Systematic Review

# Opioid-free Anesthesia for Enhancing Recovery Quality at Postoperative 24 Hours: A Systematic Review and Meta-analysis

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**Background:** Opioid-free anesthesia (OFA) is becoming increasingly common, yet its effects on early postoperative recovery remain unclear.

**Objective:** Our study assessed the effect of OFA on postoperative recovery compared to opioid-based anesthesia (OBA).

**Study Design:** Systematic review and meta-analysis.

**Methods:** We searched MEDLINE, the Cochrane Library, Embase, BIOSIS, and Web of Science concluding on December 19, 2024, for randomized controlled trials comparing OFA and OBA in adults (≥ 18 years). Data were extracted, and risk of bias was assessed using the Cochrane RoB 2.0 tool (The Nordic Cochrane Centre for The Cochrane Collaboration). The primary outcome was recovery quality at postoperative 24 hours. Random-effects meta-analyses were conducted. Evidence certainty was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. Our meta-analysis was registered with PROSPERO (ID CRD42024621490).

**Results:** Sixteen trials with a total of 1,968 patients were included in our meta-analysis. OFA was statistically significance associatedwith an improved Quality of Recovery (QoR)-40 score (mean difference 6.33; 95% CI, 3.48–9.17; very low certainty) and QoR-15 score at postoperative 24 hours (mean difference 10; 95% CI, 2.25–17.74; low certainty) compared to OBA. OFA was a statistical significance associated with a reduced risk of postoperative nausea and vomiting, as well as a shorter stay in the postanesthesia care unit. OFA did not reduce postoperative pain and extubation time.

**Limitations:** Our meta-analysis has high heterogeneity, with a predominance of women and middle-aged populations in the included studies. Additionally, side effects related to OFA were not analyzed.

**Conclusions:** Our systematic review and meta-analysis concluded that it is uncertain whether OFA is superior to OBA in improving postoperative recovery quality. However, OFA leads to a statistically significant reduction in the incidence of postoperative nausea and vomiting. The evidence was primarily drawn from small trials involving elective surgeries. While our results support using OFA, larger and high-quality studies are needed to validate its effect on postoperative recovery quality.

**Key words:** Opioid-free anesthesia, postoperative, recovery quality, adverse events

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Opioids are a cornerstone of general anesthesia due to their potent analgesic effects and their role in maintaining hemodynamic stability during surgery. Despite their critical importance in perioperative care, opioids can cause a broad range of adverse effects which pose significant concerns. These adverse effects include nausea and vomiting, respiratory depression, urinary retention, constipation, pruritus, and hyperalgesia (1-4). Such complications can notably impair postoperative recovery, increase patient discomfort (5), prolonging hospital stays (6), and add to health care costs (7).

Opioid-related side effects, particularly postoperative nausea and vomiting (PONV), often delay the resumption of activities of daily living and necessitate additional treatment. Moreover, respiratory depression represents a serious risk, especially for elderly patients and those with preexisting lung disease. Opioid-induced constipation contributes to significant discomfort and can result in complications such as bowel obstruction, ultimately prolonging hospital stays. Chronic opioid use may also lead to opioid-induced hyperalgesia, which is characterized by increased pain sensitivity that often requires escalating opioid doses, further promoting dependence and tolerance.

To address these challenges, opioid-free anesthesia (OFA) regimens have been developed to provide effective analgesia (8) while minimizing both the short-term and long-term side effects of opioids (9,10). These regimens eliminate using opioids during surgery and instead use a range of multimodal anesthesia strategies, including N-methyl-D-aspartate (NMDA) receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, $\alpha$–2 receptor agonists, $\beta$-blockers, and calcium channel blockers.

Previous studies have demonstrated the efficacy of OFA for delivering analgesia (8,11), maintaining hemodynamic stability (12), and reducing opioid-related adverse effects (13,14). The cumulative effects of these benefits may significantly enhance overall postoperative recovery quality. However, the effect of OFA on recovery quality remains uncertain. In light of growing concerns about the opioid crisis and the need for sustainable anesthesia practices, we conducted a systematic review and meta-analysis to provide a comprehensive, evidence-based evaluation of whether OFA improves postoperative recovery quality compared to opioid-based anesthesia (OBA).

## Methods

### Search strategy and selection criteria

Our meta-analysis was conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and was registered in the PROSPERO database on December 17, 2024 (registration number CRD42024621490). The study followed a clear PICO (Patient/Problem, Intervention, Comparison, Outcome) framework: in patients undergoing surgery, to what extent does OFA, compared with OBA, affect postoperative recovery quality?

A comprehensive literature search was performed using MEDLINE, the Cochrane Library, Embase, BIOSIS, and Web of Science, with the search concluding on December 19, 2024. The search strategy, designed by a professional medical librarian, imposed no language restrictions (Suppl. File 1). To ensure thorough coverage of relevant studies, additional searches were conducted in trial registries (ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform), conference proceedings, and reference lists of included studies.

Randomized controlled trials were included if they met the following criteria: enrolled patients aged 18 years or older; involved surgeries performed under general anesthesia or nerve blocks; and reported postoperative recovery quality outcomes. Trials were required to compare an anesthesia regimen that included opioids with one that was opioid-free. Animal studies and observational studies were excluded.

OBA was defined as opioids being the primary systemic analgesic during surgery along with inhalants and other necessary adjuvant agents. OFA was defined as anesthesia regimens that exclude systemic opioids during surgery, instead using a combination of nonopioid drugs such as $\alpha$–2 adrenergic agonists, NMDA receptor antagonists, NSAIDs, lidocaine, magnesium, and $\beta$-blockers, alongside inhalational agents (e.g., sevoflurane, desflurane) (15,16).

### Data Extraction

After removing duplicates, literature screening and data extraction were conducted using Covidence online software (Veritas Health Innovation, LTD). FW and YZ independently screened titles and abstracts for eligibility, followed by a full-text review. Disagreements were resolved through consensus or by an adjudicator. Data extracted included study titles, authors, publication years, countries, funding status, patient characteristics, and reported outcome measures. We

contacted authors by email (up to 3 times) for any missing or unclear information.

### Outcomes of Interest

The primary outcome was the quality of postoperative recovery, measured using the Quality of Recovery (QoR)-40 or QoR-15 at postoperative 24 hours. The QoR-40 includes 40 items across 5 domains: emotional state, physical comfort, psychological support, physical independence, and pain, each rated on a 5-point scale. Scores range from 40 to 200, with higher scores indicating better recovery quality. The QoR-15 consists of 15 items, each rated on a 10-point scale, yielding a total score from 0 (poorest recovery) to 150 (excellent recovery) (17). The minimal clinically important difference (MCID) for the QoR-40 and QoR-15 scores are 6.3 and 6.0, respectively (18,19).

Secondary outcomes were time to extubation; length of stay in the postanesthesia care unit (PACU); pain scores at rest or during exercise at 24 hours postsurgery; and adverse events such as nausea and vomiting. The Visual Analog Scale score's MCID was one cm (20).

### Risk of Bias and Certainty of Evidence Assessment

FW and YZ independently assessed the risk of bias using the Cochrane RoB 2.0 tool (The Nordic Cochrane Centre for The Cochrane Collaboration). This tool evaluates bias in randomization, intervention deviations, missing outcome data, outcome measurement, and selective reporting of results. Studies were classified as having low, moderate, or high risk of bias.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess the certainty of the evidence, rating it as high, moderate, low, or very low based on considerations of bias risk, inconsistency, indirectness, imprecision, and publication bias. Disagreements were resolved through discussion or by an adjudicator.

