Systematic Review

Comparative Efficacy of Dexmedetomidine and Esketamine on Postoperative Sleep Disturbances and Analgesia: A Systematic Review and Network Meta-Analysis

Ting Jiang, MBBS[1-4], Rui Zhao, MBBS[1-3], Yingli Zhang, MBBS[1-3], Rui Zhang, MBBS[1-3], Xiuqing Wu, MBBS[1,3], Lina Jin, MBBS[1,3], Yukun Huang, MBBS[5], Yiwei Zhang, MD[1-3], Wojciech Czyżewski, MD[6,7], Grzegorz Staśkiewicz, MD[8], Karol Pruszyński, MD[9], Changshun Huang, MD[1,2], and Binbin Zhu, MD[1-3,10]

From: [1]Department of Anaesthesiology, First Affiliated Hospital of Ningbo University, Ningbo, China; [2]Anaesthesia and Pain Treatment Clinic in Bund Campus, First Affiliated Hospital of Ningbo University, Ningbo, China; [3]Health Science Center, Ningbo University, Ningbo, China; [4]Lanxi People's Hospital, Jinhua, China; [5]Medical School, Chinese University of Hong Kong, Shenzhen, China; [6]Department of Neurosurgery, Maria Sklodowska-Curie National Research Institute of Oncology, ul. W.K. Roentgena, Warsaw, Poland; [7]Department of Didactics and Medical Simulation, Medical University of Lublin, Chodzki, Lublin, Poland; [8]Department of Radiology, Medical University of Lublin, Jaczewskiego, Lublin, Poland; [9]Department of Surgical Oncology, Medical University of Lublin, Lublin, Poland; [10]Ningbo Key Laboratory of Human Microbiology and Precision Medicine, Ningbo, China

Address Correspondence:
Binbin Zhu, MD
Department of Anaesthesiology, First Affiliated Hospital of Ningbo University,
Road 247#, Jiangbei District, 315000, Ningbo, China
E-mail: pingchi1983@126.com

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Background: Postoperative sleep disturbance (PSD) is a complication that often follows surgery. The condition is closely associated with impaired recovery, heightened pain sensitivity, and increased risk of chronic postsurgical pain. While pharmacological interventions like dexmedetomidine and esketamine have been reported to improve perioperative sleep quality, their comparative efficacy—particularly in the realm of analgesia—remains uncertain.

Objectives: This review aimed to evaluate the efficacy of dexmedetomidine and esketamine in treating PSDs and providing analgesia.

Study Design: We conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs) that compared the effects of dexmedetomidine, esketamine, and control interventions on adult surgical patients.

Setting: Comprehensive literature searches were performed in 4 electronic databases from their inception to August 1st, 2025. The protocol was previously registered in the PROSPERO database under the registration number CRD420251126227.

Methods: The primary outcomes were postoperative pain scores assessed using the Visual Analog Scale (VAS) at 24 and 48 hours. Secondary outcomes included the incidence of PSD, Athens Insomnia Scale (AIS) scores, and sleep quality measured on the Numerical Rating Scale (NRS). Subjective sleep outcomes were synthesized using a Bayesian network meta-analysis. Additionally, a supplementary traditional meta-analysis was performed on studies that used polysomnography (PSG) to evaluate objective sleep architecture.

Results: Ten RCTs involving 645 patients were included in the study. Esketamine demonstrated significantly superior analgesic efficacy, substantially reducing VAS pain scores both at rest and during movement at 24 and 48 hours postoperatively. Compared to the control, both esketamine and dexmedetomidine showed a tendency to reduce the incidence of PSD on the first postoperative day (esketamine: risk ratio [RR] = 0.655, 95% credible interval [CrI]: 0.517-0.798; dexmedetomidine: RR = 0.773, 95% CrI: 0.434-1.23) and improved AIS and NRS scores. A supplementary meta-analysis of 4 PSG studies (n = 182 patients) indicated that dexmedetomidine increased the percentage of stage N2 sleep (mean difference [MD] = 13.0%, 95% confidence interval [CI]: -5.2 to 31.2) and the odds of experiencing stage N3 sleep, although the latter finding was not statistically significant (odds ratio [OR] = 2.99, 95% CI: 0.61 to 14.66).

Limitations: The primary limitation on this study is that the trials included were all conducted in China.

Conclusions: Both dexmedetomidine and esketamine improve postoperative sleep quality

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effectively. Esketamine demonstrates superior analgesic efficacy and has the higher probability being the optimal treatment for reducing early PSD incidence. In contrast, dexmedetomidine appears to objectively improve sleep architecture by promoting N2 sleep. The superior analgesic profile of esketamine likely underpins its enhanced subjective sleep benefits.

Key words: Dexmedetomidine, esketamine, analgesia, sleep disturbance, postoperative sleep, network meta-analysis, systematic review, agent

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Postoperative sleep disturbance (PSD) is increasingly recognized as a common and clinically significant complication experienced by surgical patients (1,2). The reported incidence of PSD ranges from 30% to 60%, varying with surgery type, anesthesia regimen, and patient characteristics (2). Sleep disruption not only impedes early recovery but is also linked to heightened pain perception, an increased incidence of postoperative delirium, and prolonged hospital stays (2,3). Crucially, perioperative pain is a major driver of PSD, and conversely, PSD can exacerbate pain sensitivity, establishing a vicious cycle (4,5). In the long term, PSD may predispose patients to persistent sleep disorders and chronic postsurgical pain, underscoring the critical need for perioperative strategies that address both sleep quality and pain control concurrently (5).

The pathophysiology of PSD is multifactorial. Surgical trauma, perioperative pain, opioid use, and dysregulation of circadian rhythms contribute to impaired sleep architecture (2). Conventional pharmacological approaches, such as benzodiazepines or nonbenzodiazepine hypnotics, often carry risks of respiratory depression, tolerance, or delirium, thus limiting the perioperative utility of these medications (6). Consequently, anesthesiologists have turned their attention to agents possessing sedative or analgesic properties that also modulate sleep physiology.

Dexmedetomidine, a highly selective α2-adrenergic receptor agonist, produces sedation resembling natural nonrapid eye movement (NREM) sleep (7). This drug has demonstrated potential to improve sleep continuity and reduce opioid requirements in the perioperative setting, with its analgesic effects being largely indirect (8). Esketamine, the S-enantiomer of ketamine and an N-methyl-D-aspartate (NMDA) receptor antagonist, exerts direct analgesic and rapid antidepressant effects by binding to the NMDA receptor and blocking the inward flow of calcium ions, inhibiting central sensitization and pain signaling (9). Emerging evidence suggests that esketamine may also enhance postoperative sleep quality by attenuating pain and neuroinflammation (10).

Although both agents appear promising, their relative efficacy in preventing or mitigating PSD, and the specific role their distinct analgesic properties play in this effect, remain unclear. Previous studies have been limited by small sample sizes and heterogeneous outcomes, frequently relying solely on subjective sleep assessment scales, which complicates direct clinical translation. While subjective scales offer valuable patient-reported insights, objective measures like polysomnography (PSG) represent the gold standard for evaluating sleep architecture and can yield critical information on the physiological impacts of these drugs.

