0.72$), and

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen H 2024	+	+	+	+	+	+	-
Chen Y 2025	+	+	+	+	+	+	+
Geng X 2025	+	+	+	+	+	+	+
He Q 2024	+	?	+	+	+	-	-
Lin X 2024	+	+	+	+	+	+	+
Ma C 2024	+	+	+	+	+	+	+
Qiu D 2022	+	+	+	+	+	+	+
Shang Y 2025	+	+	+	+	+	+	-
Song Z 2025	+	+	+	+	+	+	+
Wang H 2025	+	+	+	+	+	+	+
Wang P 2023	+	+	+	+	+	+	+
Wang W 2025	+	+	+	+	+	+	+
Wei Q 2024	+	?	+	+	+	+	+
Wu Y 2025	+	+	+	+	+	+	+
Yuan J 2022	+	+	+	+	+	+	+
Zhang T 2023	+	+	+	+	-	+	+
Zhang Y 2023	+	+	+	+	+	+	+
Zhao Y 2025	+	+	+	+	+	+	+
Zhou R 2023	+	+	+	+	+	+	+
Zhou Y 2025	+	+	+	+	+	+	+
Zhu M 2022	+	?	+	+	+	+	+

Figure 3 Risk of bias summary.

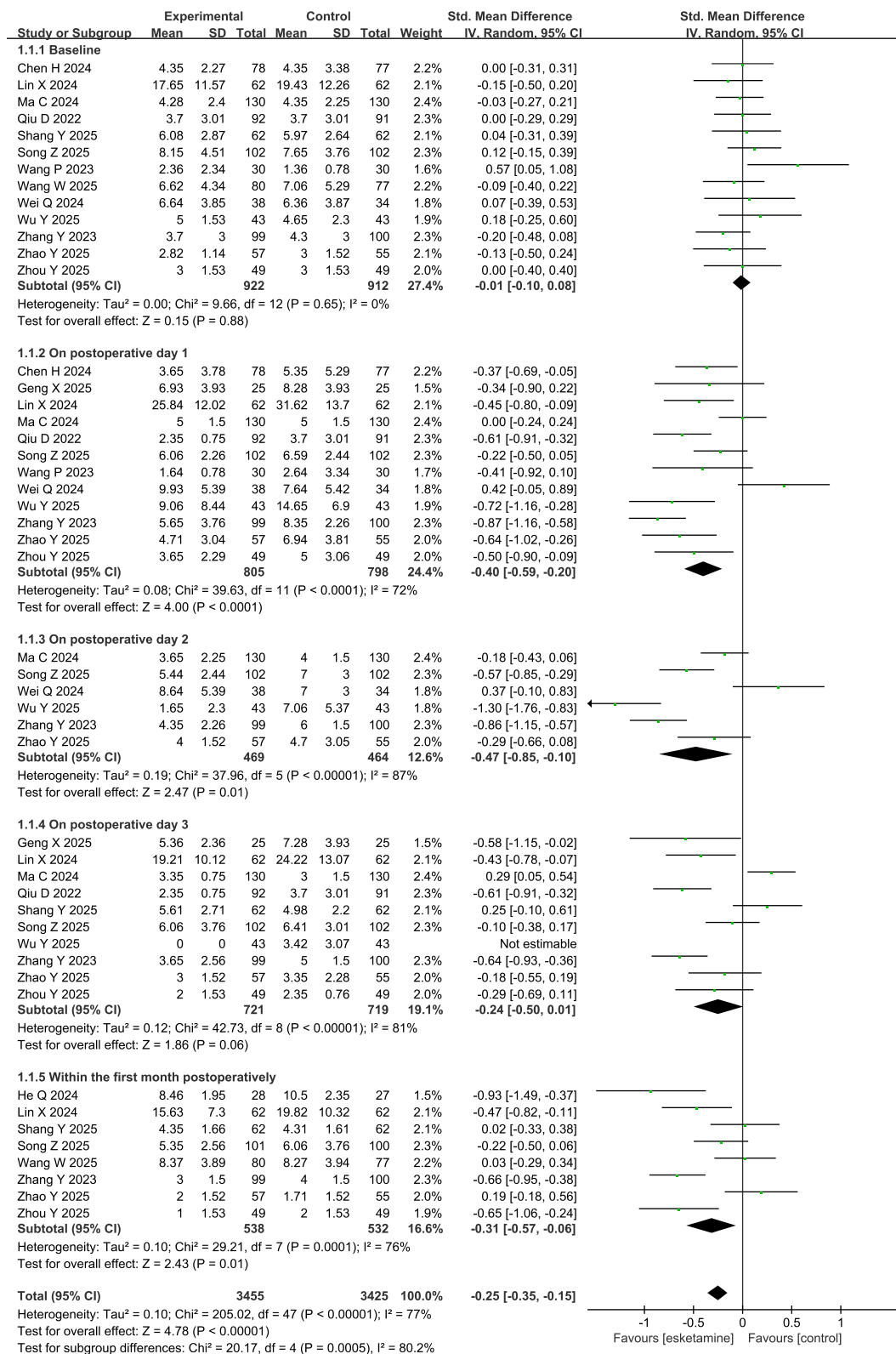


Figure 4 The effect of esketamine on the subjective sleep quality scores at preoperative baseline, postoperative day 1, 2, 3, and within one month after surgery.