### Statistical Analysis

Statistical analyses were conducted using Stata 18.0 (StataCorp LLC). Medians with interquartile ranges or 95% CIs from the included studies were converted to mean (SD) for meta-analysis. The different scales used to assess pain were uniformly converted to the Visual Analog Scale, the pain measurement instrument most commonly used in acute pain trials (21,22). A random-effects model was used due to the inherent clinical heterogeneity. Mean difference (MD) was calculated for quality of recovery or continuous outcomes, and relative risk for dichotomous outcomes. A continuity correction was applied for trials with zero events in either group by adding 0.5 to all cells in 2×2 tables with empty cells (23). Results were presented in forest plots, with heterogeneity assessed using the $I^2$ statistic, categorized as low (< 50%), moderate (50%–74%), or high (> 75%).

Subgroup analyses and meta-regressions were performed to explore potential sources of heterogeneity. Classifying surgical procedures was based on the POSSUM (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) system of surgical audit (24). Publication bias was assessed using Egger's and Begg's tests for outcomes with at least 10 studies. We used Trial Sequential Analysis (TSA) Version 0.9.5.10 Beta (Copenhagen Trial Unit) was for the primary outcome to confirm whether the required sample size had been reached. A $P$ value of $< 0.05$ was considered significant.

## Results

Out of 709 unique articles identified, 57 were reviewed in full text. Of these, 41 studies were excluded; 16 studies met the inclusion criteria for meta-analysis (8,25-39) (Fig. 1). The key characteristics of the included studies are summarized in Table 1. Among the 1,968 patients, 63.8% were women, with an average age ranging from 30 to 58 years. Most of the studies were conducted in The People's Republic of China, accounting for 50% of the total. Thirteen studies reported industry funding. The OFA regimens primarily consisted of dexmedetomidine, esketamine, lidocaine, ketamine, clonidine, and magnesium sulfate, while the OBA regimens mainly included sufentanil, fentanyl, and remifentanil.

The risk-of-bias assessment showed that 56.3% (9 trials) had a low risk, 37.5% (6 trials) had some concerns, and one trial had a high risk (Suppl. File 2). The assessment of evidence certainty is presented in Suppl. File 3. A total of 16 trials evaluated recovery quality at 24 hours postsurgery, with 12 trials using the QoR-40 score and 4 trials using the QoR-15 score. Very low-certainty evidence (12 trials, 1,612 patients) indicated that OFA was associated with an increased QoR-40 score at postoperative 24 hours (MD 6.33; 95% CI, 3.48 to 9.17; Fig. 2a). Begg-Mazumdar Kendall's Tau (Kendall's $\tau$-a = 0.394, $P$ = 0.087) and Egger tests (intercept = 3.111, $P$ = 0.077) showed no publication bias. A subgroup analysis

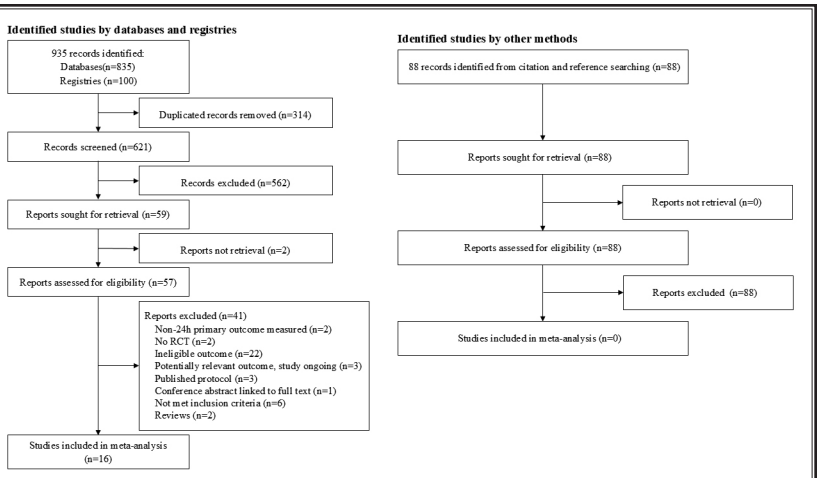



Fig. 1. *(Preferred Reporting Items for Systematic Reviews and Meta-analyses) PRISMA flow chart of study selection.*

(Fig. 2b) and meta-regression (Suppl. File 4) did not identify any sources of heterogeneity. Trial sequential analysis confirmed that robust evidence was reached for QoR-40 score (Fig. 2c).

Low-certainty evidence (4 trials, 355 patients) suggested potential improvements in QoR-15 scores at postoperative 24 hours (MD 10.00; 95% CI, 2.25 to 17.74; Fig. 3) with OFA. The 95% CI crossed the MCID thresholds for both QoR-40 and QoR-15 score, indicating that the clinical significance of OFA in improving recovery quality at postoperative 24 hours is uncertain.

Moderate-certainty evidence indicated that OFA was associated with a reduced incidence of postoperative adverse events. Nausea (7 trials, 1,287 patients) occurred more frequently in the OBA group, with a pooled relative risk of -1.02 (95% CI, -1.35 to -0.69), as shown in Fig. 4a's forest plot. Vomiting (5 trials, 1,074 patients) also occurred more frequently in the OBA group, with a pooled relative risk of -1.03 (95% CI, -1.47 to -0.59), as shown in Fig. 4b's forest plot. In addition, the combined occurrence of nausea and vomiting (6 trials, 1,206 patients) was higher in the OBA group, with a pooled relative risk of -0.85 (95% CI, -1.15 to -0.56), as shown in Fig. 4c's forest plot.

A total of 10 trials involving 1,423 patients reported pain at rest at postoperative 24 hours and were included in the meta-analysis. Very low-certainty evidence showed that OFA was associated with a reduction in pain scores at rest at postoperative 24 hours (MD -0.62; 95% CI, -0.89 to -0.35; Fig. 5a). The 95% CI fell within MCID thresholds, suggesting OFA likely has no significant clinical effect on postoperative pain relief at rest.

The Begg-Mazumdar Kendall's Tau (Kendall's tau-a = 0.111; $P$ = 0.721) and Egger's tests (intercept = 0.520; $P$ = 0.652) indicated no publication bias. Moderate-certainty evidence showed no significant between-group differences for pain scores during exercise at postoperative 24 hours (4 trials, 336 patients; MD -0.17; 95% CI, -0.47 to 0.13; Fig. 5b).

Eight trials involving 1,387 patients reported time to extubation and were included in the meta-analysis. Low-certainty evidence indicated that OFA was not associated with a shortened extubation time (MD -0.01; 95% CI, -1.27 to 1.25; Supplementary File 5).

Ten trials involving 1,581 patients reported the length of stay in the PACU and were included in the meta-analysis. Very low-certainty evidence indicated that OFA was associated with a reduced length of stay in the PACU (MD 0.05; 95% CI, 0.00 to 0.10; Suppl. File 6). The Begg-Mazumdar Kendall's Tau (Kendall's tau-a = 0.111; $P$ = 0.721) and Egger's tests (intercept = 3.110; $P$ = 0.089) showed no evidence of publication bias.