Network meta-analysis enables the integration of direct and indirect evidence to compare multiple interventions comprehensively, thereby allowing for robust treatment ranking.

Therefore, we conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs) to evaluate the comparative effects of dexmedetomidine and esketamine on postoperative sleep quality and analgesia. We analyzed pain-related outcomes (measured on the Visual Analog Scale [VAS]) as the primary endpoint, with secondary outcomes including the incidence of sleep disturbance, Athens Insomnia Scale (AIS) scores, and Numerical Rating Scale (NRS). We hypothesized that both dexmedetomidine and esketamine would offer greater improvements in postoperative sleep than would the control interventions, with esketamine potentially demonstrating superior efficacy attributable to its direct analgesic actions.

Methods

Search Strategy and Study Selection

A comprehensive systematic literature search was conducted across 4 electronic databases: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, from their inception to August 1st, 2025. The search strategy for PubMed included the following terms: ((“esketamine”[MeSH Terms] OR “esketamine”[All Fields] OR “S-ketamine”[All

Fields] OR "ketamine, S"[All Fields] OR "ketamine, esketamine"[All Fields]) OR ("dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[All Fields] OR "premedication, dexmedetomidine"[All Fields])) AND ("sleep disturbance"[All Fields] OR "sleep quality"[All Fields] OR "sleep disorder"[All Fields] OR "postoperative sleep"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized trial"[All Fields] OR "RCT"[All Fields]). Similar search strategies were adapted for the other databases, using appropriate subject headings and keywords.

Two independent reviewers screened the titles and abstracts, followed by a full-text assessment of potentially eligible studies. Any disagreements were resolved through consensus or by consulting a third reviewer. The reference lists of included studies and relevant systematic reviews were searched manually to identify additional eligible publications.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) studies designed as randomized controlled trials (RCTs); (2) a population of adult patients (≥18 years of age) undergoing surgical procedures; (3) interventions that took the form of the intravenous administration of dexmedetomidine or esketamine during the perioperative period; (4) comparators: placebo, usual care, or direct comparison between dexmedetomidine and esketamine; (5) outcomes: at least one sleep-related outcome measure assessed postoperatively; (6) language: No restrictions were applied.

The exclusion criteria comprised: (1) nonrandomized studies, case reports, case series, and review articles; (2) studies involving pediatric populations (patients < 18 years); (3) the involvement of nonintravenous routes of drug administration; (4) studies focusing on minor procedures (e.g., induced abortion); (5) studies reporting only objective sleep-monitoring data (e.g., polysomnography, electroencephalography) without validated subjective sleep assessment scales; (6) studies with incomplete outcome data or insufficient data for analysis; (7) duplicate publications or studies with overlapping patient populations.

Data Extraction

Data were extracted independently by 2 reviewers using a standardized, pre-piloted data collection form. The following information was extracted from each included study: (1) study characteristics (first author, publication year, country, study design); (2) patient characteristics (sample size, age, gender distribution, type of surgery, anesthesia type); (3) intervention details (drug type, dosage, timing and duration of administration); (4) control group characteristics; (5) outcome measures (sleep assessment tools, assessment time points, outcome data); (6) study methodology (randomization method, blinding, follow-up duration). Any discrepancies in data extraction were resolved through discussion between the reviewers.

Outcome Measures

The primary outcomes were VAS scores for pain at rest and during movement at 24 and 48 hours postoperatively.

Secondary outcomes included: (1) incidence of sleep disturbance on the first and third after the operation; (2) AIS scores; (3) sleep quality scores on the NRS.

Quality Assessment

The methodological quality of the included RCTs was assessed independently by 2 reviewers using the Cochrane risk of bias tool, version 2.0 (RoB 2). The following domains were evaluated: the randomization process, deviations from the intended interventions, missing outcome data, the measurement of the outcome, and selection of the reported result. Each domain was judged as presenting a low risk, some concerns, or a high risk of bias.

Network Meta-Analysis

Network meta-analysis was performed using R software (version 4.4.0) with the "gemtc" package in conjunction with the Just Another Gibbs Sampler program. This performance was done within a Bayesian framework employing the Markov Chain Monte Carlo (MCMC) method. Both direct and indirect evidence were synthesized to estimate the relative effects between all interventions.

Supplementary Meta-Analysis of Objective Sleep Outcomes

To provide objective evidence on sleep architecture, we conducted a separate, traditional random-effects meta-analysis on all included RCTs that reported PSG data for dexmedetomidine and compared them to those of a control group. Data for the mean, standard deviation (SD), and sample size of each group were extracted. For studies reporting median and interquartile range (IQR), the mean was estimated as the median

and the SD as IQR/1.35. For dichotomous outcomes (presence of N3 sleep), the number of events and the total sample size were extracted. The mean difference (MD) was calculated for continuous outcomes (N2 sleep percentage) and the odds ratio (OR) for dichotomous outcomes. This analysis was performed using the "meta" package in R (version 4.4.0).

Statistical Models and Convergence

The simulation analysis utilized 4 Markov chains. Each chain underwent 20,000 burn-in iterations for annealing, followed by 50,000 iterations for sampling to ensure model convergence. The Deviance Information Criterion (DIC) was used to evaluate the relative goodness-of-fit between fixed-effect and random-effect models, with lower DIC values indicating a superior model fit. A DIC difference greater than 5 was considered to favor the random-effects model substantially. Consistency between direct and indirect evidence was assessed using node-splitting analysis.

Network Geometry

Network plots were constructed to visualize the available direct comparisons between interventions. The node size represented the number of studies for each intervention, and the edge thickness represented the number of direct comparisons.

Effect Size Measures

For dichotomous outcomes (sleep disturbance incidence), the relative risk (RR) was calculated. For continuous outcomes (AIS, NRS, and VAS scores), the weighted mean difference (WMD) was estimated. Statistical significance was determined if the 95% credible interval (95% CrI) of the pooled effect size did not include one for RR or 0 for WMD.

Assessment of Consistency

Where applicable, node-splitting analysis was employed to assess local (loop-specific) inconsistencies within each closed network, measuring discrepancies between direct and indirect evidence. Statistical inconsistency was considered present if $P < 0.05$.

Treatment Ranking

Treatment ranking was assessed using the surface under the cumulative ranking curve (SUCRA), which represents the cumulative ranking probability. SUCRA values range from 0% (worst treatment) to 100% (best treatment).

Analysis Outputs

Analysis outputs included network evidence relationship diagrams, forest plots, ranking probability bar charts, and league tables for each outcome measure.

Quality Control

Statistical analysis was conducted by one researcher, with results cross-validated by 2 additional researchers to ensure accuracy.

Sensitivity Analysis

Sensitivity analyses were planned to assess the robustness of the findings by excluding studies with a high risk of bias, provided that enough studies were available.

Publication Bias

Publication bias was assessed using comparison-adjusted funnel plots when at least 10 studies were available for a particular outcome.

Protocol Registration

The protocol for this systematic review was registered in PROSPERO (registration number: CRD420251126227).

