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REVIEW

Esketamine for Postoperative Multimodal Analgesia in Laparoscopic Surgery: A Systematic Review and Meta-Analysis

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Purpose: Postoperative pain management after laparoscopic surgery remains challenging. Esketamine, a potent N-methyl-D-aspartate receptor antagonist, may improve multimodal analgesia while mitigating opioid-related side effects. This meta-analysis evaluates the efficacy and safety of perioperative intravenous esketamine in adults undergoing laparoscopic surgery.

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials according to PRISMA guidelines. Databases were searched from inception to October 1, 2025. Primary outcomes were postoperative pain intensity (at rest and during movement at 24 hours) and 24-hour opioid consumption. Secondary outcomes included rescue analgesia, postoperative nausea and vomiting (PONV), hallucinations, and depressive symptoms. Data were pooled using random-effects models, and evidence certainty was assessed with GRADE.

Results: Twenty-eight RCTs (3160 patients), all conducted in China, were included. Esketamine significantly reduced pain at rest (SMD −0.65, 95% CI −0.90 to −0.40) and during movement (SMD −0.64, 95% CI −1.09 to −0.19), and decreased 24-hour opioid consumption (SMD −16.83, 95% CI −31.60 to −2.05). It also reduced rescue analgesia requirements (RR 0.51, 95% CI 0.35 to 0.76) and PONV incidence (RR 0.76, 95% CI 0.63 to 0.93) without increasing hallucinations (RR 1.11, 95% CI 0.41 to 3.03). A reduction in postoperative depressive symptoms was observed (SMD −0.67, 95% CI −1.29 to −0.05). Subgroup analyses suggested greater analgesic benefit with low-dose regimens (<0.5 mg/kg) and in biliary surgeries. Evidence certainty was low to very low for primary outcomes. Twenty-eight RCTs (3160 patients), all conducted in China, were included, which may limit the generalizability of the findings. Esketamine was associated with reductions in pain at rest (SMD −0.65, 95% CI −0.90 to −0.40) and during movement (SMD −0.64, 95% CI −1.09 to −0.19), and decreased 24-hour opioid consumption (SMD −16.83, 95% CI −31.60 to −2.05), although substantial heterogeneity was observed. It also reduced rescue analgesia requirements (RR 0.51, 95% CI 0.35 to 0.76) and PONV incidence (RR 0.76, 95% CI 0.63 to 0.93) without increasing hallucinations (RR 1.11, 95% CI 0.41 to 3.03). A reduction in postoperative depressive symptoms was observed (SMD −0.67, 95% CI −1.29 to −0.05). Subgroup analyses suggested greater analgesic effects with low-dose regimens (<0.5 mg/kg) and in biliary surgeries. Evidence certainty was low to very low for primary outcomes.

Conclusion: Perioperative intravenous esketamine may be associated with improvements in postoperative pain, opioid requirements, rescue analgesia, and PONV in laparoscopic surgery without increasing neuropsychiatric adverse events. However, the certainty of the evidence is low and substantial heterogeneity limits confidence in these estimates. Therefore, these findings should be interpreted with caution, and high-quality, international RCTs are needed to confirm efficacy and establish optimal dosing.

Keywords: esketamine, laparoscopic surgery, postoperative pain, systematic review, meta-analysis

Introduction

Postoperative pain remains a significant clinical challenge, with inadequate management contributing to patient suffering, delayed recovery, and the development of persistent postsurgical pain.[1] While opioids have traditionally been the cornerstone of postoperative analgesia, their use is fraught with well-documented adverse effects, including respiratory depression, sedation, nausea, vomiting, and the potential for misuse and dependence.[2] In response, the paradigm of

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postoperative care has shifted decisively towards multimodal analgesia, which combines non-opioid analgesics acting on different pain pathways to enhance pain control while minimizing opioid-related side effects.[3]

Laparoscopic surgery, while minimally invasive, is not pain-free. Patients can experience significant postoperative pain arising from diaphragmatic irritation, visceral manipulation, residual pneumoperitoneum, and incisional trauma.[4] Effective pain management is crucial to realizing the full benefits of enhanced recovery after surgery (ERAS) protocols, which are widely applied in laparoscopic procedures.[5] However, current ERAS guidelines for specific laparoscopic surgeries (eg, colorectal) offer only conditional recommendations for perioperative ketamine, citing low-quality evidence and uncertainty regarding optimal dosing and patient selection.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has long been recognized as a valuable adjunct in multimodal analgesia. By blocking NMDA receptors, ketamine inhibits central sensitization, a key mechanism in the development of hyperalgesia and allodynia, thereby providing potent analgesic and antihyperalgesic effects.[6] Previous meta-analyses of perioperative racemic ketamine have confirmed its ability to reduce postoperative pain and opioid consumption,[6] but its clinical utility remains limited by dose-dependent psychotomimetic side effects, such as hallucinations and nightmares.[7]

Esketamine, the S(+)-enantiomer of ketamine, has emerged as a potentially superior alternative. It possesses a three to four times greater affinity for the NMDA receptor than its R(-)-counterpart and approximately two times the potency of the racemic mixture.[8] Beyond this enhanced potency, esketamine exhibits distinct clinical differences, including faster plasma clearance and a potentially lower incidence of dysphoric hallucinations. Its recent regulatory approval for treatment-resistant depression further highlights its unique neuropharmacological profile.[9] Consequently, esketamine is increasingly being incorporated into multimodal regimens, including opioid-free anesthesia (OFA) protocols, as a core non-opioid agent to facilitate complete perioperative opioid avoidance. Intravenous esketamine is currently approved for clinical use in China and several European countries (including Germany, the United Kingdom, and France), while in the United States only the intranasal formulation (Spravato) has received FDA approval, highlighting the international relevance of this evidence synthesis.

Beyond its analgesic properties, esketamine's neuropharmacological profile provides a compelling rationale for including postoperative depressive symptoms as a clinically relevant outcome. New-onset postoperative depression affects an estimated 10–30% of surgical patients and is associated with increased pain chronification, prolonged recovery, and impaired quality of life. Perioperative neuroinflammation and dysregulation of glutamatergic signaling are recognized contributors to this vulnerability. Esketamine (Spravato®, intranasal formulation) received FDA and EMA approval for treatment-resistant depression in 2019, establishing that transient NMDA receptor modulation can produce rapid and sustained antidepressant effects. These mechanistic considerations justify the prospective examination of perioperative esketamine as a potential prophylactic strategy against post-surgical depression.[9]

Despite growing interest, the literature on perioperative esketamine in laparoscopic surgery remains fragmented and inconclusive. Key sources of heterogeneity across trials include wide variability in surgical invasiveness (eg, minor cholecystectomy vs major colectomy), the timing of esketamine administration (preoperative bolus vs intraoperative infusion vs postoperative continuation), and inconsistent outcome measures. Furthermore, it remains unclear whether esketamine offers clinically meaningful advantages over racemic ketamine beyond simple potency equivalence, and how its side-effect profile compares in the perioperative setting.