## Discussion

Based on 16 trials involving 1,968 patients, our systematic review and meta-analysis concludes that it is uncertain whether OFA is superior to OBA in improving postoperative recovery quality. However, OFA was associated with a reduced risk of postoperative nausea and vomiting and PACU length of stay. No MCIDs were observed in time to extubation and postoperative pain scores. Together, these findings provide valuable insights for optimizing anesthesia protocols for patients having surgery.

Opioid-free multimodal anesthesia strategies are increasingly popular for pain relief and reducing opioid reliance. Dexmedetomidine, as well as other $\alpha$–2 adrenergic receptor agonists, enhance inhibitory pathways and reduce neuronal hyper-responsiveness (40). Ketamine is a noncompetitive antagonist of NMDA receptors, which explains its anesthetic and analgesic effects (41). NSAIDs reduce peripheral inflammation by inhibiting cyclooxygenase, thereby reducing nociceptive input. Calcium channel blockers such as gabapentin decrease neurotransmitter release and pain

Table 1. *Study characteristics*.

| Study | Country | Industry Funding | Surgery | Sample size | Age, yrs, mean (SD) | Women, n (%) | Opioid-free Anesthesia | Opioid-based Anesthesia |
|---|---|---|---|---|---|---|---|---|
| Léger, 2023 | France Republic | Yes | Major surgery (plastic, gastrointestinal, urologic, gynecologic, and Ear-Nose-Throat (ENT) surgeries) | 133 | 45.9 (15.70) | 116 (87.2%) | At least 2 drugs among ketamine, lidocaine, clonidine, and magnesium sulfate | Sufentanil or remifentanil |
| Krishnasamy Yuvaraj, 2023 | Republic of India | No | Modified radical mastectomy | 60 | 46.2 (8.70) | 60 (100%) | Ketamine, lignocaine (lidocaine), dexmedetomidine | Fentanyl |
| Ibrahim, 2022 | Arab Republic of Egypt | No | Laparoscopic sleeve gastrectomy | 103 | 30.3 (11.46) | 63 (61.2%) | Dexmedetomidine, ketamine, lidocaine, | Fentanyl |
| Zhou, 2023 | People's Republic of China | Yes | Endoscopic sinus surgery | 773 | 42.27 (19.76) | 304 (39.3%) | Dexmedetomidine, lidocaine, | Sufentanil, remifentanil |
| Liu, 2023 | People's Republic of China | No | Thyroid surgery | 66 | 49.35 (10.98) | 55 (83.3%) | Dexmedetomidine, s-ketamine, | Remifentanil |
| Cha, 2023 | People's Republic of China | Yes | Hysteroscopy | 90 | 38.8 (6.62) | 90 (100%) | Lidocaine | Sufentanil |
| Saravanaperumal, 2022 | Republic of India | No | Oocyte retrieval | 62 | 30.1 (2.78) | 62 (100%) | Dexmedetomidine | Fentanyl |
| Zhang, 2023 | People's Republic of China | Yes | Breast cancer surgery | 80 | 50.85 (10.93) | 80 (100%) | Lidocaine | Fentanyl |
| Hontoir, 2016 | Kingdom of Belgium | unclear | Total mastectomy or lumpectomy | 64 | 53.54 (12.76) | 64 (100%) | Clonidine, ketamine, lidocaine, | Remifentanil |
| Wang, 2022 | People's Republic of China | Yes | Video-assisted thoracic surgery | 79 | 57.91 (11.91) | 51 (64.6%) | Dexmedetomidine, lidocaine | Sufentanil, remifentanil |
| Hao, 2023 | People's Republic of China | Yes | Laparoscopic cholecystectomy | 80 | 44.1 (10.14) | 45 (56.3%) | Dexmedetomidine, esketamine | Sufentanil, remifentanil |
| Hakim, 2019 | Arab Republic of Egypt | No | Gynecological laparoscopic surgery | 80 | 36.15 (6.92) | 80 (100%) | Dexmedetomidine | Fentanyl |
| Mulier, 2018 | Kingdom of Belgium | unclear | Laparoscopic bariatric surgery | 45 | 43.07 (11.08) | 28 (50.9%) | Dexmedetomidine, ketamine, lidocaine | Sufentanil |
| Wang, 2024 | People's Republic of China | unclear | Oral and maxillofacial surgery, thyroid surgery, urinary short surgery, and lower extremity vascular surgery | 120 | 48.15 (15.00) | 59 (49.2%) | Dexmedetomidine, esketamine | Sufentanil |
| Gao, 2024 | People's Republic of China | Yes | Retroperitoneoscopic renal surgery | 58 | 53.15 (11.31) | 23 (39.7%) | Dexmedetomidine, esketamine | Sufentanil, remifentanil |
| Choi, 2022 | Republic of Korea | Yes | Gynecological laparoscopy | 75 | 42.52 (10.05) | 75 (100%) | Dexmedetomidine, lidocaine | Remifentanil |