Results

Study Selection

The initial database search yielded 142 potentially relevant records. After 8 duplicates were removed, 134 records underwent title and abstract screening. Of these, 34 studies proceeded to full-text evaluation. Upon full-text assessment, 24 studies were excluded for the following reasons: nonintravenous drug administration (n = 3), incomplete or insufficient outcome data (n = 11), study protocol only (n = 5), and reporting only objective sleep data without subjective scales (n = 5). Ultimately, 10 RCTs met the inclusion criteria and were included in the network meta-analysis. The study selection process is detailed in the PRISMA flow diagram (Fig. 1).

Study Characteristics

The 10 included studies enrolled a total of 645 patients, with individual study sample sizes ranging from 50 to 200 individuals. All studies were published between 2022 and 2025 and were conducted in China, employing double-blind, randomized controlled trial designs (Appendix Fig. S1).

Patient Demographics: The mean age of the pa-

tients across the studies ranged from 31 to 73 years, encompassing a diverse surgical population from young adults to the elderly. Gender distribution varied among the studies. The surgical procedures included lumbar interbody fusion, gynecological laparoscopy, various laparoscopic abdominal surgeries, radical mastectomy, laparoscopic cholecystectomy, breast cancer surgery, colorectal cancer surgery, total hip or knee arthroplasty, and surgical abortion (Fig. S1).

Intervention Characteristics: Esketamine was administered intravenously in all relevant studies, with protocols involving both intraoperative infusions and postoperative patient-controlled analgesia. Dexmedetomidine administration regimens varied across studies, including different dosing schedules (e.g., 200μg and 400μg groups) and combination therapies with other anesthetic agents (sevoflurane, propofol) or analgesics (sufentanil). One study directly compared esketamine, dexmedetomidine, and a combination of the 2 agents against a placebo. Control groups received either normal saline placebos or standard analgesic protocols without the study medications (Fig. S1).

Outcome Assessment: Pain was assessed on the VAS at rest and during movement at 24 and 48 hours postoperatively. Sleep quality was evaluated using multiple validated instruments: 7 studies used the AIS, 6 used the Sleep Quality NRS, and 9 reported the incidence of sleep disturbances. Assessment time points were generally consistent, with primary evaluations on the first and third days after the operation and some studies extending the follow-up to day 7. Several studies also reported anxiety and depression scores using the Hospital Anxiety and Depression Scale (HADS) (Fig. S1).

Study Quality: All included studies were RCTs with double-blind designs. The methodological quality was generally acceptable, with most studies providing adequate information on randomization procedures and outcome measurement. All studies reported complete follow-up data for the primary sleep-related outcomes, ensuring robust data for the network meta-analysis. Detailed risk of bias assessments are presented in Fig. 2.

Network Characteristics

The network meta-analysis included 4 main treatment nodes: esketamine, dexmedetomidine, combination therapy (dexmedetomidine plus esketamine), and control interventions (placebo or standard care). Direct comparisons were available between esketamine and control in 8 studies (1,11-17), between dexmedetomidine and control in 3 studies (13,18,19), among combination therapy and individual agents and control in one study (13), and among various combinations involving different anesthetic agents and dosing regimens. The network formed multiple closed loops, allowing for the comprehensive assessment of consistency between direct and indirect evidence. The complexity of the network was enhanced by the inclusion of different control conditions and combination therapies, providing robust indirect comparisons between esketamine and dexmedetomidine (18,19).

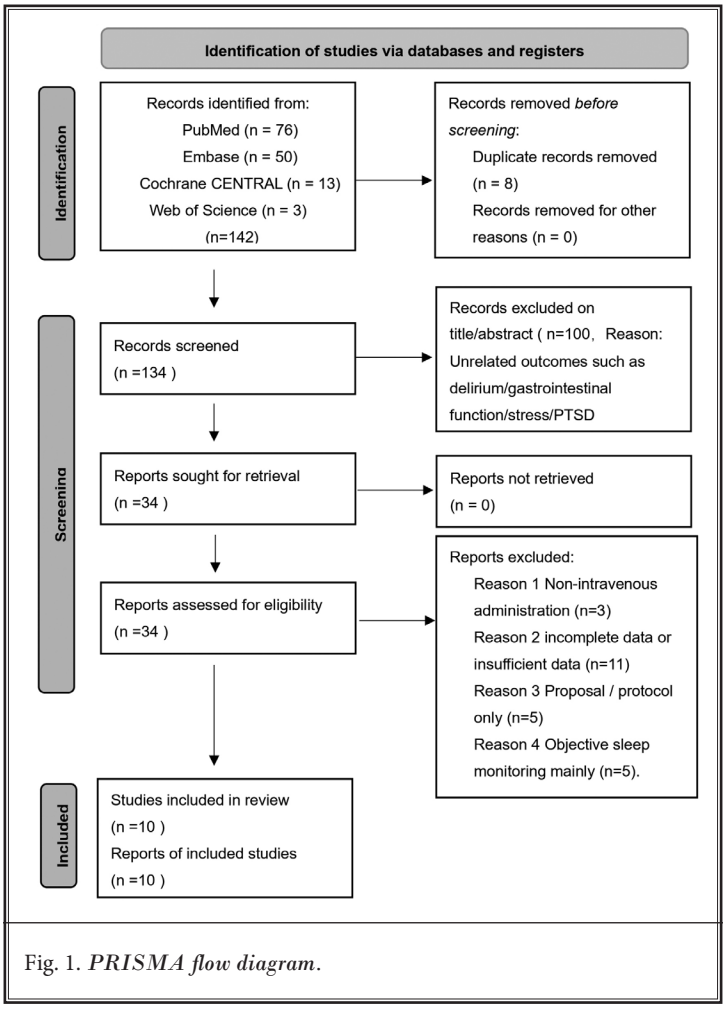


Fig. 1. *PRISMA flow diagram.*

Network Meta-Analysis Results

Model Selection and Convergence

The DIC comparison indicated that random-effects models provided a superior fit for most outcomes, with DIC differences exceeding 5 points. All models achieved satisfactory convergence, as indicated by the presence of Gelman-Rubin diagnostic values below 1.1 and stable trace plots across the 4 Markov chains.

Pain Scores (VAS)

24-Hour Postoperative Pain

Analysis of VAS pain scores at 24 hours postoperatively included data from 8 studies. At rest, esketamine