Table 3 Effect Sizes of the Overall and Subgroup Analysis of the Effects of Esketamine on Sleep Quality on the First Postoperative Day

Title	Number of Trials	Number of Participants	Statistical Method	Effect Size	Overall Effect, p Value	Heterogeneity I ² Value
1. Overall effect	12	1603	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.59, -0.20]	p < 0.0001	72%
2. Subgroup analysis by dosage	10	Test for subgroup differences: p = 0.0007				
2.1 ≤ 0.25 mg/kg	4	679	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.39, -0.02]	p = 0.02	30%
2.2 > 0.25 mg/kg	6	653	Std. Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.72, -0.40]	p < 0.00001	0%
3. Subgroup analysis by timing of administration	12	Test for subgroup differences: p = 0.60				
3.1 Only intraoperative administration	7	836	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.57, -0.30]	p < 0.00001	0%
3.2 Only postoperative administration	3	383	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-1.09, 0.32]	p = 0.29	91%
3.3 Both intraoperative and postoperative administration	2	384	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.64, 0.23]	p = 0.36	76%
4. Subgroup analysis by co-administration	12	Test for subgroup differences: p = 0.26				
4.1 Esketamine combined with dexmedetomidine	2	249	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-1.17, -0.15]	p = 0.01	63%
4.2 Esketamine	10	1354	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.54, -0.15]	p = 0.0005	68%
5. Subgroup analysis by age	12	Test for subgroup differences: p = 0.74				
5.1 < 60 years	9	1107	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.65, -0.19]	p = 0.0003	70%
5.2 ≥ 60 years	3	496	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.75, 0.06]	p = 0.10	79%
6. Subgroup analysis by sex	12	Test for subgroup differences: p = 0.85				
6.1 Female-dominant	4	535	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.22]	p < 0.0001	21%
6.1 Mixed population	8	1068	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.67, -0.10]	p = 0.008	80%

(Continued)

Table 3 (Continued).

Title	Number of Trials	Number of Participants	Statistical Method	Effect Size	Overall Effect, p Value	Heterogeneity I ² Value
7. Subgroup analysis by surgical type	12	Test for subgroup differences: $p = 0.12$				
7.1 Abdominal surgery	4	491	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.75, -0.38]	$p < 0.00001$	0%
7.2 Orthopedic surgery	4	643	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.83, 0.26]	$p = 0.30$	91%
7.3 Others	4	469	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.49, -0.12]	$p = 0.0010$	0%
8. Subgroup based on anesthesia type	12	Test for subgroup differences: $p = 0.75$				
8.1 General anesthesia	8	1178	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.65, -0.20]	$p = 0.0002$	71%
8.2 Non-general anesthesia	4	425	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.79, 0.11]	$p = 0.14$	80%
9. Subgroup based on evaluation scale	12	Test for subgroup differences: $p = 0.002$				
9.1 AIS	6	790	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.63, -0.30]	$p < 0.00001$	24%
9.2 PSQI	1	72	Std. Mean Difference (IV, Random, 95% CI)	0.42 [-0.05, 0.89]	$p = 0.08$	NA
9.3 Other scales	5	741	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.79, -0.09]	$p = 0.01$	81%

Abbreviation: NA: not applicable.

evaluation scale ($p = 0.002$). Overall, these subgroup analyses suggest that differences in dosage and evaluation scale may contribute to the observed heterogeneity, although these findings should be interpreted with caution.

Sensitivity Analyses

A sensitivity analysis excluding studies assessed as having a high risk of bias was conducted. After exclusion, the pooled effect on postoperative day 1 subjective sleep quality remained significant (SMD = -0.40, 95% CI [-0.62, -0.18], $I^2 = 75\%$, $p = 0.0003$). For postoperative day 3, the pooled effect became statistically significant after exclusion of Shang et.al' study (SMD = -0.30, 95% CI [-0.57, -0.04], $I^2 = 80\%$, $p = 0.02$), whereas the primary analysis showed no significant difference. At 1 month postoperatively, the results remained significant (SMD = -0.30, 95% CI [-0.57, -0.02], $I^2 = 76\%$, $p = 0.04$).

Leave-one-out sensitivity analyses were also conducted for subjective sleep quality at postoperative day 1, day 2, day 3, and 1 month. Sequential exclusion of each study did not alter the pooled effect estimate ([Supplementary Material: Figure S6](#)).

Secondary Outcome Assessment

Incidence of Sleep Disturbance

A total of 7 studies^{20,22–24,26,28,39} involving 1662 patients (834 in the esketamine group and 828 in the control group) reported the incidence of postoperative sleep disturbance. The pooled analysis demonstrated that esketamine significantly reduced the incidence of postoperative sleep disturbance compared with control treatments. On the first postoperative day, patients receiving esketamine had a markedly lower risk of sleep disturbance (RR = 0.63, 95% CI [0.55, 0.73], $I^2 = 23\%$, $p < 0.00001$). This beneficial effect remained evident on the third postoperative day (RR = 0.44, 95% CI [0.31, 0.61], $I^2 = 0\%$, $p < 0.00001$) ([Figure 5](#)).

Pain Score

A total of 15 studies reported postoperative day 1 pain scores, of which 10 studies assessed pain at rest, 9 studies evaluated pain on movement, and 5 studies reported pain scores without distinguishing between rest and movement ([Figure 6](#)). Esketamine demonstrated significant analgesic benefits both at rest (SMD = -0.46 , 95% CI [-0.83 , -0.09], $I^2 = 92\%$, $p = 0.01$) and during movement (SMD = -0.39 , 95% CI [-0.63 , -0.16], $I^2 = 78\%$, $p = 0.001$). The reduction in pain scores without distinguishing between rest and movement was also statistically significant (SMD = -0.37 , 95% CI [-0.67 , -0.08], $I^2 = 59\%$, $p = 0.01$).