Therefore, we conducted this systematic review and meta-analysis of RCTs to critically evaluate the existing evidence regarding the efficacy and safety of perioperative intravenous esketamine in adult patients undergoing laparoscopic surgery. By explicitly addressing variability in surgical invasiveness, dosing regimens, and timing of administration, we aimed to provide a quantitative synthesis to inform clinical practice and future ERAS guideline development. The primary aims were to determine its effects on postoperative pain intensity and opioid consumption. Secondary aims included assessing its impact on the need for rescue analgesia, postoperative depressive symptoms, and adverse events, including postoperative nausea and vomiting (PONV) and neuropsychiatric effects.

Methods

Study Design

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[10] The PRISMA checklist is provided in Appendix 1. The study protocol was prospectively designed to evaluate the analgesic and psychological effects of perioperative esketamine administration in adult patients undergoing laparoscopic surgery.

Literature Search

A comprehensive literature search was conducted in PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from their inception to October 1, 2025. In addition, ClinicalTrials.gov registry was searched to identify ongoing or unpublished studies. The search strategy combined controlled vocabulary (eg, MeSH and Emtree terms) with free-text keywords related to esketamine, ketamine enantiomers, and laparoscopic surgery, and was adapted for each database as needed. No restrictions were applied for language, publication year, or surgical subspecialty. Reference lists of all included studies and relevant reviews were additionally screened to identify further eligible trials. The full search strategy is provided in Appendix 2.

Eligibility Criteria

We included randomized controlled trials (RCTs) enrolling adults (≥18 years) undergoing any laparoscopic surgery that reported at least one predefined outcome, comparing perioperative intravenous esketamine with placebo or standard analgesic management, with no restrictions on anesthesia, multimodal analgesia, or surgical subspecialty. We excluded non-randomized studies, observational designs, case reports, pediatric studies, and trials without a placebo or standard-care control group. No language restrictions were applied.

Outcomes Measures

The primary outcomes of this study were postoperative pain intensity (at rest and during movement within 72 hours after surgery) and postoperative opioid consumption within the first 24 hours. Pain scores assessed using validated instruments (eg, Visual Analog Scale [VAS] or Numeric Rating Scale [NRS]) were prioritized.[11] When different scales were used across studies, we harmonized scores via unit conversion or by pooling them as standardized mean differences, in line with Cochrane recommendations.[12]

Secondary outcomes included postoperative depressive symptoms measured using validated instruments (eg, Hospital Anxiety and Depression Scale [HADS]),[13] neuropsychiatric adverse events (including hallucinations and nightmares), postoperative nausea and vomiting (PONV), and use of rescue analgesia. Outcome extraction was performed according to prespecified time points detailed in the study protocol.

Study Screening and Data Extraction

Two reviewers (JL and XW) independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Discrepancies were resolved through discussion among the authors, and consensus was reached. Two reviewers also independently extracted data using a predefined template. Extracted variables included study characteristics, patient demographics, type of laparoscopic procedure, esketamine dose and timing, multimodal analgesia components, pain scores, opioid consumption, psychological outcomes, and adverse events. For continuous outcomes, we extracted means and standard deviations (SDs) when available. When studies reported medians and interquartile ranges instead of means and SDs, we estimated these values using validated methods described by Luo et al and McGrath et al.[14,15]

Risk of Bias Assessment

Two reviewers (JL and XW) independently assessed risk of bias using the Cochrane Risk of Bias Tool.[16] The assessment covered the following domains: sequence generation, allocation concealment, blinding of participants and personnel,

blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Each domain was rated as having low, unclear, or high risk of bias, and an overall risk-of-bias judgment was assigned to each study.

Data Analysis

Meta-analyses were performed using R (version 4.5.1)[17] with the meta[18] and metafor[19] packages. For continuous outcomes, we calculated standardized mean differences (SMD) with 95% confidence intervals (CI) when different scales were used, or MD when the same scale was used. For outcomes reported in heterogeneous units across studies (eg, opioid consumption measured in micrograms of sufentanil in some studies and milligrams of tramadol or morphine in others), the SMD is unitless and standardizes each study by its own within-group standard deviation; under such conditions, the magnitude of the pooled SMD should be interpreted with particular caution alongside the I^2 statistic and confidence interval width. For dichotomous outcomes, risk ratios (RR) using the Mantel–Haenszel method were computed. A random-effects model was applied due to expected clinical heterogeneity related to surgical type, anesthetic regimen, and esketamine dosing. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test, with I^2 values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively.[20] Publication bias was assessed using funnel plots and Egger's test[21] when ≥10 studies were available for an outcome.

Subgroup analyses were prespecified to explore potential sources of clinical heterogeneity. We planned subgroup analyses based on: (1) type of surgical system, categorized as biliary, gastrointestinal, gynecological, urological, bariatric, or mixed/general abdominal surgery; and (2) esketamine dose, dichotomized into low-dose (<0.5 mg/kg) and high-dose (≥0.5 mg/kg).

Sensitivity analyses were conducted to test the robustness of the pooled estimates. We repeated the meta-analyses by sequentially excluding studies with high risk of bias, studies with unclear or unreported esketamine dosing, and studies contributing extreme effect sizes.

Grading of Evidence

The certainty of evidence was evaluated and negotiated by two authors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.[22] In accordance with GRADE guidance, evidence from RCTs was initially rated as high certainty and then downgraded when concerns in any of these domains were identified.[23]

Results

A total of 1847 records were identified through database searches and registry screening. After removing duplicates (n = 487), 1360 titles and abstracts were screened, and 142 full-text articles were assessed for eligibility. Ultimately, 28 RCTs met the inclusion criteria and were included in the review. The most common reasons for exclusion were non-RCT design (n = 45), pediatric population (n = 23), non-laparoscopic surgery (n = 19), and lack of relevant outcomes (n = 27). Detailed reasons for full-text exclusions are provided in Appendix 3. The PRISMA flowchart of this review is illustrated in Figure 1.

Study Characteristics

The 28 included randomized controlled trials were all conducted in China and enrolled a total of 3160 patients, with 1694 patients allocated to esketamine groups and 1466 patients to control groups. The studies were published between 2020 and 2025.