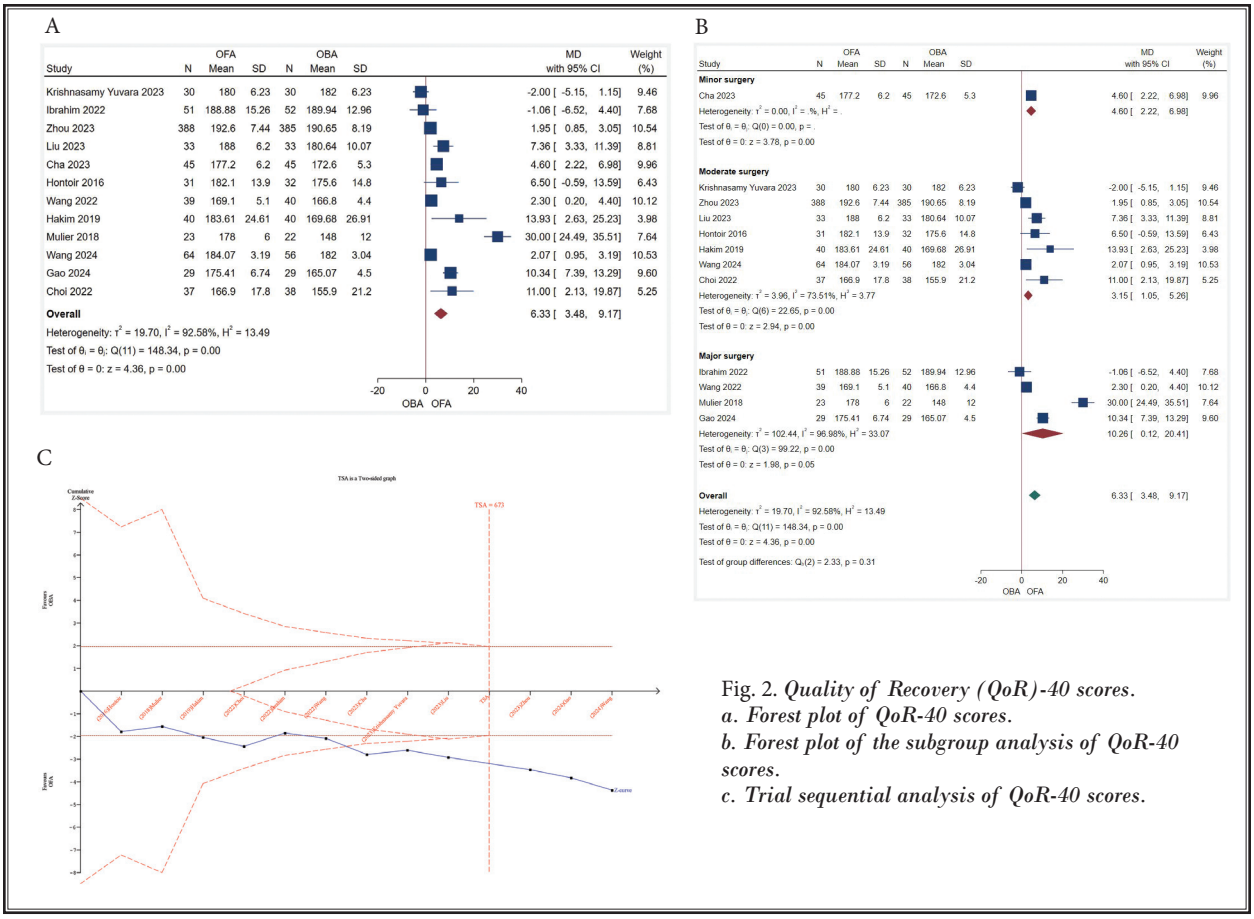



Fig. 2. *Quality of Recovery (QoR)-40 scores.*
*a. Forest plot of QoR-40 scores.*
*b. Forest plot of the subgroup analysis of QoR-40 scores.*
*c. Trial sequential analysis of QoR-40 scores.*

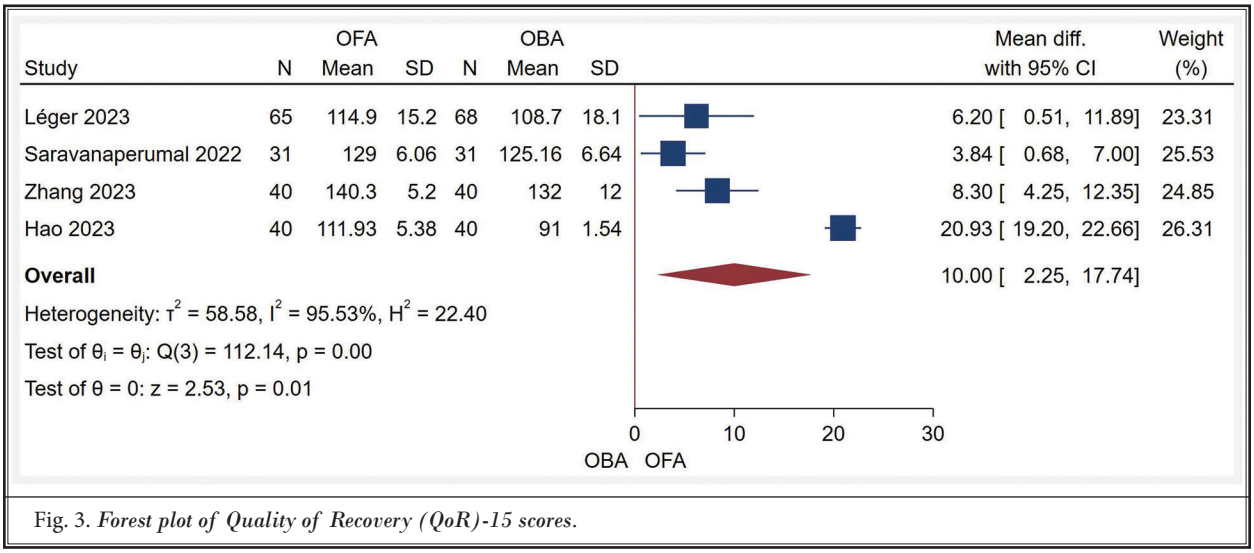
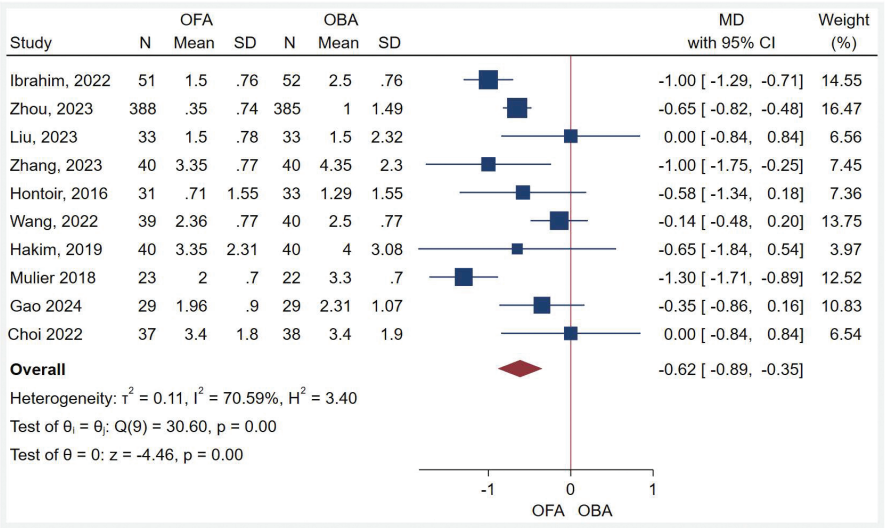


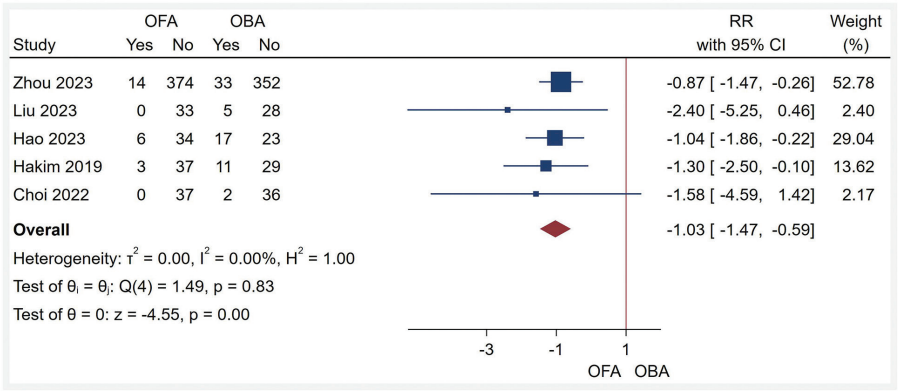

Fig. 3. *Forest plot of Quality of Recovery (QoR)-15 scores.*

signal transmission. Local anesthetics block sodium channels and prevent action potential propagation in peripheral nerves. Esmolol and other β-adrenergic receptor antagonists mitigate sympathetic activation, reduce stress responses, and may also exert central antihyperalgesic effects (42). Findings from Léger and colleagues (29) demonstrated that, compared with standard anesthesia, protocols incorporating at least 2