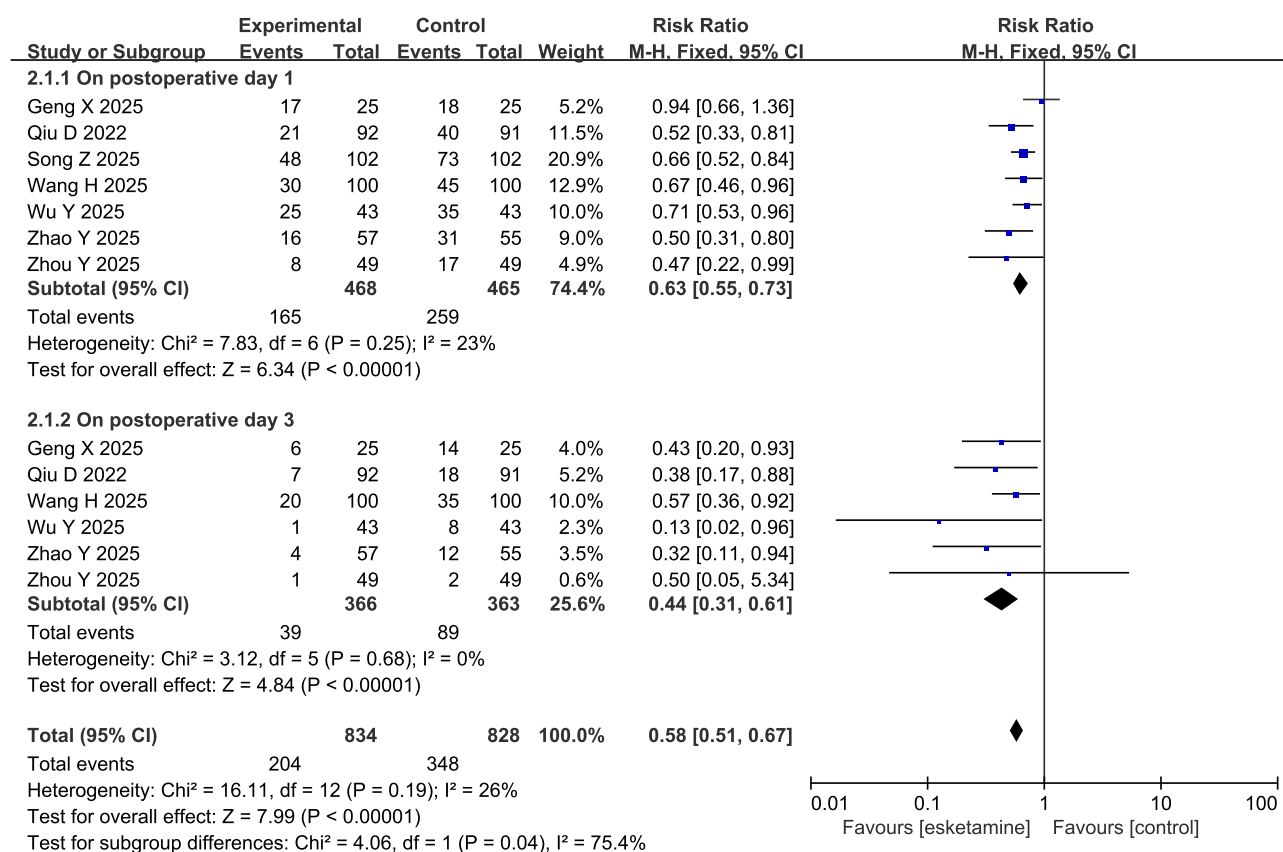


Figure 5 The effect of esketamine on the incidence of sleep disturbance on postoperative day 1 and 3.