The laparoscopic procedures evaluated covered a wide spectrum of surgical specialties, including biliary surgery (10 trials),[24–32] gastrointestinal surgery (7 trials),[27,33–37] gynecological surgery (6 trials),[38–43] bariatric surgery (3 trials),[44–46] and urological surgery (2 trials).[47,48]

Esketamine was administered intravenously in all studies. With respect to dosing strategies, low-dose esketamine (<0.5 mg/kg) was used in the majority of trials, whereas high-dose regimens (≥0.5 mg/kg) were evaluated in approximately eight studies. Control groups received either placebo (normal saline) or standard analgesic regimens without esketamine.

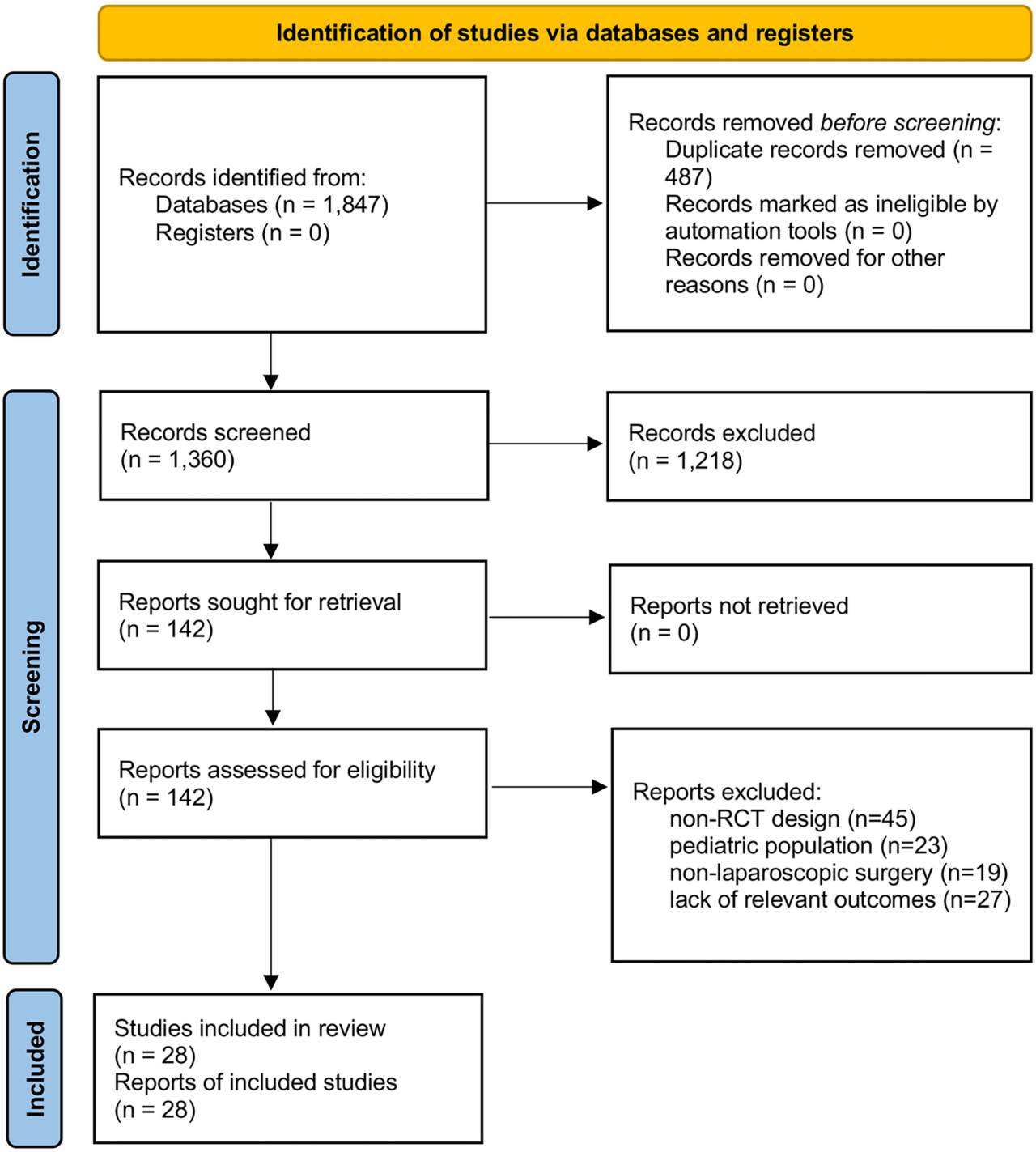

Figure 1 PRISMA 2020 Flow Diagram for Study Selection.
Notes: Adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/.

A multimodal analgesic background was employed in 27 of the 28 studies, typically consisting of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Key characteristics of the included studies are summarized in Table 1.

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Table 1 Characteristics of Included Studies

