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Safety and effectiveness of multimodal opioid-free anaesthesia for pain and recovery after laparoscopic surgery: a systematic review and meta-analysis

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ABSTRACT

Objectives This study aimed to investigate the safety and effectiveness of opioid-free anaesthesia (OFA) versus conventional opioid anaesthesia (OA) for postoperative pain management and recovery in patients undergoing laparoscopic surgery.

Design Systematic review and meta-analysis.

Data sources The databases of PubMed, Embase, Cochrane Library and Web of Science were searched from inception to August 2023.

Eligibility criteria for selecting studies We included any randomised controlled trial comparing OFA (at least two drugs or two more alternatives to opioids) with OA for laparoscopic surgery. The primary outcomes included postoperative pain scores, measured on a Numerical Rating Scale or Visual Analogue Scale ranging from 0 to 10, at 0–2 hours and 24 hours postoperatively; postoperative analgesic consumption, measured in morphine equivalent doses (mg); and quality of recovery, assessed using the QoR-40 score (ranging from 40 to 200). The secondary outcomes included the incidence of postoperative nausea and vomiting (PONV), antiemetic use, extubation time (measured in minutes), post-anaesthesia care unit discharge time (measured in minutes), shivering, bradycardia, hypotension and pruritus.

Data extraction and synthesis Meta-analyses were performed using Stata16 software, using the DerSimonian and Laird's method and inverse variance to summarise effect sizes for each outcome under a random effects model for all outcomes. Outcomes were reported as OR for binary outcome indicators and mean difference (MD) for continuous outcome indicators, with corresponding 95% CIs. I^2 coefficients were used to assess high, medium and low heterogeneity. RoB was used to assess the risk of bias of the included studies. GRADE assessed the certainty of the evidence using a systematic framework for rating the quality of evidence and strength of recommendations.

Results Ultimately, 12 studies involving 983 patients undergoing laparoscopic surgery were included in this systematic evaluation and meta-analysis. The results of the meta-analysis showed an association of OFA with reduced early postoperative 0–2-hour pain response (MD −1.29; 95% CI −2.23 to −0.36; I^2=92%; p<0.001) and the consumption of analgesics (MD −0.43; 95% CI −0.60 to −0.26; I^2=1.8%; p=0.405) in patients undergoing laparoscopic compared with OA.

The results of the meta-analysis suggest that OFA could improve the quality of early postoperative recovery (MD 1.37; 95% CI 0.36 to 2.39; I^2=94.2%; p<0.001) and reduce the incidence of PONV (OR 0.38; 95% CI 0.24 to −0.59; I^2=37.6%; p=0.108) and antiemetics (MD 0.29; 95% CI 0.14 to 0.61; I^2 = 0%; p=0.473) in patients. The other variables presented no significant differences between the groups.

Conclusions OFA may be more beneficial for postoperative pain management and recovery in patients undergoing laparoscopic surgery compared with conventional OA. Future studies could further extend these findings to other surgical populations.

PROSPERO registration number CRD42023414848.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The studies included in this systematic review and meta-analysis were opioid-free anaesthesia randomised controlled trials of laparoscopic surgery.
⇒ Evidence certainty and outcome quality were systematically evaluated using the GRADE methodology.
⇒ The lack of a standardised analgesic regimen for the drugs used in opioid-free anaesthesia may introduce variability in the primary outcome.
⇒ The search is limited to English articles.

INTRODUCTION

Laparoscopic surgery is commonly used in a variety of fields. Despite advances in laparoscopic technology, addressing postoperative pain and complications remains critical to further improving patient prognosis and enhancing the overall outcomes of laparoscopic surgery.[1–3] Moreover, laparoscopic surgery is also an independent risk factor for postoperative nausea and vomiting (PONV), which is highly prevalent with estimated incidences of around 30% in the general surgical population and up to 80% in high-risk populations.[4] The high risk of PONV not only aggravates postoperative pain but also seriously affects the patient's postoperative recovery.[5] Additionally, it can lead to

prolonged post-anaesthesia care unit (PACU) discharge time, unexpected admissions and increased medical costs.[6] Therefore, clinical practice has increasingly focused on opioid-reduction strategies, driving the exploration of opioid-free anaesthesia (OFA).[7 8]

As part of multimodal analgesia, opioid-free in OFA is not analgesia-free but is based on the multimodal anaesthesia concept of providing opioid-free, quality general anaesthesia using relevant drugs and/or methods.[9] The growing concerns regarding opioids have sparked significant interest in OFA for surgical procedures. Thus, multimodal OFA has emerged as a viable alternative.[7 8] In the study by Mauermann *et al*,[10] a truly multimodal concept of OFA was presented.