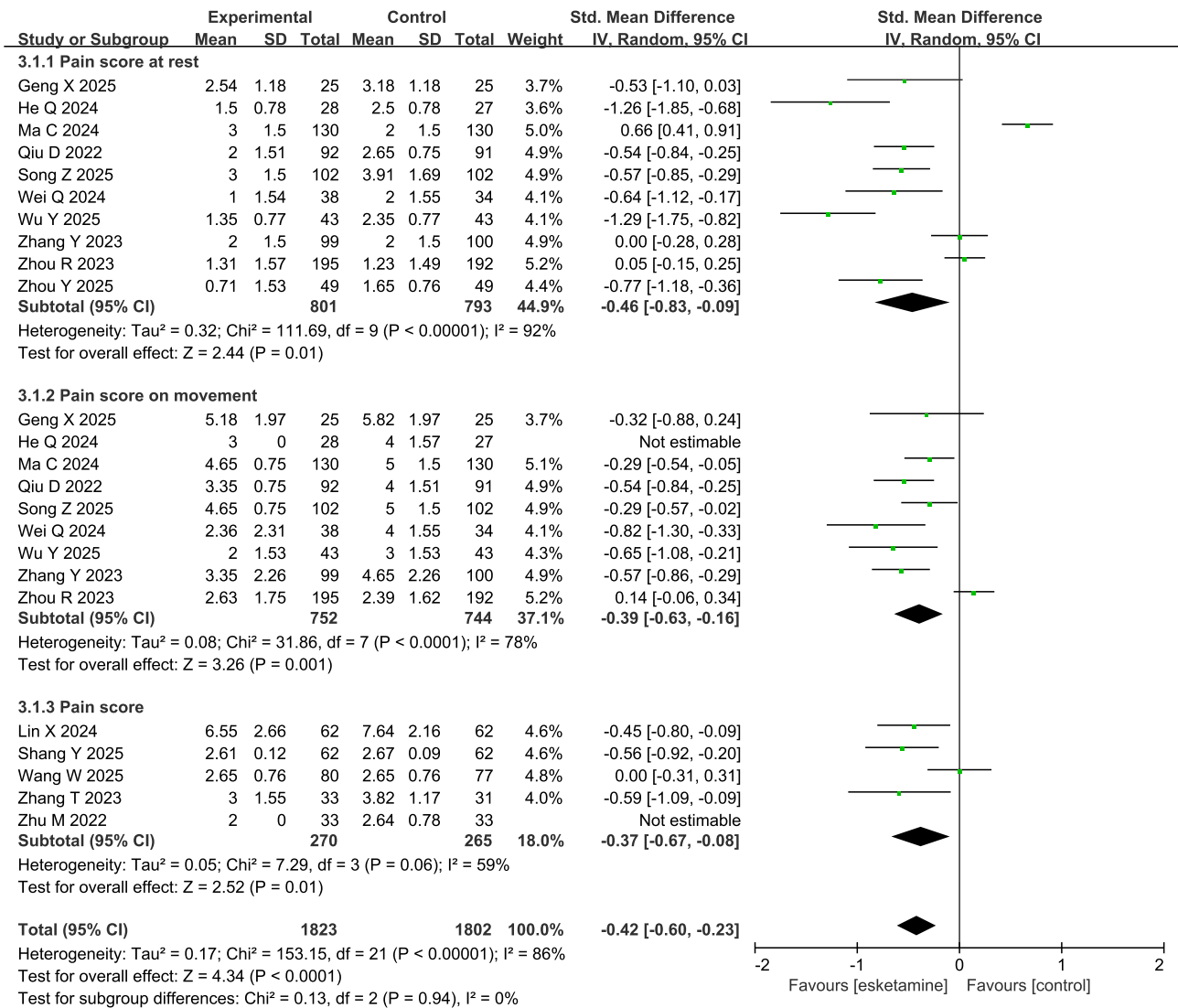


Figure 6 The effect of esketamine on postoperative day 1 pain scores at rest, during movement, and without differentiation between rest or movement.

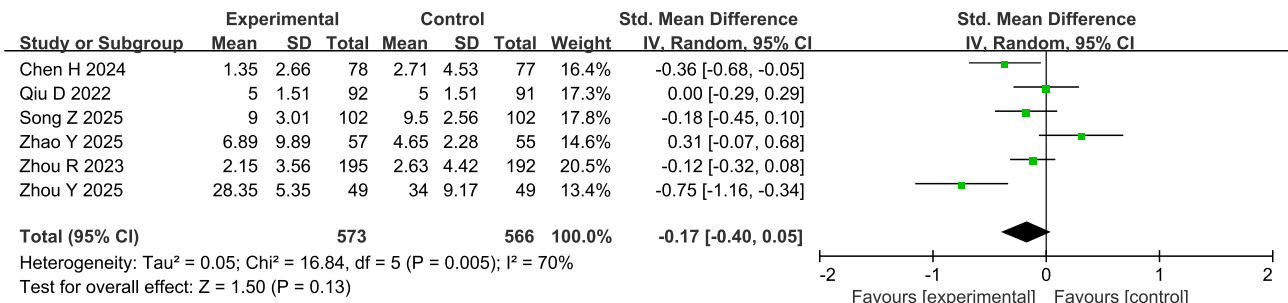


Figure 7 The effect of esketamine on the postoperative anxiety scores.

Anxiety Score

A total of 6 studies^{20,23,28,33,36,39} involving 1,139 patients (573 in the esketamine group and 566 in the control group) reported postoperative anxiety scores (Figure 7). The meta-analysis revealed no significant difference between the esketamine and control groups (SMD = -0.17, 95% CI [-0.40, 0.05], $I^2 = 70\%$, $p = 0.13$).

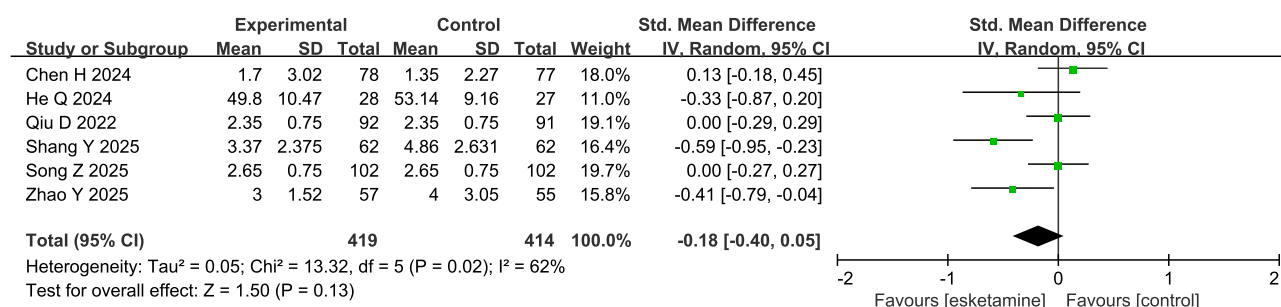


Figure 8 The effect of esketamine on the postoperative depression scores.

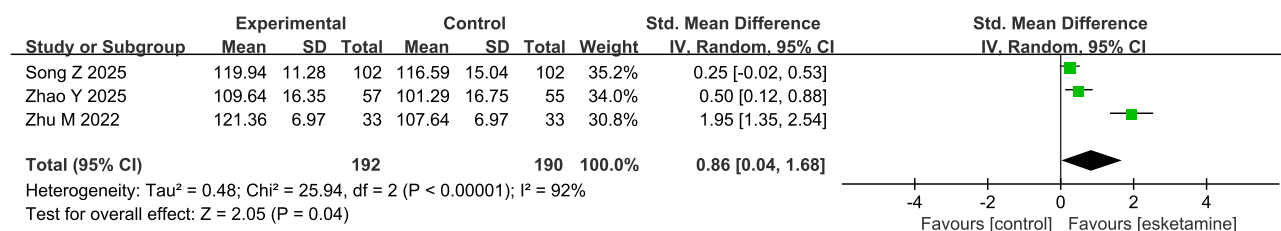


Figure 9 The effect of esketamine on the postoperative QoR-15 scores.

Depression Score

A total of 6 studies^{20,21,28,32,33,39} including 833 patients (419 in the esketamine group and 414 in the control group) reported postoperative depression scores (Figure 8). The pooled results showed no statistically significant difference in postoperative depression between the two groups (SMD = -0.18, 95% CI [-0.40, 0.05], $I^2 = 62\%$, $p = 0.13$).