Study	Surgery Type	N (Esk/Ctrl)	Esketamine Intervention	Comparator	Outcomes Reported
Dai J 2025[44]	Laparoscopic bariatric surgery	40/80	IV bolus, 0.2 mg/kg (low-dose), single bolus	0.9% saline	PHQ-9, PONV
Deng B 2024[24]	Laparoscopic cholecystectomy	26/26	PCIA, 1.5 mg/kg (high-dose), postoperative	Dezocine 0.3 mg/kg	Opioid (24h), PONV, Hallucinations
Hu Y 2024[25]	Laparoscopic cholecystectomy	38/38	PCIA, 1 mg/kg (high-dose), postoperative	Sufentanil 2 μg/kg	Pain (rest), Opioid, Rescue, Depression, PONV, Hallucinations
Li G 2025[33]	Laparoscopic gastric cancer surgery	41/41	0.5 mg/kg loading + 0.12 mg/kg/h infusion (high-dose), intraoperative	Remifentanil + Sufentanil	Pain (rest), Opioid, Rescue, PONV
Li T 2025[34]	Laparoscopic colorectal surgery	64/32	IV bolus, 0.3 mg/kg (low-dose), after induction	Dexmedetomidine / Saline	Pain (rest), Opioid, Rescue, PONV
Liu J 2024[38]	Laparoscopic myomectomy	30/30/30/30	IV bolus, 0.2/0.3/0.5 mg/kg (dose-ranging), before incision	0.9% saline	Pain (rest), Opioid, Rescue, PONV, Hallucinations
Qi Y 2025[47]	Laparoscopic nephrectomy	53/53	Continuous infusion, 0.2 mg/kg/h (low-dose), intraoperative	Normal saline	Opioid (24h)
Qiu D 2022[39]	Laparoscopic myomectomy/ hysterectomy	92/91	Continuous infusion, 0.3 mg/kg/h (low-dose), intraoperative	Normal saline	Opioid, Depression
Ren L 2024[48]	Laparoscopic nephrectomy	33/35/35	Continuous infusion, 0.125/0.25 mg/kg/h (low-dose), intraoperative	Normal saline	Pain (movement), Opioid, Rescue, PONV
Shen Y 2025[40]	Gynecological laparoscopy (benign)	46/46	OFA, 0.3 mg/kg bolus (low-dose), at induction	Sufentanil 0.3 μg/kg	Pain (rest/movement), Opioid, PONV, Hallucinations
Sun Q 2023[41]	Laparoscopic total hysterectomy	50/50	Intraoperative infusion (dose NR)	Normal saline	NR
Tang J 2025[35]	Laparoscopic GI tumor resection	34/33	Continuous infusion, 0.2 mg/kg/h (low-dose), intraoperative	Normal saline	Pain (rest), Opioid
Tu K 2025[26]	Laparoscopic cholecystectomy	24/24	OFA with esketamine + dexmedetomidine (dose NR)	Sufentanil + remifentanil	NR
Wang H 2025[49]	Mixed laparoscopic abdominal surgery	100/100	Continuous infusion, 0.3 mg/kg/h (low-dose), intraoperative	Normal saline	PONV
Wang J 2020[42]	Laparoscopic radical hysterectomy	104/104/104/ 105	IV bolus, 0.25/0.5 mg/kg + racemic 0.5 mg/kg, 1h post-induction	Normal saline 50mL	Pain (rest), Depression
Wang J 2023[36]	Laparoscopic GI cancer resection	31/32/32	PCIA, 0.5/1 mg/kg (high-dose), postoperative	Sufentanil PCIA	Pain (rest/movement), Opioid, Rescue, PONV, Hallucinations
Wang W 2025[50]	Laparoscopic major abdominal surgery	80/77	Continuous infusion, 0.2–0.5 mg/kg/h (mixed dose), intraoperative	Remifentanil	Pain (rest), Rescue, PONV
Wu Y 2025[27]	Laparoscopic cholecystectomy	43/43	Continuous infusion, 0.5 mg/kg/h (high-dose), intraoperative	Normal saline	Pain (rest/movement), Opioid, Rescue, PONV, Hallucinations
Xu Y 2023[51]	Laparoscopic colorectal cancer resection	45/43	0.25 mg/kg loading + 0.12 mg/kg/h (low-dose), intraoperative	Saline	Opioid, Rescue, PONV, Hallucinations
Xu Z 2023[28]	Laparoscopic cholecystectomy	27/27	IV bolus, 0.3 mg/kg (low-dose), before incision	Saline	Pain (rest/movement), Rescue, PONV, Hallucinations
Yu JM 2023[29]	Laparoscopic cholecystectomy (3-port)	75/75	0.25 mg/kg bolus + 0.25 mg/kg/h infusion (low-dose), perioperative	Remifentanil infusion	Pain (rest), Opioid, PONV
Zhang C 2022[30]	Laparoscopic cholecystectomy	23/24	IV bolus, 0.2 mg/kg (low-dose), at induction	Normal saline	PONV
Zhang J 2023[45]	Laparoscopic bariatric surgery	35/35	Continuous infusion, 0.5 mg/kg/h (high-dose), intraoperative	Normal saline	NR
Zhang J 2025[43]	Laparoscopic hysterectomy	53/53	IV bolus, 0.25 mg/kg (low-dose), at induction	Normal saline	NR
Zhang X 2025[31]	Laparoscopic cholecystectomy	70/70	IV bolus, 0.3 mg/kg (low-dose), before incision	Normal saline	Pain (rest), Rescue, Depression, PONV
Zhang Y 2025[37]	Laparoscopic GI tumor surgery	70/70	0.2 mg/kg ×2 IV + 0.02 mg/kg/h PCIA (low-dose)	Saline	NR
Zhao L 2024[32]	Laparoscopic cholecystectomy	30/30/30	0.5/1.0 mg/kg loading + continuous infusion (high-dose)	Normal saline	Hallucinations
Zhou X 2024[46]	Laparoscopic sleeve gastrectomy	39/36	OFA, 0.2 mg/kg bolus + 0.2 mg/kg/h infusion (low-dose)	Sufentanil-based	Rescue, PONV

Abbreviations: Esk, esketamine; Ctrl, control; GI, gastrointestinal; Gyn, gynecological; NR, not reported; OFA, opioid-free anesthesia; PCIA, patient-controlled intravenous analgesia; PONV, postoperative nausea and vomiting.

Risk of Bias Assessment

The detailed risk of bias assessment for the 28 included studies is provided in Appendix 4 and Appendix 5. Random sequence generation was generally well reported, with most studies (89.3%) rated as low risk.[24,25,27–38,49] In contrast, allocation concealment was poorly described; only 10.7% of studies reported adequate concealment procedures,[32,39,50] and the remainder were judged unclear.

Blinding was also a common methodological limitation. For blinding of participants and personnel, only one-quarter of studies were rated as low risk.[25,27,28,31,32,39,51] Similarly, blinding of outcome assessment was adequately performed in only a quarter of trials.[25,27,28,31,32,39,51] Many studies either did not report blinding methods or used designs where blinding was difficult—particularly those involving active comparators or subjective outcomes such as pain—leading to frequent unclear or high-risk judgments for performance and detection bias.

Incomplete outcome data were generally well handled, with 92.9% of trials judged at low risk.[24,25,27–38,40,42–48,50–54] In contrast, selective reporting was often rated as unclear due to unavailable or unregistered study protocols; only 10.7% of trials demonstrated clearly low reporting bias.[27,39,50] Other sources of bias were uncommon, aside from occasional concerns such as imbalanced group sizes.

Overall, the methodological quality was mixed. Although randomization processes were typically sound, insufficient reporting of allocation concealment and blinding contributed to predominantly unclear or high overall risk of bias across the evidence base.

Primary Outcomes

The certainty of evidence for each outcome was evaluated using the GRADE approach and is summarized in Table 2.