A




B




C

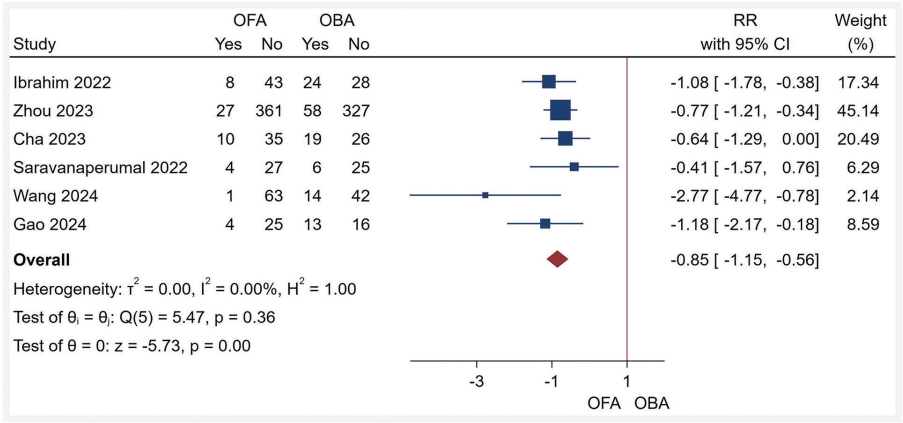



Fig. 4. *Postoperative nausea and vomiting. a. Forest plot of nausea incidences. b. Forest plot of vomiting incidences. c. Forest plot of nausea and vomiting incidences.*

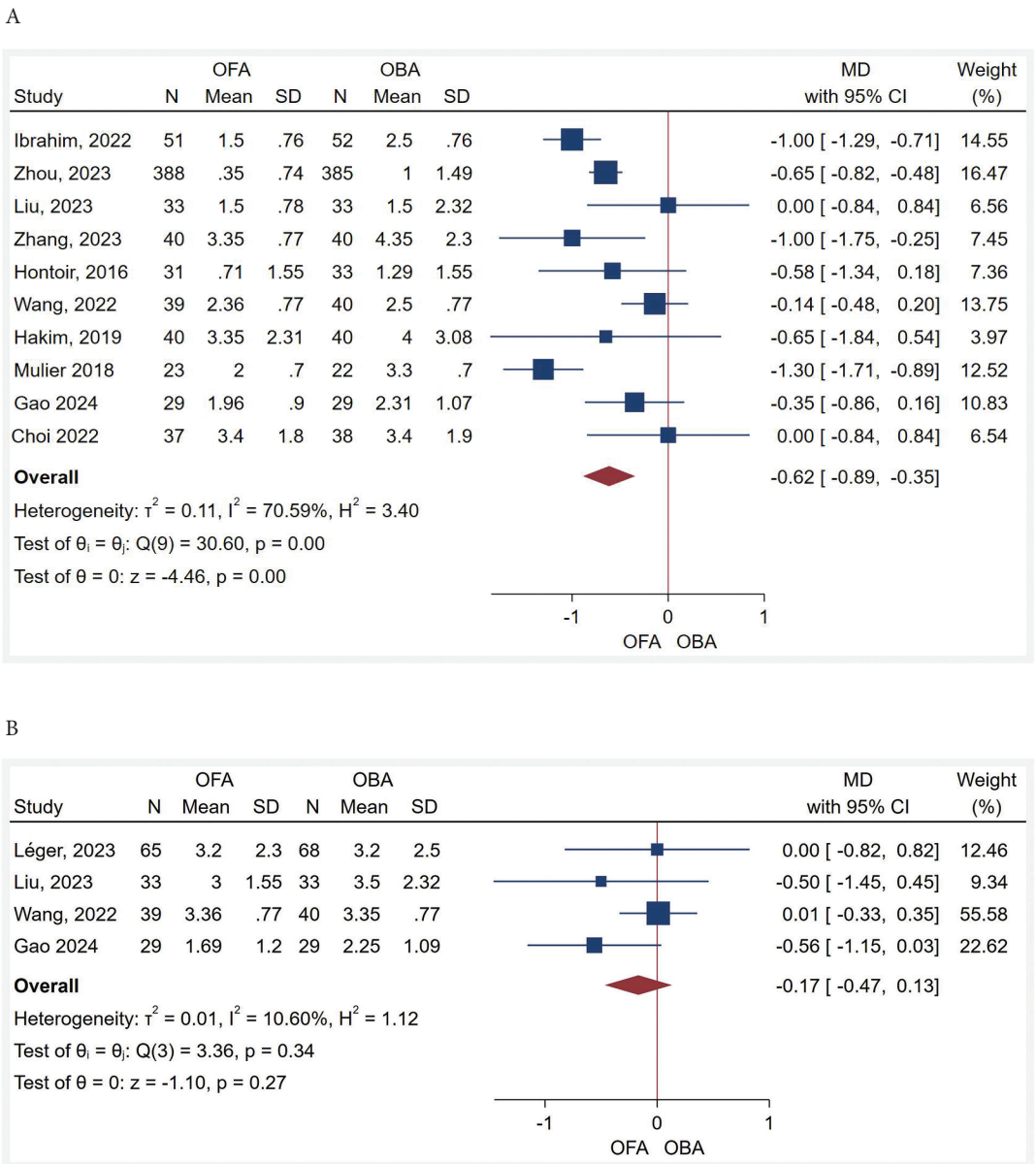



Fig. 5. *Postoperative pain scores. A. Forest plot of postoperative pain scores at rest. B. Forest plot of postoperative pain scores during exercise.*

nonopioid agents (e.g., ketamine, lidocaine, clonidine, magnesium sulfate) were associated with statistically (but not clinically) significant improvement in postoperative recovery quality (29).

Recent recommendations for enhanced postoperative recovery emphasize using alternative medications to reduce perioperative opioid use and mitigate opioid-related side effects (43). A key strength of our meta-analysis is that it addresses a significant knowledge gap regarding the effect of OFA vs OBA on postoperative recovery quality. While QoR-40 and QoR-15 scores showed statistically significant differences between the 2 groups, and trial sequential analysis for the QoR-40 score provided robust evidence of improved recovery quality with OFA, the 95% CI crossed the MCID thresholds, suggesting clinical relevance was uncertain. Sub-

group analyses and meta-regressions were conducted to address high heterogeneity; however, no sources of heterogeneity were identified.

We observed a trend toward improved recovery quality with OFA in minor to moderate surgeries, while results for major surgeries were inconsistent. The variability in surgical procedures, diverse OFA combinations, and small sample sizes limited our ability to classify studies based on surgery type and scale. Despite these limitations, we adopted a robust methodology, including a comprehensive search strategy for randomized controlled trials without language restrictions, adhering to PRISMA standards, interpreting results using MCID, and assessing evidence quality through the GRADE approach. Although results using TSA software suggest that the current sample size is sufficient for drawing statistically significant conclusions, the high heterogeneity underscores the need for future research to focus on mitigating this variability. This can be achieved by strategies such as standardizing drug combinations, refining the classification of patient and surgical types, and increasing sample sizes. Notably, expanding the sample size offers significant advantages, particularly in reducing heterogeneity and strengthening the external validity of the findings.

The pain scores at rest at postoperative 24 hours showed statistically significant differences between OFA and OBA. Nevertheless, the 95% CI for MD values fell within the MCID thresholds (-1 cm to 1 cm), indicating no clinical significance. These findings align with several previous meta-analyses that have shown comparable analgesia between OFA and OBA (10,13,44,45). Interestingly, meta-analyses conducted by Malo-Manso, et al (46) and Hung, et al (47) reported that OFA has a significant advantage over OBA for reducing pain intensity at postoperative 24 hours (46,47). The variability in outcomes across studies may be attributed to differences in opioid-free formulations, surgical procedures, and patient populations. These results highlight the need for further investigation into the efficacy of OFA.

Our meta-analysis shows that OFA has a clear benefit over OBA for reducing the incidence of PONV. This finding is consistent with previous meta-analyses (10,13,48) and reinforces the association between OFA and a lower risk of PONV. Given this advantage, incorporating OFA into protocols for preventing PONV is particularly recommended for patients at high risk of nausea and vomiting.