QoR-15 Scale Score

A total of 3 studies^{20,28,38} including 382 patients (192 in the esketamine group and 190 in the control group) reported postoperative 15-item Quality of Recovery (QoR-15) scores (Figure 9). The pooled analysis showed that patients who received esketamine had higher QoR-15 scores compared with those in the control group (SMD = 0.86, 95% CI [0.04, 1.68], $I^2 = 92\%$, $p = 0.04$). However, given the substantial heterogeneity and the limited number of included studies, this finding should be interpreted with caution.

Adverse Events

Pooled analyses showed that perioperative esketamine was associated with a higher risk of dizziness (RR = 1.24, 95% CI [1.05, 1.46], $I^2 = 33\%$, $p = 0.009$), but a lower risk of tachycardia (RR = 0.55, 95% CI [0.32, 0.93], $I^2 = 51\%$, $p = 0.03$). No significant differences were found for nausea, vomiting, postoperative nausea and vomiting, headache, delirium, nightmare, hallucination, hypertension, or respiratory depression (Supplementary Material: Figure S7).

Discussion

Principal Findings

The present systematic review and meta-analysis synthesized evidence from 21 randomized controlled trials evaluating the effects of esketamine on postoperative sleep quality. Overall, the results showed that perioperative use of esketamine led to a marked improvement in subjective sleep quality, especially on the first postoperative day, and reduced the incidence of sleep disturbance compared with control treatments. Improvements in pain scores and QoR-15 recovery scores further supported the beneficial role of esketamine in enhancing analgesia and recovery quality. However, no significant differences were observed in postoperative anxiety or depression scores. Overall, esketamine did not significantly affect most reported adverse events, suggesting a favorable safety profile. Collectively, these results indicate

that esketamine exerts a measurable and clinically relevant improvement in postoperative sleep quality and overall recovery, particularly during the early postoperative period.

Comparison with Previous Research

Recent meta-analyses have explored the effects of esketamine in perioperative and postpartum populations, but the evidence regarding its influence on sleep has been largely inconclusive. Two studies focusing on the prophylactic use of esketamine to prevent postpartum depression after cesarean section found no significant differences in the incidence of nightmares between the esketamine and control groups.^{41,42} Similarly, a meta-analysis evaluating esketamine for the prevention of postoperative depression reported that, although some trials suggested improved sleep quality, the pooled results did not demonstrate a statistically significant benefit, with considerable heterogeneity among studies.⁴³ These findings indicate that the previously reported sleep-related outcomes of esketamine were inconsistent and often secondary to its antidepressant or analgesic effects. In contrast, the present meta-analysis is, to our knowledge, the first to systematically and quantitatively assess postoperative sleep quality as a primary outcome, providing more focused and reliable evidence of esketamine's potential to improve perioperative sleep and recovery.

Mechanisms

The beneficial effects of esketamine on postoperative sleep quality may be explained by its unique pharmacological profile and neurophysiological mechanisms. Esketamine may influence sleep-related pathways through modulation of glutamatergic neurotransmission.¹² By decreasing excessive excitatory neurotransmission and enhancing γ -aminobutyric acid (GABA)-mediated inhibition, esketamine can stabilize neuronal activity within cortical and thalamic circuits, thereby improving sleep architecture and promoting deeper non-rapid eye movement (NREM) sleep.^{44,45} In addition, esketamine has been shown to affect mood-related pathways, which may indirectly influence sleep perception.^{13,46} Furthermore, by providing effective analgesia through NMDA blockade and descending pain pathway modulation, esketamine reduces postoperative pain—a key factor in sleep disturbance and fragmented sleep recovery.⁴⁷ Taken together, these neurochemical and physiological actions suggest that esketamine may promote postoperative sleep restoration through an integrated mechanism involving pain control, neuroprotection, and normalization of sleep–wake regulation.

Our findings are consistent with and extend prior evidence regarding the role of NMDA receptor antagonists and α_2 -adrenergic agonists in modulating postoperative sleep. Previous narrative and systematic reviews have highlighted that racemic ketamine can alleviate perioperative sleep disturbances by reducing pain, neuroinflammation, and depressive symptoms, while promoting rapid restoration of normal sleep architecture.^{48,49} However, compared with ketamine, esketamine—the S-enantiomer—has approximately twofold higher NMDA receptor affinity, leading to more potent analgesic and antidepressant effects with fewer psychotomimetic adverse reactions. Similarly, recent meta-analyses have reported that dexmedetomidine improves postoperative sleep quality through sedation resembling natural NREM sleep and by attenuating sympathetic activation.^{7,8} Nevertheless, dexmedetomidine's hemodynamic side effects (eg., bradycardia and hypotension) and its limited antidepressant potential constrain its broader clinical use. In contrast, esketamine not only enhances sleep quality but also provides effective analgesia and rapid mood stabilization, offering a multifaceted approach to improving postoperative recovery. Taken together, these findings suggest that esketamine represents a promising adjunctive agent that may complement or even surpass traditional sedative strategies in restoring postoperative sleep integrity.