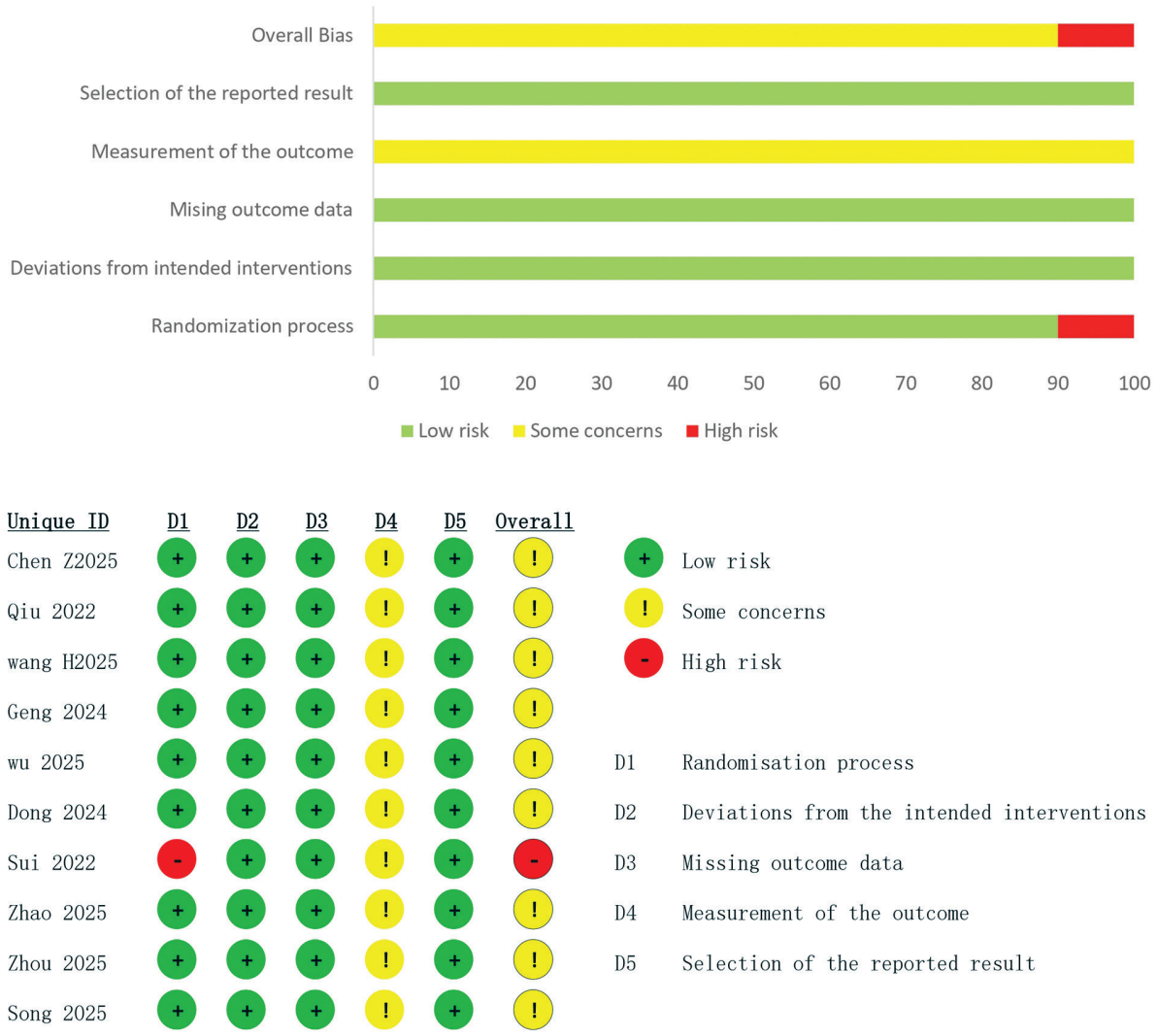


Fig. 2. *Quality assessment of the selected studies, using the Cochrane risk of bias tool version 2.0.*
(Upper panel) Risk-of-bias graph: a review of the authors' judgments about each risk-of-bias item, presented as percentages across all included studies.
(Lower panel) Risk-of-bias summary: a review of the authors' judgments about each risk-of-bias item for each included study.

reduced pain scores significantly (WMD = -0.971, 95% CrI: -1.79 to -0.158), whereas dexmedetomidine showed no clear effect (WMD = 0.0182, 95% CrI: -1.80 to 1.82) (Fig. 3). During movement, esketamine demonstrated significant pain reduction (WMD = -1.00, 95% CrI: -1.36 to -0.638), and dexmedetomidine showed a similar, though less precise, trend (WMD = -0.984, 95% CrI: -1.90 to -0.059) (Fig. 4).

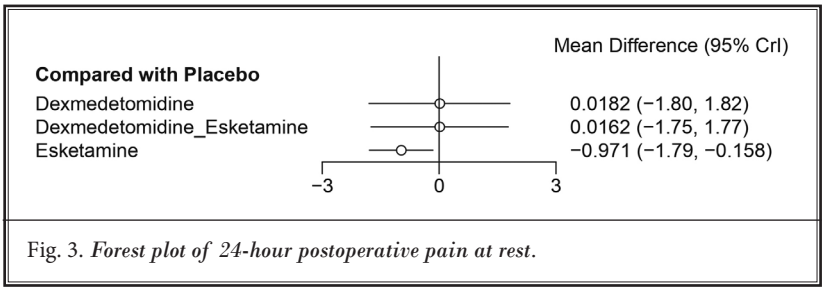


Fig. 3. *Forest plot of 24-hour postoperative pain at rest.*

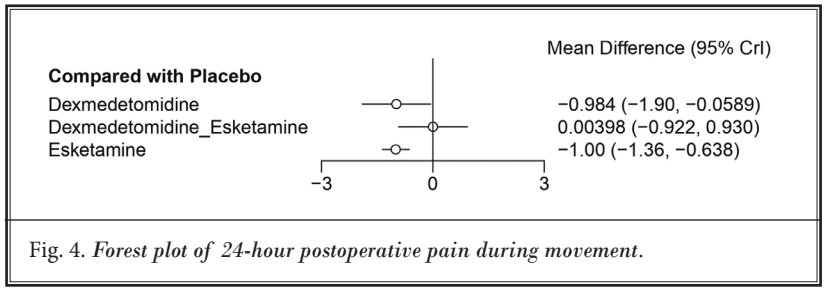


Fig. 4. *Forest plot of 24-hour postoperative pain during movement.*

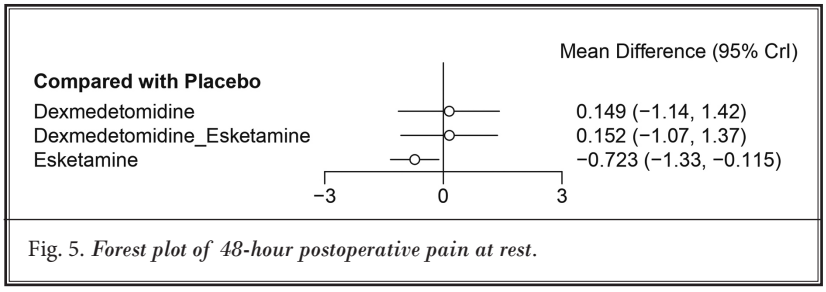


Fig. 5. *Forest plot of 48-hour postoperative pain at rest.*

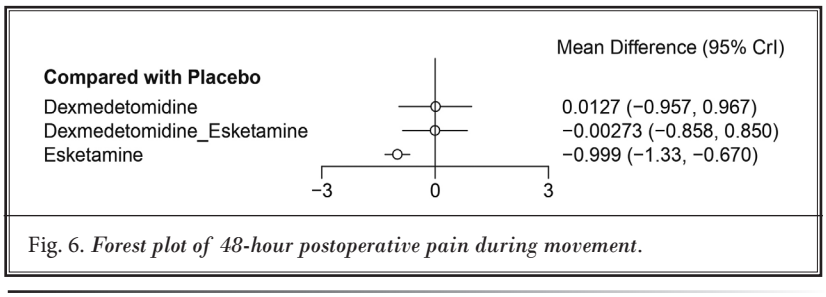


Fig. 6. *Forest plot of 48-hour postoperative pain during movement.*

48-Hour Postoperative Pain

At 48 hours, esketamine continued to show significant pain reduction both at rest (WMD = -0.723, 95% CrI: -1.33 to -0.115) and during movement (WMD = -0.999, 95% CrI: -1.33 to -0.670) (Figs. 5 and 6). Dexmedetomidine showed nonsignificant trends toward pain reduction, with credible intervals crossing 0 (Figs. 5 and 6).