Several limitations warrant consideration in our review. First, substantial heterogeneity in the primary outcome may stem from factors such as varying types of surgeries, diverse OFA regimens, small sample sizes, and methodological inconsistencies, including blinding approaches. Despite attempts to investigate the sources of heterogeneity, the underlying causes remain unresolved, highlighting the need for future studies with standardized opioid-free combinations and larger sample sizes. Second, the overrepresentation of women and middle-aged patients in the included studies may restrict the generalizability of the findings to broader populations. Furthermore, our review did not include statistical analyses of side effects specifically associated with OFA, such as hypertension, hypotension, bradycardia, and tachycardia, leaving these aspects unexplored.

The findings of our meta-analysis indicate that while it is uncertain whether OFA is superior to OBA for enhancing the quality of postoperative recovery, it does substantially reduce the incidence of PONV. However, this finding primarily originates from small trials conducted in elective surgical settings. Although these findings support using OFA, larger and high-quality studies are essential to validate its impact on improving postoperative recovery quality.

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## Author Contributions

Fei Wang and Yihao Zhu are first co-authors and they have equal contribution. Fei Wang: concept, methodology, analysis, first draft, manuscript review, editing. Yihao Zhu: concept, methodology, analysis, first draft. Zhongyu Shi: supervision, methodology, data analysis, manuscript review, editing. Mengxue Liu: concept, analysis. Fei Peng: methodology, analysis. Tao Zhu: supervision, data analysis, manuscript review, editingn.

## Disclaimer

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## References


1. Egan TD. Are opioids indispensable for general anaesthesia? *Br J Anaesth* 2019; 122:e127-e135.
2. Fawcett WJ, Jones CN. Bespoke intra-operative anaesthesia - The end of the formulaic approach? *Anaesthesia* 2018; 73:1062-1066.
3. Levy N, Quinlan J, El-Boghdadly K, et al. An international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients. *Anaesthesia* 2021; 76:520-536.
4. Oderda GM, Gan TJ, Johnson BH, Robinson SB. Effect of opioid-related adverse events on outcomes in selected surgical patients. *J Pain Palliat Care Pharmacother* 2013; 27:62-70.
5. Tochie JN, Bengono Bengono RS, Metogo JM, et al. The efficacy and safety of an adapted opioid-free anesthesia regimen versus conventional general anesthesia in gynecological surgery for low-resource settings: A randomized pilot study. *BMC Anesthesiol* 2022; 22:325.
6. Fortier J, Chung F, Su J. Unanticipated admission after ambulatory surgery--A prospective study. *Can J Anaesth* 1998; 45:612-619.
7. Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. *Anesthesiology* 2000; 92:958-967.
8. Hontoir S, Saxena S, Gatto P, et al. Opioid-free anesthesia: What about patient comfort? A prospective, randomized, controlled trial. *Acta Anaesthesiol Belg* 2016; 67:183-190.
9. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. *Br J Anaesth* 2014; 112:906-911.
10. Salomé A, Harkouk H, Fletcher D, Martinez V. Opioid-free anesthesia benefit-risk balance: A systematic review and meta-analysis of randomized controlled trials. *J Clin Med* 2021; 10:2069.
11. Toleska M, Dimitrovski A. Is opioid-free general anesthesia more superior for postoperative pain versus opioid general anesthesia in laparoscopic cholecystectomy? *Pril (Makedon Akad Nauk Umet Odd Med Nauki)* 2019; 40:81-87.
12. Hwang W, Lee J, Park J, Joo J. Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: A randomized controlled study. *BMC Anesthesiol* 2015; 15:21.
13. Ao Y, Ma J, Zheng X, Zeng J, Wei K. Opioid-sparing anesthesia versus opioid-free anesthesia for the prevention of postoperative nausea and vomiting after laparoscopic bariatric surgery: A systematic review and network meta-analysis. *Anesth Analg* 2025; 140:385-396.
14. Hublet S, Galland M, Navez J, et al. Opioid-free versus opioid-based anesthesia in pancreatic surgery. *BMC Anesthesiol* 2022; 22:9.
15. Beloeil H, Garot M, Lebuffe G, et al. Balanced opioid-free anesthesia with dexmedetomidine versus balanced anesthesia with remifentanil for major or intermediate noncardiac surgery. *Anesthesiology* 2021; 134:541-551.
16. Yan H, Chen W, Chen Y, et al. Opioid-free versus opioid-based anesthesia on postoperative pain after thoracoscopic surgery: The use of intravenous and epidural esketamine. *Anesth Analg* 2023; 137:399-408.
17. Léger M, Campfort M, Cayla C, Parot-Schinkel E, Lasocki S, Rineau E. Validation of an alternative French version of the Quality of Recovery-15 Score: The FQoR-15. *Br J Anaesth* 2020; 125:e345-e347.
18. Myles PS, Myles DB, Galagher W, Chew C, MacDonald N, Dennis A. Minimal clinically important difference for three quality of recovery scales. *Anesthesiology* 2016; 125:39-45.
19. Myles PS, Myles DB. An updated minimal clinically important difference for the QoR-15 Scale. *Anesthesiology* 2021; 135:934-935.
20. Myles PS, Myles DB, Galagher W, et al. Measuring acute postoperative pain using the visual analog scale: The minimal clinically important difference and patient acceptable symptom state. *Br J Anaesth* 2017; 118:424-429.
21. Gewandter JS, Eisenach JC, Gross RA, et al. Checklist for the preparation and review of pain clinical trial publications: A pain-specific supplement to CONSORT. *Pain Rep* 2019; 4:e621.
22. Gilron I, Carr DB, Desjardins PJ, Kehlet H. Current methods and challenges for acute pain clinical trials. *Pain Rep* 2019; 4:e647.
23. Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC Med Res Methodol* 2007; 7:5.
24. Copeland GP. The POSSUM system of surgical audit. *Arch Surg* 2002; 137:15-19.
25. Mulier JP, Wouters R, Dillemans B, Dekock M. A randomized controlled, double-blind trial evaluating the effect of opioid-free versus opioid general anaesthesia on postoperative pain and discomfort measured by the QoR-40. *J Clin Anesth Pain Med* 2018; 6:2.
26. Liu Z, Bi C, Li X, Song R. The efficacy and safety of opioid-free anesthesia combined with ultrasound-guided intermediate cervical plexus block vs. opioid-based anesthesia in thyroid surgery—A randomized controlled trial. *J Anesth* 2023; 37:914-922.
27. Wang P, Zhou X, Wang S, et al. Opioid-free anesthesia improves postoperative recovery quality of small and medium-sized surgery: A prospective, randomized controlled study. *Minerva Anestesiol* 2024; 90:759-768.
28. Gao H, Xu Z, Zhang L, et al. Superiority of opioid free anesthesia with regional block over opioid anesthesia with regional block in the quality of recovery after retroperitoneiscopic renal surgery: A randomized controlled trial. *Minerva Anestesiol* 2024; 90:845-854.
29. Léger M, Perrault T, Pessiot-Royer S, et al. Opioid-free anesthesia protocol on the early quality of recovery after major surgery (SOFA trial): A randomized clinical trial. *Anesthesiology* 2024; 140:679-689.
30. Choi H, Song JY, Oh EJ, Chae MS, Yu S, Moon YE. The effect of opioid-free anesthesia on the quality of recovery after gynecological laparoscopy: A prospective randomized controlled trial. *J Pain Res* 2022; 15:2197-2209.
31. Ibrahim M, Elnabtity AM, Hegab A, Alnujaidi OA, El Sanea O. Combined opioid free and loco-regional anaesthesia enhances the quality of recovery in sleeve gastrectomy done under ERAS protocol: A randomized controlled trial. *BMC Anesthesiol* 2022; 22:29.
32. Yuvaraj AK, Gayathri B, Balasubramanian N, Mirunalini G. Patient comfort during postop period in breast cancer surgeries: A randomized controlled trial comparing opioid and opioid-free anesthesia. *Cureus* 2023; 15:e33871.
33. Cha N, Hu Y, Zhu G, Long X, Jiang J,

Gong Y. Opioid-free anesthesia with lidocaine for improved postoperative recovery in hysteroscopy: A randomized controlled trial. *BMC Anesthesiol* 2023; 23:192.