Clinical Implications

Postoperative sleep disturbance is a common yet underrecognized complication that affects up to 60–80% of surgical patients, particularly within the first few nights after major surgery.^{2,50} Disrupted sleep is closely linked to heightened pain sensitivity, impaired immune recovery, delayed wound healing, and an increased risk of postoperative neurocognitive disorders (PND).³ Given these profound clinical consequences, there is growing interest in exploring the therapeutic potential of anesthetic and sedative agents for the prevention and management of perioperative sleep disorders.⁵¹ Recent studies have suggested that anesthesiology may play a pivotal role in perioperative sleep medicine,

with agents such as dexmedetomidine, propofol, and ketamine analogs exerting direct effects on sleep–wake regulation beyond anesthesia itself.⁵² The present findings add to this evolving paradigm by demonstrating that esketamine—traditionally used as an anesthetic and antidepressant—can also improve postoperative sleep quality and enhance multidimensional recovery. From a broader perspective, these results highlight a potential new direction for perioperative sleep clinics and multidisciplinary recovery programs. Integrating sleep-focused pharmacologic strategies such as esketamine into perioperative care could mitigate postoperative sleep disruption, shorten recovery time, and possibly prevent chronic insomnia or neurocognitive decline. Future studies integrating objective sleep monitoring (eg., polysomnography or actigraphy) and long-term outcomes will be essential to translate these findings into clinical protocols.

Sources of Heterogeneity

The use of different sleep assessment tools (eg., AIS, PSQI, and ICU-based scales such as RCSQ) represents an important source of heterogeneity. These instruments differ in their underlying constructs (eg., insomnia severity vs perceived sleep quality), recall periods, and clinical contexts, which may limit direct comparability. Although most studies used validated Chinese-language versions of these scales, their performance in postoperative settings may vary. This variability should be considered when interpreting pooled estimates. Subgroup findings should be interpreted cautiously, as these analyses are exploratory and may be influenced by limited study numbers and residual heterogeneity. A formal dose–response relationship could not be established.

Limitations

Several limitations should be recognized. First, there was notable methodological heterogeneity among the studies, particularly in sleep assessment tools. Various instruments—including the AIS, PSQI, and NRS—were used to evaluate subjective sleep quality at different time points after surgery, which might have contributed to the variability in pooled estimates. Second, moderate to high heterogeneity (I^2 values up to 87%) was observed in several pooled analyses, possibly reflecting differences in dosing regimens, administration timing, surgical types, and baseline sleep status. Third, objective sleep measures such as polysomnography or actigraphy were not used in any included trials; thus, the results rely solely on patient-reported outcomes, which may be influenced by subjective perception and recall bias. Fourth, the follow-up duration was short, typically limited to within one postoperative month, precluding evaluation of the long-term effects of esketamine on sustained sleep recovery or chronic insomnia prevention. In addition, potential publication bias was detected in the analysis of postoperative pain scores at rest, which may partly influence the pooled effect estimate.

Another important limitation is that all included studies were conducted in China. This geographic concentration may reflect differences in regulatory approval timelines, clinical adoption patterns, and research priorities across regions. In recent years, esketamine has been more widely adopted and investigated in China, whereas in other countries, racemic ketamine has traditionally been more commonly used in perioperative settings. Future high-quality, multicenter, and multiethnic randomized trials incorporating both objective sleep parameters and longitudinal follow-up are warranted to validate and extend these findings.

Conclusions

This meta-analysis showed that perioperative administration of esketamine significantly improved postoperative subjective sleep quality during the early postoperative period (postoperative days 1–2) and reduced the incidence of sleep disturbance. Esketamine also reduced postoperative pain and enhanced the overall quality of recovery. These findings suggested that esketamine might have therapeutic potential for managing perioperative sleep disorders. However, this conclusion was based on low to moderate-certainty evidence and should be interpreted with caution. The generalizability of these findings is limited by the geographic concentration of the included studies. Further multicenter randomized trials using objective sleep assessments and extended follow-up are warranted to determine optimal dosing and timing strategies.

Data Sharing Statement

All data generated or analysed during this study are included in this published article [and its [Supplementary Information Files](#)].

Author Contributions

Jiacheng Zhao: Conceptualization, Visualization, Investigation, Data curation, Writing - original draft, Writing - review and editing. Yanan Yan: Data curation, Software, Writing - original draft, Writing - review and editing. Xiaohan Wang: Formal analysis, Methodology, Writing - original draft, Writing - review and editing. Chao Zhang: Formal analysis, Writing - original draft, Writing - review and editing. Jie Wang: Validation, Project administration, Supervision, Writing - original draft, Writing - review and editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