Postoperative Pain Intensity

At Rest (24 Hours)

The pooled analysis of 13 studies demonstrated that esketamine significantly reduced postoperative pain at rest compared to control, with a large effect size (Standardized Mean Difference [SMD] = −0.65, 95% CI: −0.90 to −0.40; I^2 = 84.8%;

Table 2 Summary of Findings

Outcome (Time Frame)	№ of Participants (Studies)	Effect Estimate (95% CI)	Certainty of the Evidence (GRADE)*	Comments
Postoperative pain at rest (24h)	1332 (13 RCTs)	SMD −0.65 (−0.90 to −0.40)	⊕◯◯◯ VERY LOW[a,b,g]	The effect on pain at rest is very uncertain.
Postoperative pain during movement (24h)	361 (5 RCTs)	SMD −0.64 (−1.09 to −0.19)	⊕⊕◯◯ LOW[a,b,h]	Esketamine may reduce pain during movement.
Postoperative opioid consumption (24h)	1269 (14 RCTs)	SMD −16.83 (−31.60 to −2.05)	⊕◯◯◯ VERY LOW[a,b,c,g]	The effect on opioid use is very uncertain.
Rescue analgesia	1137 (12 RCTs)	RR 0.51 (0.35 to 0.76)	⊕⊕⊕◯ MODERATE[d]	Esketamine likely reduces the need for rescue analgesia.
Postoperative depressive symptoms	608 (4 RCTs)	SMD −0.67 (−1.29 to −0.05)	⊕◯◯◯ VERY LOW[a,e,f,h]	The effect on depressive symptoms is very uncertain.
Postoperative nausea and vomiting (PONV)	1586 (16 RCTs)	RR 0.76 (0.63 to 0.93)	⊕⊕⊕◯ MODERATE[a]	Esketamine likely reduces PONV.
Hallucinations	727 (8 RCTs)	RR 1.11 (0.41 to 3.03)	⊕⊕⊕◯ MODERATE[c,h]	Esketamine probably results in little to no difference in hallucinations.

Notes: *⊕ represents a full level of evidence, and ◯ represents a missing level. Thus, ⊕⊕⊕◯ indicates moderate-certainty evidence (the true effect is likely close to the estimate, but there is a possibility it is substantially different), ⊕⊕◯◯ indicates low-certainty evidence (our confidence is limited), and ⊕◯◯◯ indicates very low-certainty evidence (we have very little confidence). The full GRADE quality ratings are defined as follows: high (⊕⊕⊕⊕), moderate (⊕⊕⊕◯), low (⊕⊕◯◯), and very low (⊕◯◯◯). [a]Downgraded one level for risk of bias: >30% of contributing studies had high risk of bias, with majority having unclear risk in key domains. [b]Downgraded one level for inconsistency: considerable statistical heterogeneity (I^2 > 75%) was present. [c]Downgraded one level for imprecision: the 95% confidence interval is wide and includes values that suggest both significant benefit and negligible effect. [d]Downgraded one level for inconsistency: moderate statistical heterogeneity (I^2 ~60%) was present. [e]Downgraded one level for inconsistency: considerable statistical heterogeneity (I^2 > 85%) was present. [f]Downgraded one level for imprecision: the estimate is based on a small number of studies and patients, with a wide confidence interval. [g]Downgraded one level for high risk of publication bias: Eggers' test indicates the presence of funnel plot asymmetry ($p < 0.05$). [h]As the meta-analysis included less than 10 studies, we were unable to detect publication bias.

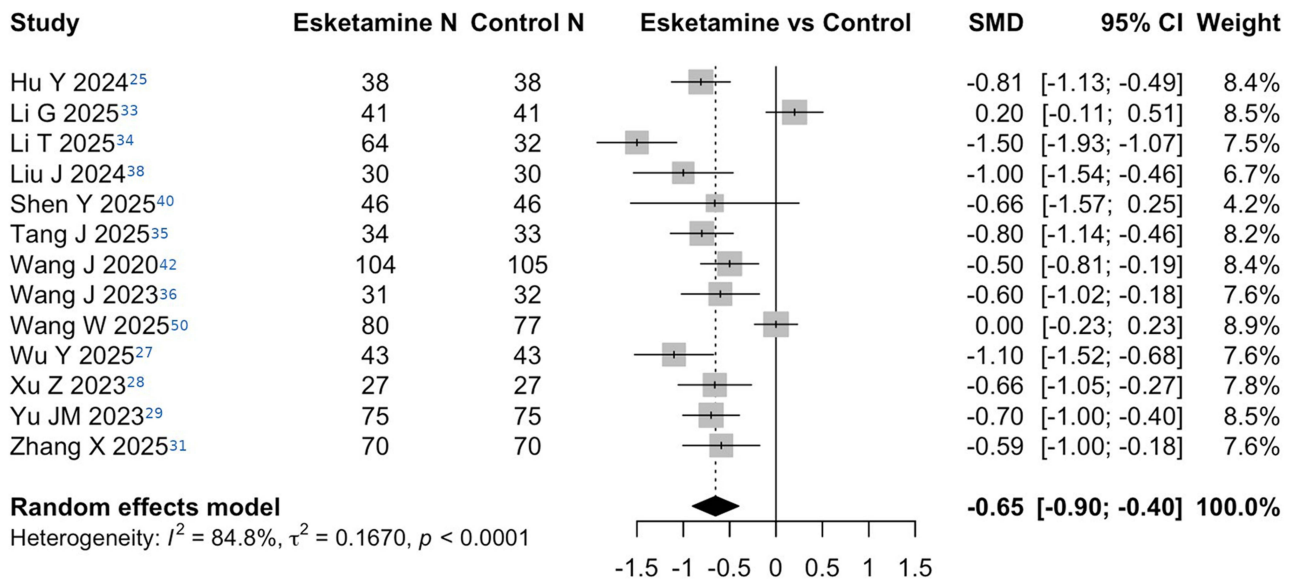

Figure 2 Forest Plot of the Effect of Esketamine on Postoperative Pain at Rest.
Notes: A negative SMD favors the esketamine group (lower pain scores). The diamond represents the overall pooled estimate from the random-effects model. The size of the data markers corresponds to the study's weight in the meta-analysis. Bold values in the bottom row indicate the overall pooled random-effects model estimate (summary statistic, 95% CI, and cumulative weight).
Abbreviation: SMD, Standardized Mean Difference.

forest plot in Figure 2; very low certainty evidence).[25,27,29,31,33–36,38,40,42,50,53] Publication bias is suspected (p = 0.049; funnel plot of pain at rest in Appendix 6).

During Movement (24 Hours)

Data from 5 studies showed that esketamine also significantly reduced dynamic pain (SMD = −0.64, 95% CI: −1.09 to −0.19; p = 0.0049; I^2 = 75.6%; forest plot in Figure 3; low certainty evidence).[27,28,36,40,48]

Postoperative Opioid Consumption

Meta-analysis of 14 studies found that esketamine administration led to a significant reduction in 24-hour postoperative opioid consumption (SMD = −16.83, 95% CI: −31.60 to −2.05; p = 0.0256; I^2 = 96.7%; forest plot in Figure 4; very low certainty evidence).[24,25,27,29,33–36,38–40,47,48,51] Publication bias is suspected (p = 0.003; funnel plot of postoperative opioid consumption in Appendix 7). Note that the large absolute SMD for this outcome (SMD = −16.83) reflects the