34. Saravanaperumal G, Udhayakumar P. Opioid-free TIVA improves post-operative quality of recovery (QOR) in patients undergoing oocyte retrieval. *J Obstet Gynaecol India* 2022; 72:59-65.
35. Zhang Q, Wu Y, An H, Feng Y. Postoperative recovery after breast cancer surgery: A randomised controlled trial of opioid-based versus opioid-free anaesthesia with thoracic paravertebral block. *Eur J Anaesthesiol* 2023; 40:552-559.
36. Zhou F, Cui Y, Cao L. The effect of opioid-free anaesthesia on the quality of recovery after endoscopic sinus surgery: A multicentre randomised controlled trial. *Eur J Anaesthesiol* 2023; 40:542-551.
37. Wang XR, Jia XY, Jiang YY, Li ZP, Zhou QH. Opioid-free anesthesia for postoperative recovery after video-assisted thoracic surgery: A prospective, randomized controlled trial. *Front Surg* 2023; 9:1035972.
38. Hakim KYK, Wahba WZB. Opioid-free total intravenous anesthesia improves postoperative quality of recovery after ambulatory gynecologic laparoscopy. *Anesth Essays Res* 2019; 13:199-203.
39. Hao C, Xu H, Du J, et al. Impact of opioid-free anesthesia on postoperative quality of recovery in patients after laparoscopic cholecystectomy-A randomized controlled trial. *Drug Des Devel Ther* 2023; 17:3539-3547.
40. Tang C, Xia Z. Dexmedetomidine in perioperative acute pain management: A non-opioid adjuvant analgesic. *J Pain Res* 2017; 10:1899-1904.
41. Mion G, Himmelseher S. Esketamine: Less drowsiness, more analgesia. *Anesth Analg* 2024; 139:78-91.
42. Kianian S, Bansal J, Lee C, Zhang K, Bergese SD. Perioperative multimodal analgesia: A review of efficacy and safety of the treatment options. *Anesth Periop Sci* 2024; 2:9.
43. Smith TW, Wang X, Singer MA, Godellas CV, Vaince FT. Enhanced recovery after surgery: A clinical review of implementation across multiple surgical subspecialties. *Am J Surg* 2020; 219:530-534.
44. Feenstra ML, Jansen S, Eshuis WJ, van Berge Henegouwen MI, Hollmann MW, Hermanides J. Opioid-free anesthesia: A systematic review and meta-analysis. *J Clin Anesth* 2023; 90:111215.
45. Mathew DM, Fusco PJ, Varghese KS, et al. Opioid-free anesthesia versus opioid-based anesthesia in patients undergoing cardiovascular and thoracic surgery: A meta-analysis and systematic review. *Semin Cardiothorac Vasc Anesth* 2023; 27:162-170.
46. Malo-Manso A, Fontaneda-Heredia A, Romero-Molina S, Sepúlveda-Haro E, Escalona-Belmonte JJ, Guerrero-Orriach JL.. Opioid-free anaesthesia improves anaesthesia recovery when compared with that of opioid-based anaesthesia. Systematic review and meta-analysis of clinical trials. *Curr Med Chem* 2023; 30:1667-1681.
47. Hung KC, Chiu CC, Hsu CW, et al. Impact of opioid-free anesthesia on analgesia and recovery following bariatric surgery: A meta-analysis of randomized controlled studies. *Obes Surg* 2022; 32:3113-3124.
48. da Silveira CA, Rasador AC, Medeiros HJ, et al. Opioid-free anesthesia for minimally invasive abdominal surgery: A systematic review, meta-analysis, and trial sequential analysis. *Can J Anaesth* 2024; 71:1466-1485.

Suppl. File 1. *Search strategy.*

## Search Strategy

***MEDLINE by PubMed search:***

#1 ((opioid-free anaesthesia[Title/Abstract]) OR (opioid-free analgesia[Title/Abstract])) OR (opioid-free anesthesia[Title/Abstract])

#2 ((randomized controlled trial[Publication Type]) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])

#3 #1 AND #2

***Cochrane Library by Ovid search:***

#1 'opioid-free anesthesia'.ab,ti.

#2 'opioid-free anaesthesia'.ab,ti.

#3 'opioid-free analgesia'.ab,ti.

#4 1 or 2 or 3

***Embase by Ovid:***

#1 'opioid-free anesthesia'.ab,ti.

#2 'opioid-free anaesthesia'.ab,ti.

#3 'opioid-free analgesia'.ab,ti.

#4 1 or 2 or 3

#5 exp randomized controlled trial/

#6 4 and 5

***Web of Science:***

#1 opioid-free anaesthesia (Topic) or opioid-free anesthesia (Topic) or opioid-free analgesia (Topic)

#2 randomized controlled trial (Topic) or randomized (Topic) or placebo (Topic)

#3 #1 AND #2

***BIOSIS by Ovid search:***

#1 opioid-free anesthesia.ab,ti.

#2 opioid-free anaesthesia.ab,ti.

#3 opioid-free analgesia.ab,ti.

#4 1 or 2 or 3

Suppl. File 2. *Risk of bias assessment*.

| Study | Bias Resulting From Randomization | Bias Resulting From Allocation Concealment | Bias Resulting From Missing Outcome Data | Bias Resulting From Blinding Outcome Measurement | Bias Resulting From Selective Reporting | Overall Risk of Bias |
|---|---|---|---|---|---|---|
| Léger (2023) | Low | Low | Low | Low | Low | Low |
| Krishnasamy Yuvaraj (2023) | Low | Low | Low | Low | Low | Low |
| Ibrahim (2022) | Low | Low | Low | Low | Low | Low |
| Zhou (2023) | Low | Some concern | Low | Low | Low | Some concern |
| Liu (2023) | Low | Low | Low | Low | Low | Low |
| Cha (2023) | Low | Low | Low | Low | Low | Low |
| Saravanaperumal (2022) | Low | Some concern | Low | Some concern | Some concern | Some concern |
| Zhang (2023) | Some concern | Low | Low | Low | Low | Some concern |
| Hontoir (2016) | Low | Some concern | Low | Low | Low | Some concern |
| Wang (2022) | Low | Low | Low | Low | Low | Low |
| Hao (2023) | Low | Low | Low | Low | Low | Low |
| Hakim (2019) | Low | Some concern | Low | Low | Low | Some concern |
| Mulier (2018) | Low | Some concern | Low | Some concern | High | High |
| Wang (2024) | Low | Some concern | Low | Low | Low | Some concern |
| Gao (2024) | Low | Low | Low | Low | Low | Low |
| Choi (2022) | Low | Low | Low | Low | Low | Low |