References

- Butris N, Tang E, Pivetta B, et al. The prevalence and risk factors of sleep disturbances in surgical patients: a systematic review and meta-analysis. *Sleep Med Rev*. 2023;69:101786. doi:10.1016/j.smrv.2023.101786
- Gögenur I, Wildschütz G, Rosenberg J. Circadian distribution of sleep phases after major abdominal surgery. *Br J Anaesth*. 2008;100(1):45–49. doi:10.1093/bja/aem340
- Wang X, Hua D, Tang X, et al. The Role of Perioperative Sleep Disturbance in Postoperative Neurocognitive Disorders. *Nat Sci Sleep*. 2021;13:1395–1410. doi:10.2147/NSS.S320745
- Todd OM, Gelrich L, MacLulich AM, Driessen M, Thomas C, Kreisel SH. Sleep Disruption at Home As an Independent Risk Factor for Postoperative Delirium. *J Am Geriatr Soc*. 2017;65(5):949–957. doi:10.1111/jgs.14685
- Bryant PA, Trinder J, Curtis N. Sick and tired: does sleep have a vital role in the immune system? *Nat Rev Immunol*. 2004;4(6):457–467. doi:10.1038/nri1369
- Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J. Postoperative sleep disturbances: mechanisms and clinical implications. *Br J Anaesth*. 1996;76(4):552–559. doi:10.1093/bja/76.4.552
- Wang L, Liang XQ, Sun YX, Hua Z, Wang DX. Effect of perioperative dexmedetomidine on sleep quality in adult patients after noncardiac surgery: a systematic review and meta-analysis of randomized trials. *PLoS One*. 2024;19(12):e0314814. doi:10.1371/journal.pone.0314814
- Liu H, Wei H, Qian S, et al. Effects of dexmedetomidine on postoperative sleep quality: a systematic review and meta-analysis of randomized controlled trials. *BMC Anesthesiol*. 2023;23(1):88. doi:10.1186/s12871-023-02048-6
- de Mendonça FMR, de Mendonça GPRR, Souza LC, et al. Benzodiazepines and Sleep Architecture: a Systematic Review. *CNS Neurol Disord Drug Targets*. 2023;22(2):172–179. doi:10.2174/1871527320666210618103344
- Brown EN, Lydic R, Schiff ND. General Anesthesia, Sleep, and Coma. *N Engl J Med*. 2010;363(27):2638–2650. doi:10.1056/NEJMr0808281
- Cruz-Sanabria F, Bruno S, Crippa A, et al. Optimizing the Time and Dose of Melatonin as a Sleep-Promoting Drug: a Systematic Review of Randomized Controlled Trials and Dose–Response Meta-Analysis. *J Pineal Res*. 2024;76(5). doi:10.1111/jpi.12985
- Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. 2018;23(4):801–811. doi:10.1038/mp.2017.255
- Abdallah CG, Sanacora G, Duman RS, Krystal JH. Ketamine and Rapid-Acting Antidepressants: a Window into a New Neurobiology for Mood Disorder Therapeutics. *Annu Rev Med*. 2015;66(1):509–523. doi:10.1146/annurev-med-053013-062946
- Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. *J Clin Anesth*. 2021;68:110071. doi:10.1016/j.jclinane.2020.110071
- Cheng MCH, Dri CE, Ballum H, et al. The Effects of Ketamine and Esketamine on Measures of Quality of Life in Major Depressive Disorder and Treatment-Resistant Depression: a Systematic Review. *J Affect Disord*. 2025;382:438–442. doi:10.1016/j.jad.2025.04.119
- Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;2019:ED000142. doi:10.1002/14651858.ED000142
- 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. doi:10.1136/bmj.l4898.
- 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(6):1785–1805. doi:10.1177/0962280216669183
- 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(1):135. doi:10.1186/1471-2288-14-135