Sleep Disturbance Incidence

Postoperative Day One Sleep Disturbance

The network meta-analysis of sleep disturbance incidence on the first day after the operation included 9 studies (network geometry shown in Fig. 7A). Compared with control interventions, esketamine was associated with a significant reduction in sleep disturbance incidence (RR = 0.655, 95% CrI: 0.517-0.798). Dexmedetomidine showed a trend toward reduction, but the result was not statistically significant (RR = 0.773, 95% CrI: 0.434-1.23). The direct comparison between dexmedetomidine and esketamine showed no statistically significant difference (RR = 0.824, 95% CrI: 0.472-1.30) (Fig. 8). SUCRA ranking indicated that esketamine had the highest probability of being the most effective treatment (SUCRA = 73.0%), followed by dexmedetomidine (SUCRA = 54.6%) and control (SUCRA = 22.7%) (Fig. 9).

Postoperative Day 3 Sleep Disturbance

Eight studies provided data for the third day after the operation (network geometry shown in Fig. 7B). Both esketamine (RR = 0.465, 95% CrI: 0.233-0.789) and dexmedetomidine (RR = 0.344, 95% CrI: 0.0838-1.18) showed trends toward reducing sleep disturbance, with esketamine's effect reaching statistical significance. The comparison between dexmedetomidine and esketamine remained nonsignificant (RR = 0.804, 95% CrI: 0.251-2.45) (Fig. S2). SUCRA values ranked dexmedetomidine first (SUCRA = 81.7%) and esketamine second (SUCRA = 71.2%) (Fig. S3), although those rankings should be interpreted cautiously, given the overlapping credible intervals.

AIS Scores

Seven studies reported AIS scores. Network meta-analysis revealed that both esketamine (WMD = -1.25, 95% CrI: -3.01 to 0.392) and dexmedetomidine showed greater trends toward improving AIS scores than controls did, but those effects did not reach statistical significance.

Sleep Quality NRS Scores

Four studies utilized the NRS to measure patients' sleep quality. Both interventions demonstrated greater though nonsignificant trends toward improvement than did controls (esketamine: WMD = -0.423, 95% CrI: -1.49 to 0.550).

Consistency Assessment

Node-splitting analysis for closed loops in the network detected no significant inconsistency (all *P*-values > 0.05), indicating consistency between the direct and indirect evidence and supporting the validity of the network meta-analysis results.

Heterogeneity Assessment

Statistical heterogeneity was generally low to moderate across outcomes. The between-study variance (τ^2) ranged from 0.02 to 0.15 for different outcomes, with most I^2 values below 50%, indicating acceptable heterogeneity for network synthesis.

Supplementary Meta-Analysis of Objective PSG Outcomes

Four RCTs reporting PSG data for dexmedetomidine were included in a separate meta-analysis (20-23). The pooled results demonstrated that the dexmedetomidine group experienced a greater increase in the percentage of stage N2 sleep with the control group did, though the result was not statistically significant and heterogeneity was very high (MD = 13.0%, 95% CI: -5.2 to 31.2, I^2 = 94%; Fig. 10A). For the presence of restorative N3 sleep, 3 studies showed a nonsignificant increase in odds with dexmedetomidine (OR = 2.99, 95% CI: 0.61 to 14.66, I^2 = 0%; Fig. 10B).

Discussion

This network meta-analysis of 10 RCTs demonstrates that both dexmedetomidine and esketamine are effective in improving postoperative sleep quality,

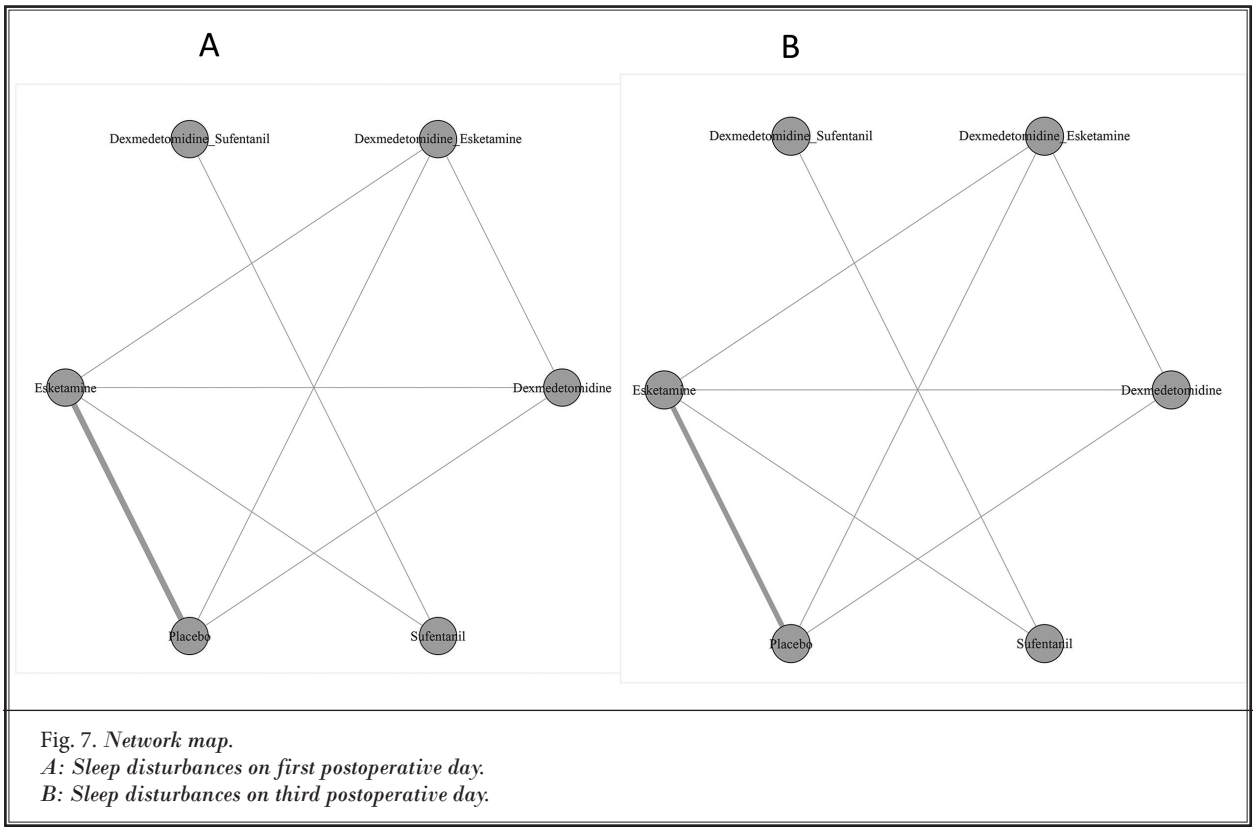


Fig. 7. *Network map.*
A: Sleep disturbances on first postoperative day.
B: Sleep disturbances on third postoperative day.