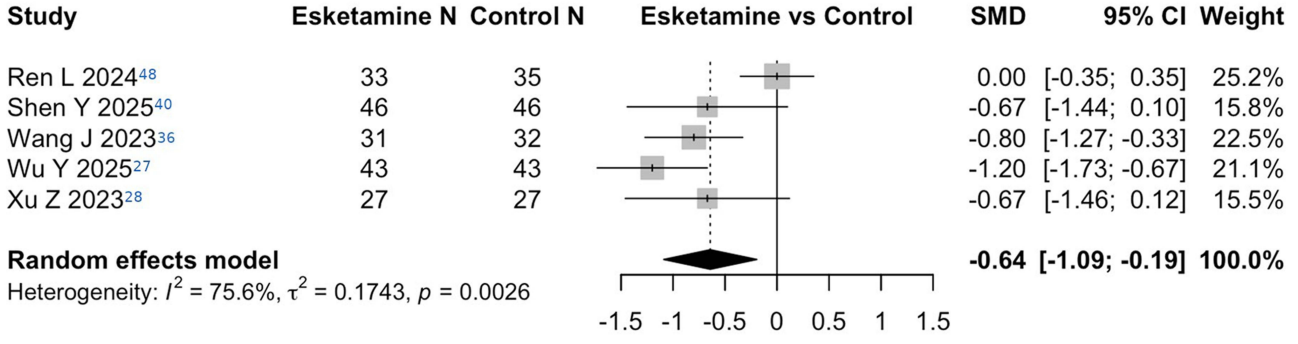

Figure 3 Forest Plot of the Effect of Esketamine on Postoperative Pain during Movement.
Notes: A negative SMD favors the esketamine group (lower pain scores). The diamond represents the overall pooled estimate from the random-effects model. The size of the data markers corresponds to the study's weight in the meta-analysis. Bold values in the bottom row indicate the overall pooled random-effects model estimate (summary statistic, 95% CI, and cumulative weight).
Abbreviation: SMD, Standardized Mean Difference.

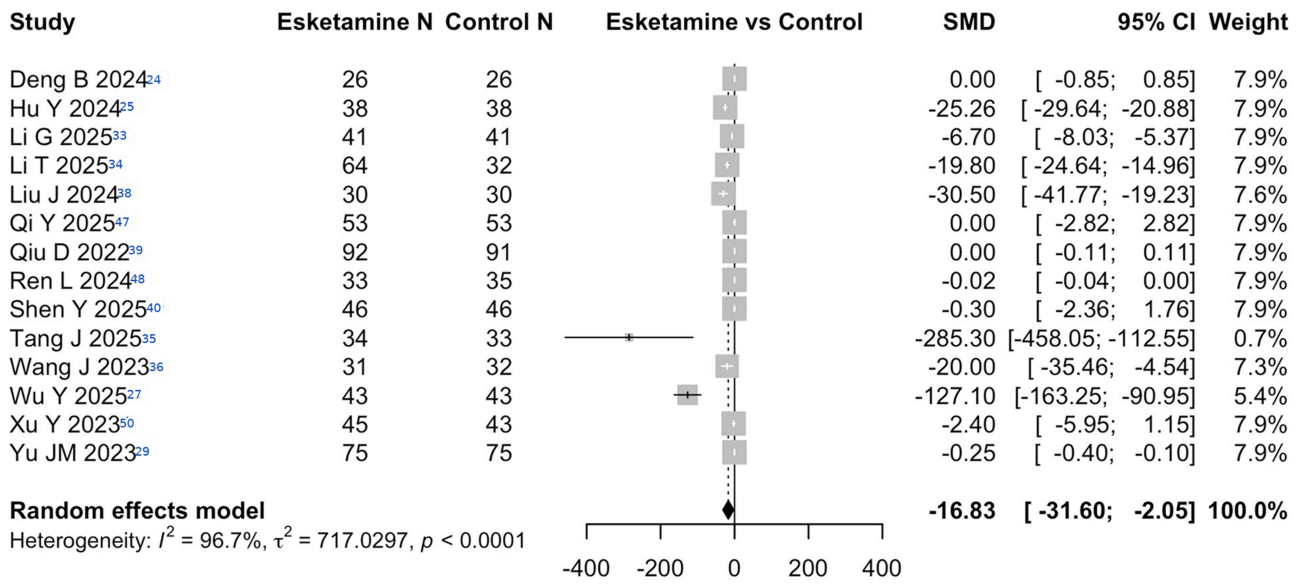

Figure 4 Forest Plot of the Effect of Esketamine on on 24-Hour Postoperative Opioid Consumption.
Notes: A negative SMD favors the esketamine group (lower opioid consumption). The diamond represents the overall pooled estimate from the random-effects model. The size of the data markers corresponds to the study's weight in the meta-analysis. Bold values in the bottom row indicate the overall pooled random-effects model estimate (summary statistic, 95% CI, and cumulative weight).
Abbreviation: SMD, Standardized Mean Difference.

heterogeneity in opioid measurement units across studies rather than an implausible effect size; the SMD standardizes each study by its own within-group variability, and its magnitude is therefore not directly interpretable as a - Cohen's d effect size. The very wide confidence interval and I^2 = 96.7% indicate that this pooled estimate should be treated as a directional signal only.

Secondary Outcomes

Rescue Analgesia

Patients receiving esketamine were significantly less likely to require rescue analgesia postoperatively (Risk Ratio [RR] = 0.51, 95% CI: 0.35 to 0.76; p = 0.0008; I^2 = 59.6%; forest plot in Figure 5; moderate certainty of evidence).[25,27,28,31,33,34,36,38,40,46,48,50,53] The funnel plot (Appendix 8) appeared symmetric, and Egger's test was not significant (p = 0.644), indicating low risk of publication bias.

Postoperative Depressive Symptoms

Pooled data from 4 studies indicated a statistically significant reduction in postoperative depressive symptoms with esketamine (SMD = −0.67, 95% CI: −1.29 to −0.05; p = 0.0349; I^2 = 85.9%; forest plot in Figure 6; very low certainty of evidence).[25,31,39,42]

Adverse Events

Postoperative Nausea and Vomiting (PONV)

Analysis of 17 studies showed that esketamine was associated with a significantly lower incidence of PONV compared to control (RR = 0.76, 95% CI: 0.63 to 0.93; p = 0.0071; I^2 = 11.0%; forest plot in Appendix 9; moderate certainty of evidence).[24,25,27–31,33,34,36,38,40,46,48,50,51,53] The funnel plot (Appendix 10) appeared symmetric, and Egger's test was not significant (p = 0.719), indicating low risk of publication bias.