20. Song Z, Miao M, Huang F, et al. Effect of a single low-dose esketamine administration during surgical abortion on postoperative sleep disturbance: a randomized controlled trial. *Nat Commun.* **2025**;16(1):7533. doi:10.1038/s41467-025-62933-1
21. Shang Y, Li S, Zheng Q, et al. The effect of low-dose esketamine on maternal depression after cesarean delivery. *J Psychosomatic Obstet Gynecol.* **2025**;46(1). doi:10.1080/0167482X.2025.2527659
22. Wu Y, Yang Y, Wang X, et al. Effect of intraoperative low-dose esketamine infusion on postoperative sleep disturbance after laparoscopic cholecystectomy: a randomized clinical trial. *BMC Anesthesiol.* **2025**;25(1):314. doi:10.1186/s12871-025-03180-1
23. Zhou YH, Li L, Gao R, et al. Effect of low-dose supplemental esketamine infusion on the intraoperative frontal electroencephalography dynamics and postoperative sleep disturbance during gynecological laparoscopic surgery: a double-blind, randomized clinical trial. *Int J Surg.* **2025**;111(12):9799–9800. doi:10.1097/JS9.0000000000002836
24. Geng X, Pu Y, Hu Z, et al. Effect of Intraoperative Intravenous Infusion of Esketamine Combined with Dexmedetomidine on Postoperative Sleep Disturbance in Patients Undergoing Radical Mastectomy. *Drug Des Devel Ther.* **2025**;19:4629–4640. doi:10.2147/DDDT.S510222
25. Wang W, Chen Y, Li G, et al. The Opioid-Sparing Effects of Intraoperative Esketamine Combined with Dexmedetomidine During Laparoscopic Major Abdominal Surgery: a Randomized Controlled Double-Blind Trial. *Drug Des Devel Ther.* **2025**;19:1971–1981. doi:10.2147/DDDT.S480700
26. Wang H, Wang L, Gao J, Zhou F. Effect of intravenous esketamine on postoperative sleep disturbance, anxiety, and depression in elderly patients undergoing laparoscopic abdominal surgery: a randomized controlled trial. *BMC Geriatr.* **2025**;25(1):148. doi:10.1186/s12877-025-05787-y
27. Chen Y, He J, Huang R, Pan Z, Zhong M, Zhang W. Effects of the subanesthetic dose of esketamine on postoperative sleep quality in patients undergoing modified radical mastectomy: a randomized, double-blind controlled trial. *Front Med Lausanne.* **2025**;12:1552934. doi:10.3389/fmed.2025.1552934
28. Zhao Y, Ye C, He Y, Bao M, Liu Y, Yan M. Effect of Esketamine for Patient-Controlled Intravenous Analgesia on Postoperative Sleep Disturbance in the Elderly After Total Hip or Knee Arthroplasty: a Prospective, Randomized, Double-Blind, and Controlled Trial. *J Arthroplasty.* **2025**;41(1):81–89. doi:10.1016/j.arth.2025.06.009
29. Zhang T, Song N, Li S, et al. S-Ketamine Improves Slow Wave Sleep and the Associated Changes in Serum Protein Among Gynecological Abdominal Surgery Patients: a Randomized Controlled Trial. *Nat Sci Sleep.* **2023**;15:903–913. doi:10.2147/NSS.S430453
30. Ma CB, Zhang CY, Gou CL, et al. Effect of Low-Dose Esketamine on Postoperative Delirium in Elderly Patients Undergoing Total Hip or Knee Arthroplasty: a Randomized Controlled Trial. *Drug Des Devel Ther.* **2024**;18:5409–5421. doi:10.2147/DDDT.S477342
31. Wei Q, Feng S, Dai W, Lin CX, Wen Zheng H. Effects of Small-Dose Esketamine on Postoperative Analgesia and Sleep Quality in Patients with Total Hip Replacement. *J College Phys Surgeons Pakistan.* **2024**;34(11):1382–1386. doi:10.29271/jcpsp.2024.11.1382
32. He Q, Liu Q, Liang B, et al. Esketamine use for primary intelligent analgesia in adults with severe burns: a double-blind randomized trial with effects on analgesic efficacy, gastrointestinal function and mental state. *Burns.* **2024**;50(9):107187. doi:10.1016/j.burns.2024.06.004
33. Chen H, Zhi J, Wang L, et al. Subanesthetic Dose of Esketamine Improves the Sedative and Analgesic Effects of Dexmedetomidine and Remifentanyl in Liposuction Anesthesia: a Prospective, Double-Blinded, Randomized Controlled Trial. *Drug Des Devel Ther.* **2024**;18:3645–3658. doi:10.2147/DDDT.S470891
34. Lin X, Feng X, Sun L, et al. Effects of esketamine on postoperative fatigue syndrome in patients after laparoscopic resection of gastric carcinoma: a randomized controlled trial. *BMC Anesthesiol.* **2024**;24(1):185. doi:10.1186/s12871-024-02513-w
35. Zhang Y, Cui F, Ma JH, Wang DX. Mini-dose esketamine–dexmedetomidine combination to supplement analgesia for patients after scoliosis correction surgery: a double-blind randomised trial. *Br J Anaesth.* **2023**;131(2):385–396. doi:10.1016/j.bja.2023.05.001
36. Zhou R, Zhang Y, Tang S, et al. A Single Preoperative Dose of S-Ketamine Has No Beneficial Effect on Chronic Postsurgical Pain in Patients Undergoing Video-Assisted Thoracoscopic Surgical Lung Lesion Resection: a Prospective Randomized Controlled Study. *J Cardiothorac Vasc Anesth.* **2023**;37(8):1433–1441. doi:10.1053/j.jvca.2023.02.046
37. Wang P, Song M, Wang X, Zhang Y, Wu Y. Effect of esketamine on opioid consumption and postoperative pain in thyroidectomy: a randomized controlled trial. *Br J Clin Pharmacol.* **2023**;89(8):2542–2551. doi:10.1111/bcp.15726
38. Zhu M, Xu S, Ju X, Wang S, Yu X. Effects of the Different Doses of Esketamine on Postoperative Quality of Recovery in Patients Undergoing Modified Radical Mastectomy: a Randomized, Double-Blind, Controlled Trial. *Drug Des Devel Ther.* **2022**;16:4291–4299. doi:10.2147/DDDT.S392784
39. Qiu D, Wang XM, Yang JJ, et al. Effect of Intraoperative Esketamine Infusion on Postoperative Sleep Disturbance After Gynecological Laparoscopy. *JAMA Netw Open.* **2022**;5(12):e2244514. doi:10.1001/jamanetworkopen.2022.44514
40. Yuan J, Chen S, Xie Y, et al. Randomized Controlled Trial Intraoperative Intravenous Infusion of Esmketamine Has Opioid-Sparing Effect and Improves the Quality of Recovery in Patients Undergoing Thoracic Surgery: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Pain Physician.* **2022**;25(9):E1389–E1397
41. Shi H, Zheng C, Shou H, Zhu B. Prophylactic esketamine for postpartum depression after cesarean section: a systematic review and meta-analysis. *J Affect Disord.* **2025**;388:119631. doi:10.1016/j.jad.2025.119631
42. Li Y, Zhao K, Cao P, Wang Q, Li K, Zhou J. Perioperative use of esketamine for the prevention of postpartum depression after cesarean section: a meta-analysis. *BMC Pregnancy Childbirth.* **2025**;25(1):775. doi:10.1186/s12884-025-07809-4
43. Niu G, Zheng X, Deng B, Du YS, Mei Y. The effects of prophylactic use of esketamine on postoperative depression and quality of life: a meta-analysis. *Minerva Anesthesiol.* **2024**;90(4). doi:10.23736/S0375-9393.24.17703-6
44. Irwin MR, Opp MR. Sleep Health: reciprocal Regulation of Sleep and Innate Immunity. *Neuropsychopharmacology.* **2017**;42(1):129–155. doi:10.1038/npp.2016.148
45. Duncan WC, Zarate CA. Ketamine, Sleep, and Depression: current Status and New Questions. *Curr Psychiatry Rep.* **2013**;15(9):394. doi:10.1007/s11920-013-0394-z
46. Li N, Lee B, Liu RJ, et al. mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists. *Science.* **2010**;329(5994):959–964. doi:10.1126/science.1190287
47. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. *Br J Clin Pharmacol.* **2014**;77(2):357–367. doi:10.1111/bcp.12094
48. Song B, Zhu J. A Novel Application of Ketamine for Improving Perioperative Sleep Disturbances. *Nat Sci Sleep.* **2021**;13:2251–2266. doi:10.2147/NSS.S341161
49. Song B, Zhu JC. Mechanisms of the Rapid Effects of Ketamine on Depression and Sleep Disturbances: a Narrative Review. *Front Pharmacol.* **2021**;12:782457. doi:10.3389/fphar.2021.782457

50. Lin D, Huang X, Sun Y, Wei C, Wu A. Perioperative Sleep Disorder: a Review. *Front Med Lausanne*. 2021;8:640416. doi:10.3389/fmed.2021.640416.
51. Pan X, Xi Y, Liang P, Huang J. Therapeutic Potential of Anesthesiology for Sleep Disorders in the Perioperative Period. *Curr Neuropharmacol*. 2025;23:1. doi:10.2174/011570159X368375250611103614.
52. Zhang JF, Williams JP, Zhao QN, et al. Multimodal sleep, an innovation for treating chronic insomnia: case report and literature review. *J Clin Sleep Med*. 2021;17(8):1737–1742. doi:10.5664/jcsm.9310

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