albeit through potentially distinct mechanisms. A key finding of this study is the potent and sustained analgesic efficacy of esketamine. Its ability to reduce VAS pain scores significantly at 24 and 48 hours after an operation, both at rest and upon movement, likely constitutes a central mechanism through which the drug improves subjective sleep quality. By directly mitigating a primary cause of sleep disruption—postoperative pain—esketamine addresses a core pathophysiological mechanism of PSD. This phenomenon aligns with the established pharmacology of esketamine as an NMDA receptor antagonist, which disrupts central sensitization and hyperalgesia. In contrast, while dexmedetomidine showed some analgesic trends, its effects were less consistent and statistically significant. This volatility may explain the medication's more variable performance on subjective sleep scales, despite the association of dexmedetomidine with a favorable SUCRA ranking for sleep disturbance incidence at day 3. The superior SUCRA values associated with esketamine on day-one PSD incidence, coupled with the drug's definitive analgesic superiority, suggest that its potent, direct analgesia confers an early and significant advantage in restoring sleep continuity.

Exploring these findings further, our supplementary meta-analysis of objective PSG data provided evidence that dexmedetomidine modulated sleep architecture, primarily by increasing the percentage of stage N2 sleep. The observed, though nonsignificant, increase in N2 sleep is consistent with dexmedetomidine's known ability to induce a state resembling natural NREM sleep. The very high heterogeneity (I^2 = 94%) in this finding precludes firm conclusions and likely reflects variations in dosing regimens, surgical stimuli, and patient factors. Dexmedetomidine's effect on deep N3 sleep remains uncertain, due to limited data. The scarcity of PSG data for esketamine precluded a direct objective comparison of how the 2 drugs modulated sleep architecture differentially, representing a critical gap for future research.

Dexmedetomidine, an α2-adrenergic receptor agonist, promotes states similar to nonrapid eye movement (NREM) sleep and has been used widely as a sedation

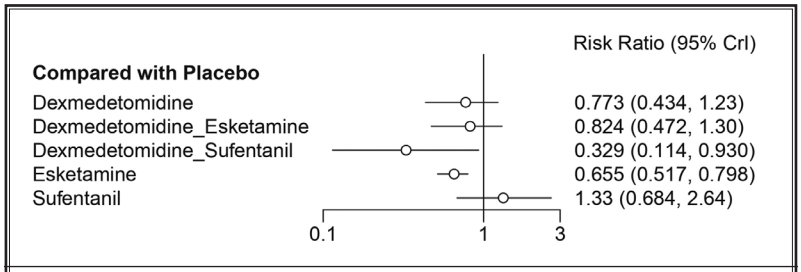


Fig. 8. *Forest plot of sleep disturbances on first postoperative day.*

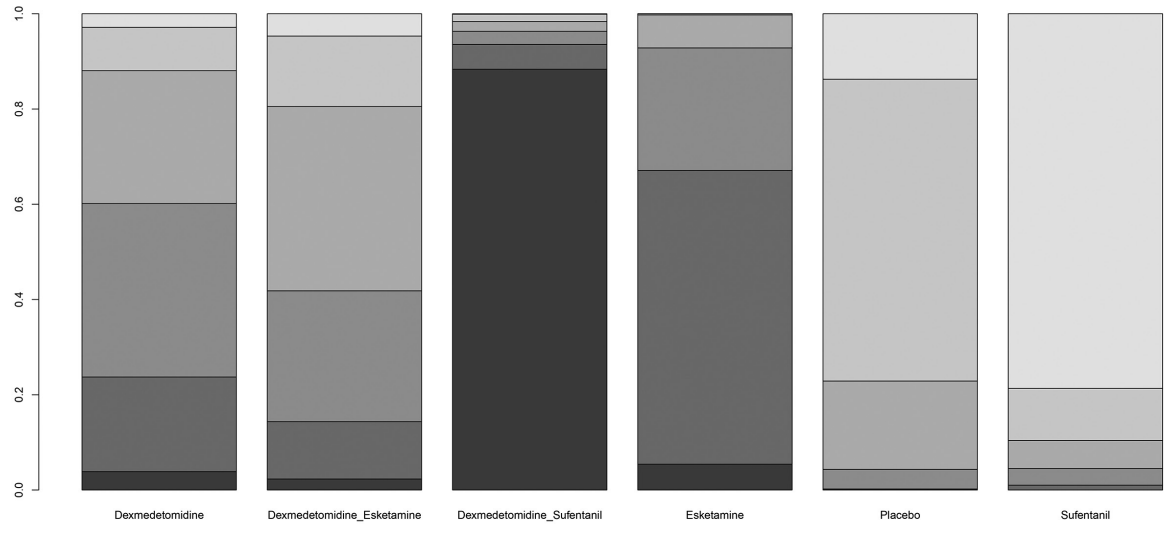


Fig. 9. *SUCRA map of sleep disturbances on first postoperative day.*

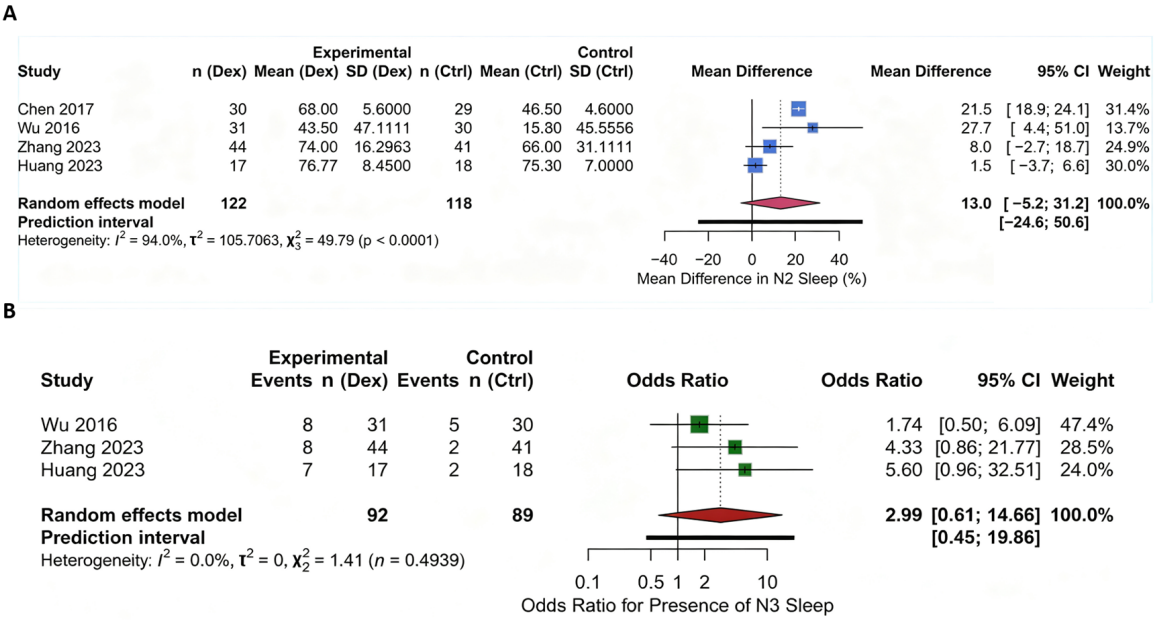


Fig. 10. *Forest plot of the effect of dexmedetomidine on the percentage of stage N2 and N3 sleep.*
The analysis shows that the dexmedetomidine group experienced a greater increase in the percentage of stage N2 sleep than the control group did, based on a random-effects model. However, significant heterogeneity was observed (I^2 = 94%). Squares represent the mean difference (MD) for each study, with the size corresponding to the study's weight. The diamond represents the pooled MD and its 95% confidence interval (CI).