Hallucinations

The incidence of hallucinations was low and not significantly different between the esketamine and control groups (RR = 1.11, 95% CI: 0.41 to 3.03; p = 0.8355; I^2 = 0; forest plot in Appendix 11).[24,25,27,28,32,36,38,40,50]

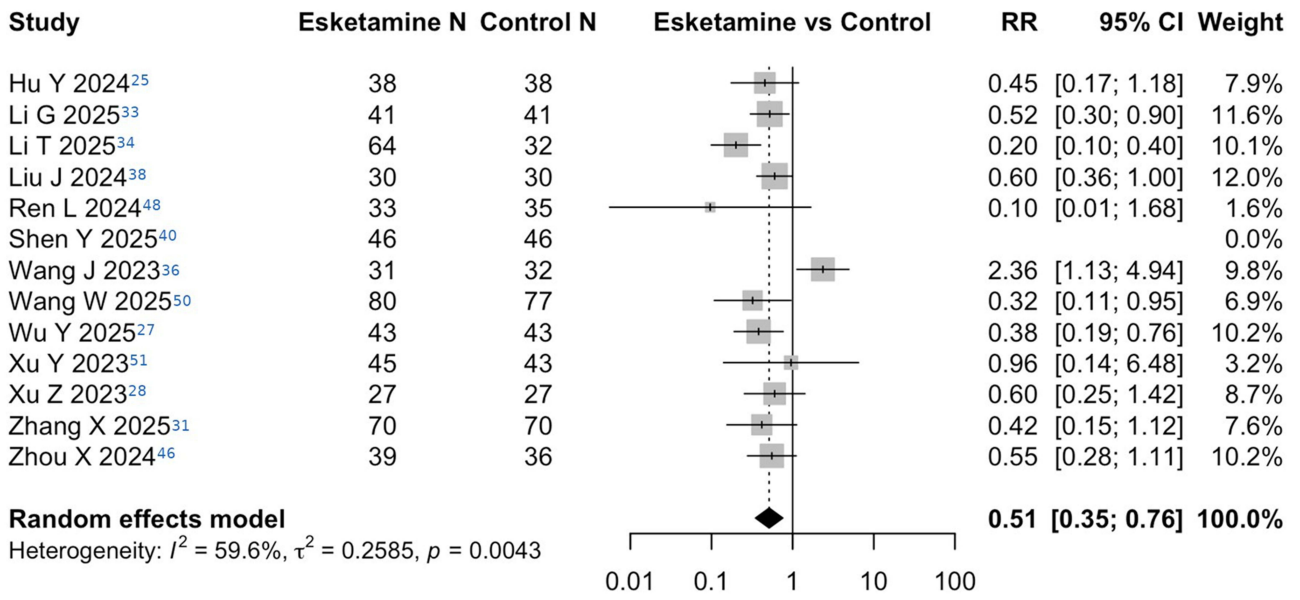

Figure 5 Forest Plot of the Effect of Esketamine on the Use of Postoperative Rescue Analgesia.
Notes: A Risk Ratio < 1.0 favors the esketamine group (lower risk of requiring rescue analgesia). The analysis was performed using a random-effects model (Mantel-Haenszel method). The size of the data markers corresponds to the study's weight in the meta-analysis. Bold values in the bottom row indicate the overall pooled random-effects model estimate (summary statistic, 95% CI, and cumulative weight).
Abbreviation: RR, Risk Ratio.

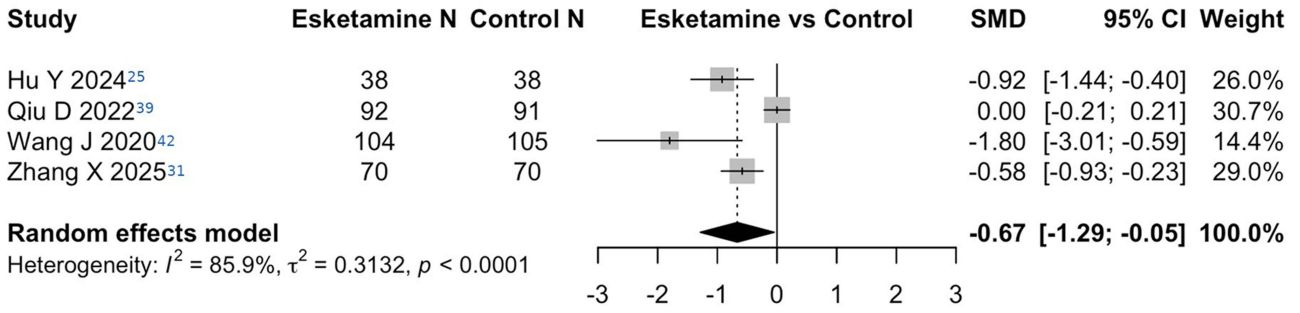

Figure 6 Forest Plot of the Effect of Esketamine on Postoperative Depressive Symptoms.
Notes: A negative SMD favors the esketamine group (lower depression scores). The size of the data markers corresponds to the study's weight in the meta-analysis. Bold values in the bottom row indicate the overall pooled random-effects model estimate (summary statistic, 95% CI, and cumulative weight).
Abbreviation: SMD, Standardized Mean Difference.

Subgroup Analyses

Subgroup analysis based on surgical type revealed statistically significant differences in the effect of esketamine on postoperative pain at rest (test for subgroup differences: $p < 0.0001$). The most pronounced benefit was observed in biliary surgery (SMD = −0.76, 95% CI: −0.92 to −0.60; 5 studies; $I^2 = 0\%$), indicating a large, consistent effect with no heterogeneity. Significant benefits were also seen in gynecological surgery (SMD = −0.67, 95% CI: −1.04 to −0.31; 3 studies) and gastrointestinal surgery (SMD = −0.67, 95% CI: −1.35 to 0.02; 4 studies), though the latter showed substantial heterogeneity ($I^2 = 93.2\%$) and a confidence interval crossing the null. Notably, the single study of mixed/general abdominal surgery showed no benefit (SMD = 0.00, 95% CI: −0.23 to 0.23). The forest plot is in Appendix 12.

Analysis by esketamine dosing regimen also showed significant subgroup differences ($p < 0.0001$). Contrary to expectations of a dose-response relationship, low-dose esketamine (<0.5 mg/kg) demonstrated a larger effect size (SMD = −0.85, 95% CI: −1.09 to −0.60; 7 studies) compared to high-dose esketamine (≥0.5 mg/kg; SMD = −0.55, 95% CI: −0.98 to −0.12; 5 studies). Both subgroups showed significant heterogeneity ($I^2 = 52.5\%$ and 87.4%, respectively). The single study using mixed dosing showed no benefit. The forest plot is in Appendix 13.

Sensitivity Analyses

To assess the robustness of the primary findings, we conducted several pre-specified sensitivity analyses. The results confirmed that the pooled estimates for postoperative pain at rest and 24-hour opioid consumption were not materially altered by the analytical approach or the inclusion of studies with specific methodological characteristics.