OFA, which involves the use of various non-opioid drugs and techniques, aims to reduce or eliminate the need for opioids during anaesthesia and improve the overall anaesthesia outcomes.[11] Alpha-2 agonists and dexmedetomidine are commonly used in OFA because of their sedative and analgesic effects. Other adjunctive medications include lidocaine, magnesium sulfate, acetaminophen, non-steroidal anti-inflammatory drugs, dexamethasone and gabapentin.[12] Non-opioid techniques such as intraspinal anaesthesia, local wound infiltration and peripheral nerve blocks also play a role in OFA.[13 14]

However, the benefits of OFA compared with conventional OA for enhancing anaesthetic efficacy and postoperative recovery remain debated.[15] Further studies are needed to determine the safety, efficacy and optimal usage of OFA. Recently, a randomised controlled trial was published in *The Lancet*.[16] The study included 347 participants suffering from lower back or neck pain, and it found that opioid painkillers did not provide any benefit compared with placebo. Instead, the use of opioids carries a risk of adverse effects and opioid abuse. A meta-analysis has demonstrated that the complete omission of opioids during general anaesthesia can improve postoperative outcomes without compromising patient safety and pain management.[17]

Moreover, OFA has demonstrated considerable potential in significantly reducing PONV, presenting a promising option for high-risk patients.[18] Studies by Marron Wong *et al*[19] have demonstrated that the combination of non-opioid drugs, surgical techniques and postoperative recovery plans in OFA can effectively alleviate pain after gynaecological laparoscopic surgery and minimise the need for opioid analgesics. However, certain studies indicate conflicting results, suggesting that OFA may not provide notable advantages over traditional OA and could potentially result in delayed postoperative recovery.[20] While previous systematic reviews have encompassed a wider range of surgical procedures,[21] our research specifically focuses on the context of laparoscopic surgery and places an emphasis on recovery quality as a key outcome measure. This refinement allows us to provide insights specifically tailored to this surgical approach. Our study identifies existing gaps in the literature, particularly the need for more research on the specific effects of OFA in patients undergoing laparoscopic surgery. By addressing these gaps, we aim to advocate for further studies in other surgical populations, as our conclusions also suggest.

The aim of this systematic review was to investigate the safety and effectiveness of multimodal OFA compared with conventional OA in postoperative pain management and recovery in patients undergoing laparoscopic surgery.

METHODS

This review was reported according to the recommended procedure of the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)' statement. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. The protocol has been registered in PROSPERO (CRD42023414848).

Search strategy

In this systematic review and meta-analysis, we searched PubMed, Embase, Cochrane Library and Web of Science. The initial search was conducted in October 2022 and subsequently updated in August 2023. The updated search identified three eligible studies that were not included in the original analysis, and these three studies have been included. The identification of these three additional studies is significant because they provide new data that could enhance the overall robustness and relevance of our findings. We employed the following key terms: "Opioid-free anesthesia" AND "Laparoscopic surgery." The search strategy was restricted to randomised controlled trials (online supplemental doc 1). Additionally, we limited our search to publications written in the English language. We limited the inclusion of studies to those published from January 2015 onwards. This decision was made to focus on the most current evidence regarding non-opioid analgesia as practices and guidelines may have evolved significantly in recent years. We manually reviewed the reference lists of all retrieved articles to identify relevant studies not found by the above strategy.

Inclusion and exclusion criteria

Inclusion criteria: (1) inclusion of studies that included participants aged 18 years and older; (2) any randomised controlled trial comparing OFA (involving at least two drugs or two more alternatives to opioids) with OA for laparoscopic surgery and (3) general anaesthesia was used.

Exclusion criteria: (1) the study excluded articles that examined preoperative opioid use in the OFA group during induction of anaesthesia, before skin closure or before emergence from anaesthesia; (2) non-randomised controlled trials, articles published as reviews, conference proceedings, case reports, newsletters, abstracts, editorials and animal studies were also excluded from the analysis.