method that causes only minimal respiratory depression (24). Several experimental studies also suggest that dexmedetomidine can modulate circadian rhythms and attenuate neuroinflammation, which may contribute to improved sleep quality. Conversely, esketamine, the S-enantiomer of ketamine, acts primarily as an NMDA receptor antagonist and has been approved recently for the treatment of refractory depression (25). The rapid antidepressant and potent anti-hyperalgesic properties of esketamine may explain the observed improvements in sleep, given that PSDs are often closely linked to both pain and mood disorders.

Importantly, our analysis underscores the clinical relevance of addressing PSD. Poor sleep quality has been associated with delayed recovery, heightened pain sensitivity, impaired immune function, and an increased risk of chronic postsurgical pain. The comparable, yet mechanistically distinct, efficacy of dexmedetomidine and esketamine offers clinicians multiple pharmacological options. The choice between the 2 medications should be guided by individual patient characteristics, surgical context, and drug safety profiles. For instance, dexmedetomidine may be preferred for patients who rank hemodynamic stability as a primary concern, while esketamine may be advantageous for patients with high baseline pain or co-existing depressive symptoms (26).

Limitation

This study has several limitations. Firstly, all included trials were conducted in China, which may limit the generalizability of the findings to other populations and health care settings. Secondly, heterogeneity existed in the studied drug regimens, including differences in dosages, timing, and routes of administration. Thirdly, while we supplemented our primary analysis with a meta-analysis of objective PSG data, the number of studies providing such data was small (4 for dexmedetomidine and none for esketamine), preventing a direct, objective comparison of the 2 drugs' effects on sleep architecture. Finally, the relatively small number of included trials restricted our ability to perform extensive subgroup or sensitivity analyses, particularly regarding surgery type and patient baseline characteristics.

Conclusions

Despite the aforementioned limitations, our find-

ings provide a clinically valuable synthesis. The choice between these agents can be informed by patient-specific factors. Esketamine may be the preferred option for patients with high anticipated pain or baseline depressive symptoms, leveraging the drug's direct analgesic and potential mood-stabilizing effects. Dexmedetomidine might be favored for patients who are concerned primarily with hemodynamic stability or for whom the medication's NREM sleep-promoting properties are particularly desirable, even though its independent analgesic contribution may be less robust. Future research should prioritize head-to-head RCTs that include diverse international populations, use standardized dosing regimens, and incorporate PSG for both drugs to elucidate their distinct impacts on sleep architecture and solidify their roles in enhanced recovery protocols.

Authors' Contributions

TJ and BZ designed the study. YZ and RZ conducted the data analysis. XW, RZ, YH, and LJ contributed to the methodology. CH, YZ, and BZ supervised the project and drafted the manuscript. TJ wrote the paper. WC, GS, KP and BZ reviewed the paper. All authors read and approved the final version of the manuscript.

Disclaimer

This study was a systematic review and meta-analysis and thus did not involve direct contact with human patients. Therefore, ethics approval and patient consent were not required. The anonymized data supporting the findings of this study are available from the corresponding authors upon reasonable request and subject to institutional approval. The authors declare that financial support was received for the research and publication of this article. This work was supported by the Ningbo Top Medical and Health Research Program (No. 2024010317) and the Phase 3 Ningbo Health and Youth Technical Backbone Talents project (QNJSGG-3-ZBB, Prof. B.Z.). The systematic review protocol was registered with PROSPERO (CRD420251126227).