Discussion

This systematic review and meta-analysis of 28 studies demonstrates that perioperative intravenous esketamine is an effective analgesic adjunct in adult patients undergoing laparoscopic surgery. The primary findings indicate that esketamine significantly reduces postoperative pain intensity, 24-hour opioid consumption, and the need for rescue analgesia. Furthermore, it is associated with a favorable side-effect profile, notably a significant reduction in PONV without a corresponding increase in neuropsychiatric adverse events such as hallucinations. A potential beneficial effect on postoperative depressive symptoms was also observed, although this finding is based on limited data. Crucially, the certainty of this evidence varies, allowing for more confident conclusions in some areas than others.

Main Findings and Interpretation

The reduction in pain scores at rest (SMD −0.65) and during movement (SMD −0.64) may represent a clinically meaningful improvement, consistent with established thresholds for minimal clinically important differences in pain scores;[55] however, the substantial heterogeneity reduces confidence in the magnitude and consistency of this effect. This subjective improvement is corroborated by objective measures: a significant reduction in opioid consumption and a nearly 50% lower likelihood of requiring rescue analgesia (RR 0.51). The concordance across these patient-centered outcomes suggests a potential clinical benefit, although the high between-study heterogeneity limits the certainty of this inference. Additionally, the conclusion should be interpreted cautiously given the exclusively China-based evidence base, which may not fully reflect global clinical practice.

The finding that esketamine reduces PONV (RR 0.76) is particularly significant. While often considered an opioid-sparing effect, it is noteworthy that this benefit persisted despite the overall reduction in opioid use, suggesting esketamine may have independent antiemetic properties, possibly through its action on other receptors, such as the dopamine D2 receptor.[56] Importantly, and consistent with its improved side-effect profile over racemic ketamine, esketamine was not associated with an increased risk of hallucinations. This is a critical finding for clinicians, as it mitigates a primary concern regarding the perioperative use of ketamine derivatives.

Our results align with and extend the findings of previous meta-analyses on perioperative ketamine and esketamine. While earlier reviews on racemic ketamine established its opioid-sparing and analgesic effects,[6,56] our study specifically focuses on the S-enantiomer, which possesses a higher affinity for the NMDA receptor.[8] The consistency of our positive results with those for racemic ketamine reinforces the central role of NMDA receptor antagonism in mediating these effects. However, our finding of a significant reduction in PONV appears more pronounced than what is typically reported for racemic ketamine, potentially reflecting esketamine's cleaner pharmacological profile.

Furthermore, our observation of a potential positive effect on postoperative depressive symptoms, while preliminary, is biologically plausible. Esketamine is a licensed antidepressant, and its transient modulation of glutamatergic signaling may help counteract the neuroinflammatory and dysphoric states that can follow surgical stress and anesthesia [Citation]. This represents a novel dimension to its perioperative utility that warrants dedicated investigation.

Subgroup Analyses and Exploration of Heterogeneity

The significant heterogeneity observed in our primary analyses was expected, given the clinical diversity of the included studies. Our pre-specified subgroup analyses provided valuable insights into potential sources of this variation.

The finding of a procedure-specific effect, with the most consistent and homogeneous benefit seen in biliary surgery, is intriguing. This may be related to the specific somatic and visceral pain components of upper abdominal procedures like cholecystectomy, which could be particularly sensitive to NMDA receptor blockade. The substantial heterogeneity

within the gastrointestinal surgery subgroup suggests other unmeasured factors, such as the extent of surgical manipulation or variations in anastomosis creation, may modulate esketamine's efficacy.

Perhaps the most unexpected finding was the apparent superior efficacy of low-dose esketamine (<0.5 mg/kg) compared to high-dose regimens. This contradicts a simple linear dose-response relationship and suggests a potential "ceiling effect" for analgesic benefit, beyond which increased doses do not confer additional advantage and may even introduce countervailing effects that blunt the net clinical benefit. This underscores the importance of adhering to lower, potentially safer doses to achieve optimal analgesic outcomes, a finding with direct clinical applicability.

Limitations

Several limitations of this review must be acknowledged when interpreting its findings. First, and most importantly, the evidence base is geographically homogeneous, as all 28 included RCTs were conducted in China. This represents a major limitation that substantially restricts the external validity of our findings. Differences in genetic background, perioperative care pathways, anesthetic practices, and opioid prescribing patterns may limit the generalizability of these results to other populations and healthcare systems. Second, methodological concerns affect the certainty of the evidence. Many included studies had an unclear or high risk of bias in key domains such as allocation concealment and blinding, and considerable statistical heterogeneity (eg, $I^2 > 75\%$ for pain and opioid outcomes) persisted despite our subgroup analyses. This led to a low or very low GRADE certainty rating for the primary outcomes of pain reduction and opioid sparing, meaning the magnitude of benefit is uncertain. Third, the exploratory subgroup analyses require cautious interpretation. While low-dose esketamine (<0.5 mg/kg) showed a larger effect size, this observation is confounded by variations in administration methods (bolus vs infusion) across studies and high within-subgroup heterogeneity. These findings should be viewed as hypothesis-generating rather than definitive proof of differential efficacy. Finally, although the direction of effect was consistently positive, the extremely high heterogeneity observed in key outcomes (eg, $I^2 = 96.7\%$ for opioid consumption) raises concerns about the appropriateness and interpretability of pooled estimates. Under such conditions, summary effect sizes should be interpreted as indicative rather than definitive, and may not reflect a consistent treatment effect across clinical settings.

Clinical and Research Implications

The findings of this review have direct implications for clinical practice. Esketamine may be considered as a potential component of multimodal analgesia,[3] although the current evidence is of low certainty and does not support definitive clinical recommendations. Our data support the use of low-dose esketamine protocols (eg, <0.5 mg/kg), which appear to provide optimal efficacy while minimizing the risk of adverse effects.

For researchers, this review highlights critical knowledge gaps. Future studies should:

1. Be adequately powered, multicenter RCTs that compare specific esketamine dosing regimens head-to-head.
2. Standardize the reporting of outcomes, especially opioid consumption (using morphine milligram equivalents), to reduce heterogeneity.
3. Prospectively investigate the potential prophylactic antidepressant effects of perioperative esketamine in surgical populations at risk for postoperative depression.
4. Explore the mechanisms behind its antiemetic effects.

Conclusion

In conclusion, while this meta-analysis suggests that perioperative esketamine may offer benefits in laparoscopic surgery, including reduced rescue analgesia and PONV, the findings should be interpreted with caution given the geographic concentration of the evidence and limited generalizability. However, the certainty of the evidence is limited by substantial heterogeneity and methodological concerns. Therefore, these findings should be interpreted cautiously, and definitive conclusions regarding efficacy and optimal use cannot yet be established.

Disclosure

The authors report no conflicts of interest in this work.

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