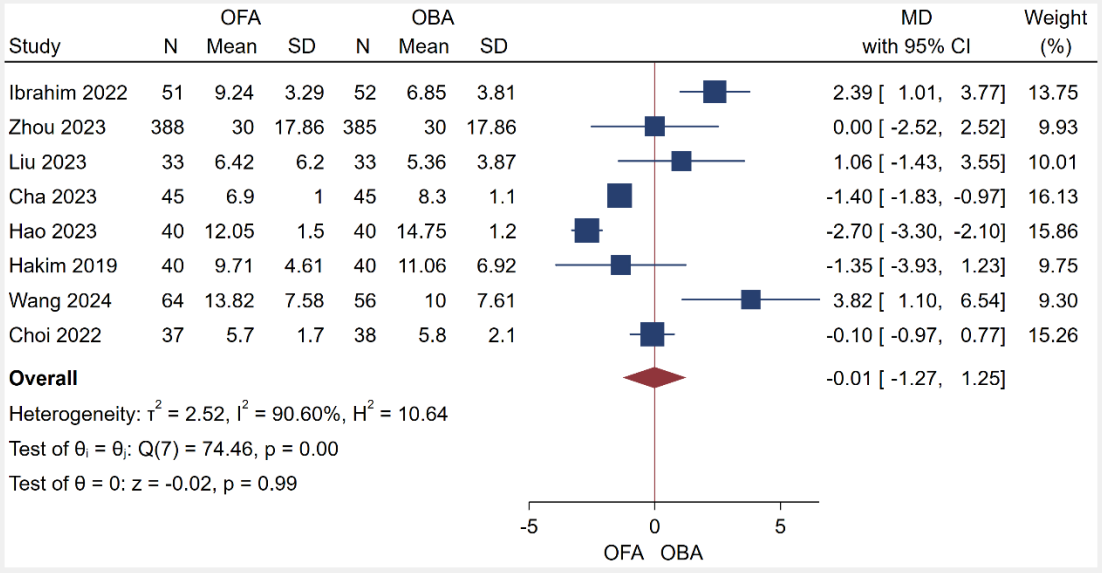
Suppl.File 3. *Quality of evidence for QoR-40 score, QoR-15 scores, extubation time, length of stay in the postanesthesia care unit (PACU), pain scores at rest and during exercise, nausea, vomiting, nausea and vomiting. QoR= quality of recovery. a We downgraded by one level due to high bias risk in studies. b As $I^2 > 75\%$, we downgraded by one level. c We downgraded by one level as optimal sample size was not met.*

| Outcome | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | No. of Patients | Effect size in relative (95% CI) or absolute (95% CI) | | Quality of Evidence |
|---|---|---|---|---|---|---|---|---|---|
| QoR-40 | Serious [a] | Serious [b] | Not serious | Serious c | None | 1,435 | - | 3.01 (2.19 to 3.83) | Very low (⊕OOO) |
| QoR-15 | Not serious | Serious [b] | Not serious | Serious c | None | 355 | - | 9.92 (0.05 to 19.89) | Low (⊕⊕OO) |
| Extubation time | Not serious | Serious [b] | Not serious | Serious c | None | 1,387 | - | 0.01 (1.25 to 1.27) | Low (⊕⊕OO) |
| Length of stay in PACU | Not serious | Serious [b] | Not serious | Serious c | None | 1,581 | - | 0.05 (0 to 0.1) | Low (⊕⊕OO) |
| Pain scores at rest | Serious [a] | Serious [b] | Not serious | Serious c | None | 1,423 | - | 0.62 (0.89 to 0.34) | Very low (⊕OOO) |
| Pain scores during exercise | Not serious | Not serious | Not serious | Serious c | None | 336 | - | 0.17 (0.47 to 0.13) | Moderate (⊕⊕⊕O) |
| Nausea | Not serious | Not serious | Not serious | Serious c | None | 1,287 | 0.34 (0.23 to 0.51) | - | Moderate (⊕⊕⊕O) |
| Vomiting | Not serious | Not serious | Not serious | Serious c | None | 1,074 | 0.36 (0.23 to 0.56) | - | Moderate (⊕⊕⊕O) |
| Nausea and vomiting | Not serious | Not serious | Not serious | Serious c | None | 1,206 | 0.42 (0.30 to 0.58) | - | Moderate (⊕⊕⊕O) |

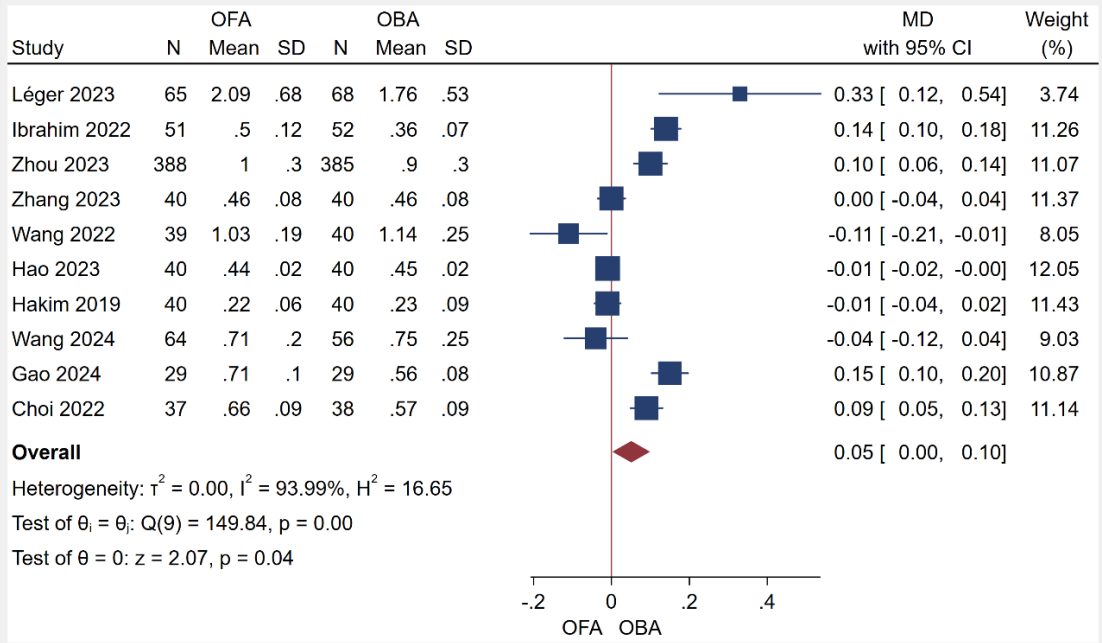
Suppl. File 4. *Meta-regression of moderators of opioids-free anesthesia on QoR-40 score*

| Moderator | Number of RCTs | Coefficient | 95% CI | *P* value | $R^2$† |
|---|---|---|---|---|---|
| Funding | 12 | 3.784 | (-2.46, 10.02) | 0.235 | 0.04 |
| Year | 12 | -1.851 | (-3.67, -0.04) | 0.046 | 0.24 |
| Type of surgery | 12 | 5.374 | (-4.89, 15.63) | 0.305 | 0.00 |

$R^2$† equal to $R^2$ analogue.




Suppl. File 5. *Forest plot for extubation time.*




Suppl. File 6. *Forest plot for the length of stay in PACU.*