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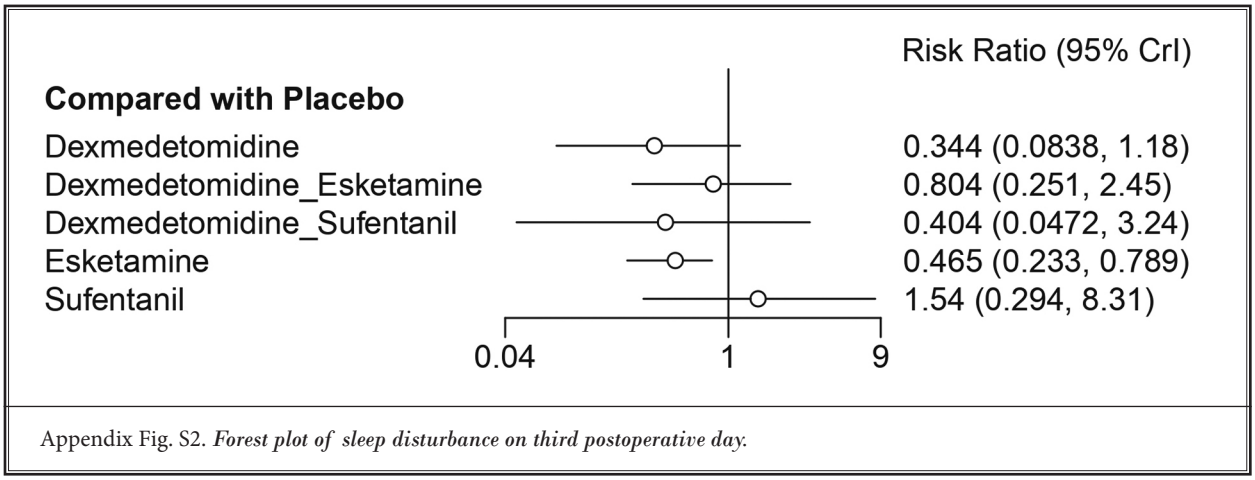
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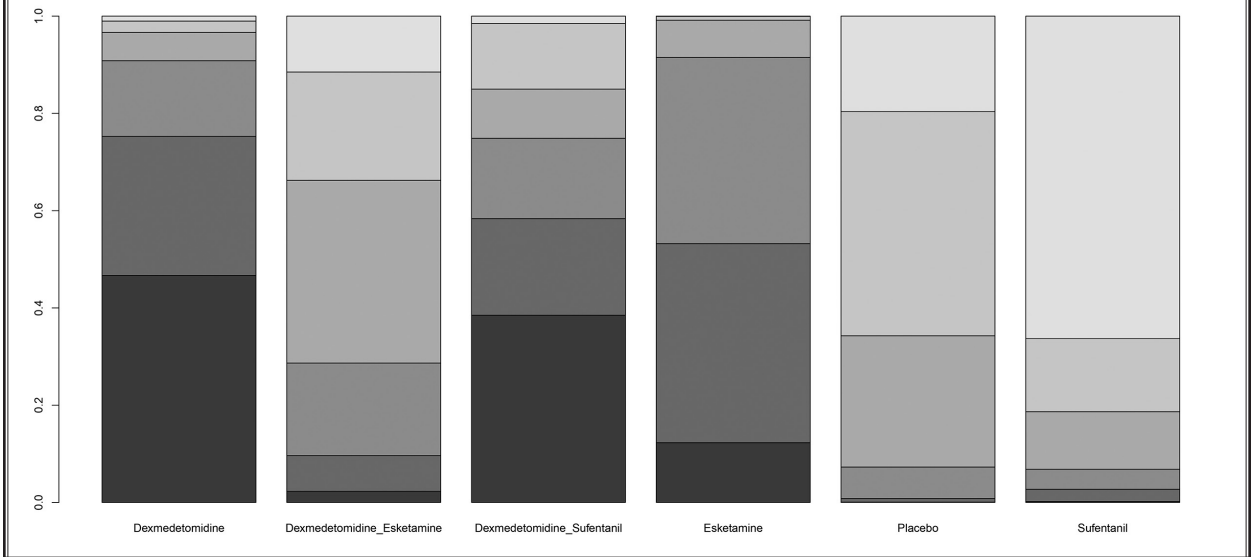
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study	author	year	region	Type of experiment	Intervention modalities	Sample size(n)		Ratio of men to women		age		Type of surgery	Follow-up time	Outcome indicators
						ntervention group	Control group	Intervention group	Control group	Intervention group	Control group			
Effects of sub-anesthetic doses of esketamine on postoperative sleep disturbance and pain in patients undergoing lumbar interbody fusion - A randomized, double-blind, placebo-controlled, two-center trial	Zheping Chen	2025	China	RCT	Esketamine	39	39	19/20	16/23	65(56-71)	59(53-66)	lumbar interbody fusion	3 D	1. Incidence of sleep disturbance 2. PSD:NRS, AIS 3. VAS-pain score 4. Ramsay Sedation Score 5. Intraoperative morphine equivalent 6. Postoperative morphine equivalent 7. Supplemental analgesics within 48 h 8. Number of demanded PCIA boluses within 48 h 9. Number of administered PCIA boluses within 48 h 10. Adverse reactions
Effect of Intraoperative Esketamine Infusion on Postoperative Sleep Disturbance After Gynecological Laparoscopy: A Randomized Clinical Trial	Di Qiu	2022	China	RCT	Esketamine	92	91	92	91	43(32-49)	45(35-49)	Gynecological Laparoscopy	3 D	1. Sleep quality(AIS, NRS) 2. PSD: No. (%) 3. HADS-A 4. HADS-D 5. Consumption of intraoperative remifentanil 6. Laryngeal mask removal time 7. VAS-pain score 8. Postoperative morphine equivalent 9. Adverse reactions
Effect of intravenous esketamine on postoperative sleep disturbance, anxiety, and depression in elderly patients undergoing laparoscopic abdominal surgery: a randomized controlled trial	Haijin Wang	2025	China	RCT	Esketamine	100	100	56/44	67/33	72.65 ± 5.33	73.02 ± 5.61	elderly patients undergoing laparoscopic abdominal surgery	3 D	1. Postoperative sleep disturbance 2. HADS-A 3. HADS-D 4. VAS-pain score 5. Postoperative opioid consumption 6. Postoperative rescue analgesia 7. Non-opioid analgesic 8. Adverse reactions
Effect of Intraoperative Intravenous Infusion of Esketamine Combined with Dexmedetomidine on Postoperative Sleep Disturbance in Patients Undergoing Radical Mastectomy	Xingyu Geng	2025	China	RCT	Group E, esketamine group; Group D, dexmedetomidine group; Group ED, dexmedetomidine combined with esketamine group; Group S, normal saline group	E 25 D 25 ED 25	S 25	E 25 D 25 ED 25	S 25	E 50.44±1.538 D 54.00±1.745 ED 50.92±1.527	50.80±1.294	Radical Mastectomy	3 D	1. POD1, 3 Sleep quality (POSD, NO. n) 2. Sleep structure 3. VAS scores 4. Adverse reactions
Effect of intraoperative low-dose esketamine infusion on postoperative sleep disturbance after laparoscopic cholecystectomy: a randomized clinical trial	Yanan Wu	2025	China	RCT	Esketamine	43	43	23/20	21/22	47.9±9.4	49.7±15.1	Laparoscopic cholecystectomy	3 D	1. PSD:NRS 2. PSD: No. (%) 3. VAS-pain score 4. Postoperative rescue analgesia 5. Adverse reactions
Effect of dexmedetomidine infusion on postoperative sleep disturbances in women with breast cancer: A monocentric randomized-controlled double-blind trial	Yushan Dong	2024	China	RCT	Group S, sevoflurane and placebo group; Group DS, sevoflurane and dexmedetomidine group; Group P, propofol and placebo group; Group DP, propofol and dexmedetomidine	S 47 DS 47	P 47 DP 47	S 47 DS 47	P 47 DP 47	S 54.4±10.7 DS 55.7±11.0	P 51.9±11.4 DP 51.9±8.9	Radical surgery for breast cancer	3 D	1. POSD(within 3 days, within 1, 7, 30) 2. AIS 3. Self-rating of daytime somnolence 4. Sleep structure 5. Adverse reactions
The effects of dexmedetomidine for patient-controlled analgesia on postoperative sleep quality and gastrointestinal motility function after surgery: A prospective, randomized, double-blind, and controlled trial	Xin Sui	2022	China	RCT	Sufentanil150 μg Dexmedetomidine200 μg+Sufentanil150 μg Dexmedetomidine400 μg+Sufentanil150	200 μg 70 400 μg 70	70	200 μg 49/21 400 μg 49/21	38/32	200 μg 58.8±10.2 400 μg 60.2±8.1	60.0±8.9	Elective colorectal cancer surgery	7 D	1. Sleep disturbance 2. VAS 3. Rescue analgesia
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	Yan Zhao	2025	China	RCT		Esketamine 57	Sufentanil 55	18/37	15/42	70 ± 4.0	70 ± 5.1	total hip arthroplasty (THA) or total knee arthroplasty (TKA)	7 D	1. PSD:NRS, AIS 2. PSD: No. (%) 3. HADS-A 4. HADS-D 5. Rescue analgesia
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	YanHong Zhou	2025	China	RCT	Esketamine	49	49	49	49	31 (28, 36)	31 (28, 37)	gynecological laparoscopic surgery		1. PSD: No. (%) 2. VAS
Effect of a single low-dose esketamine administration during surgical abortion on postoperative sleep disturbance: a randomized controlled trial	Zhenhua Song	2025	China	RCT	Esketamine	102	102	102	102	30.5 (25-34.25)	32 (25-34)	surgical abortion	7 D	1. PSD: AIS 2. PSD: No. (%) 3. HADS-A 4. HADS-D 5. VAS

Appendix Fig. S1. *Data extraction table.*



Appendix Fig. S2. *Forest plot of sleep disturbance on third postoperative day.*



Appendix Fig. S3. *SUCRA map of sleep disturbances on third postoperative day.*