Study selection and data extraction

All literature was catalogued using EndNote20. After removing duplicates, two examiners screened eligible studies independently based on the source's title and abstract. To determine their applicability to our study, two other researchers conducted a full assessment of selected articles. Any inconsistencies were resolved through dialogue.

Data extraction was conducted based on predetermined criteria by two independent reviewers who examined the full text of retrieved articles to assess eligibility. In case of disagreement between the two reviewers, a third reviewer was consulted. The extraction of data was conducted by independent reviewers using a self-designed form, and initial testing was conducted using three papers. Authors were not contacted for additional information as we wanted to evaluate the actual published material.

The extracted data consisted of author information, publication year, number of participants, type and length of surgery, types of intraoperative anaesthetics administered, country of origin, and adverse events.

The study's primary outcomes were the postoperative pain scores, measured using the Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) at 0–2-hour and 24-hour, as well as 0–2-hour postoperative analgesic consumption, total consumption and quality of recovery score (QoR-40). The total amount of postoperative opioids for each study was converted to intravenous morphine equivalent doses (10 mg of intravenous morphine=0.1 mg of intravenous fentanyl).[22] The secondary outcomes included PONV, extubation time, PACU discharge time, shivering, bradycardia, hypotension, and pruritus.

Risk-of-bias assessment

The risk of bias of included studies was assessed by two reviewers following the recommendation of the Cochrane risk-of-bias tool for randomised trials (RoB 2). This tool evaluates seven specific domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Two authors assessed the risk of bias for each included study at the study level based on the above seven items. Any disagreements were resolved by discussion between the two authors, and if consensus could not be reached, a third author made the final decision.

Data synthesis and analysis

All statistical analyses were performed in STATA 16.0 software. The random effects model with DerSimonian and Laird method was used for meta-analysis.[23] Inverse variance is a statistical method in meta-analysis that weights studies by the inverse of their variance, allowing more precise studies to have a greater influence on the overall effect estimate and improving the robustness of the conclusions.[24] Outcomes were reported as OR for binary outcome indicators and mean difference (MD) for continuous outcome indicators, with corresponding 95% CIs.

I^2 coefficients were used to assess high, medium and low heterogeneity. If distinct tools were used to evaluate the postoperative measures of patients, we approached each instrument individually to guarantee data uniformity. Statistical significance was determined using a p value threshold of <0.05. Additionally, p values <0.01 and 0.001 were reported to indicate stronger statistical significance where applicable.

For results derived from more than a dozen trials, we examined funnel plots and performed the Egger test to assess publication bias.[25] In the context of the Egger test, a p value <0.05 indicates that there is statistically significant evidence of asymmetry in the funnel plot. This suggests that the distribution of effect sizes may be biased, with smaller studies showing larger effect sizes potentially being over-represented while studies with null or negative results may be under-reported.

Sensitivity analysis

To assess the stability of the meta-analysis results, a sensitivity analysis was conducted on studies exhibiting high heterogeneity. Additionally, the bias of the included literature was examined by systematically excluding individual studies one by one and reanalysing the data.

RESULTS

Study selection and characteristics

Figure 1 presents the PRISMA flow chart illustrating the study selection process. Of the 1340 citations obtained through database searches, 550 were removed due to duplication, and another 758 were excluded after screening of titles and abstracts. Among the 32 articles eligible for full-text screening, 20 were excluded for various reasons after eligibility assessment (online supplemental table 1), leading to the inclusion of 12 randomised controlled trials.

The 12 studies included in this analysis were published between 2015 and 2023, enrolling a total of 983 participants. Table 1 provides a summary of the characteristics of these 12 studies. All studies were randomised controlled trials, and the intervention studied was OFA. The studies were conducted across eight different countries: one in Turkey, one in Belgium, three in Egypt, two in China, one in Germany, one in South Korea, one in Macedonia, one in Vietnam and one in Cameroon. All studies involved patients undergoing laparoscopic surgery; five studies were on gynaecological laparoscopic surgery,[20 26–29] three studies were on laparoscopic cholecystectomy,[30–32] three studies were on laparoscopic bariatric surgery[33–35] and one study was on laparoscopic radical colon surgery.[36]

Risk of bias

The risk of bias for each included study is shown in figure 2. 10 studies reported details of the method of

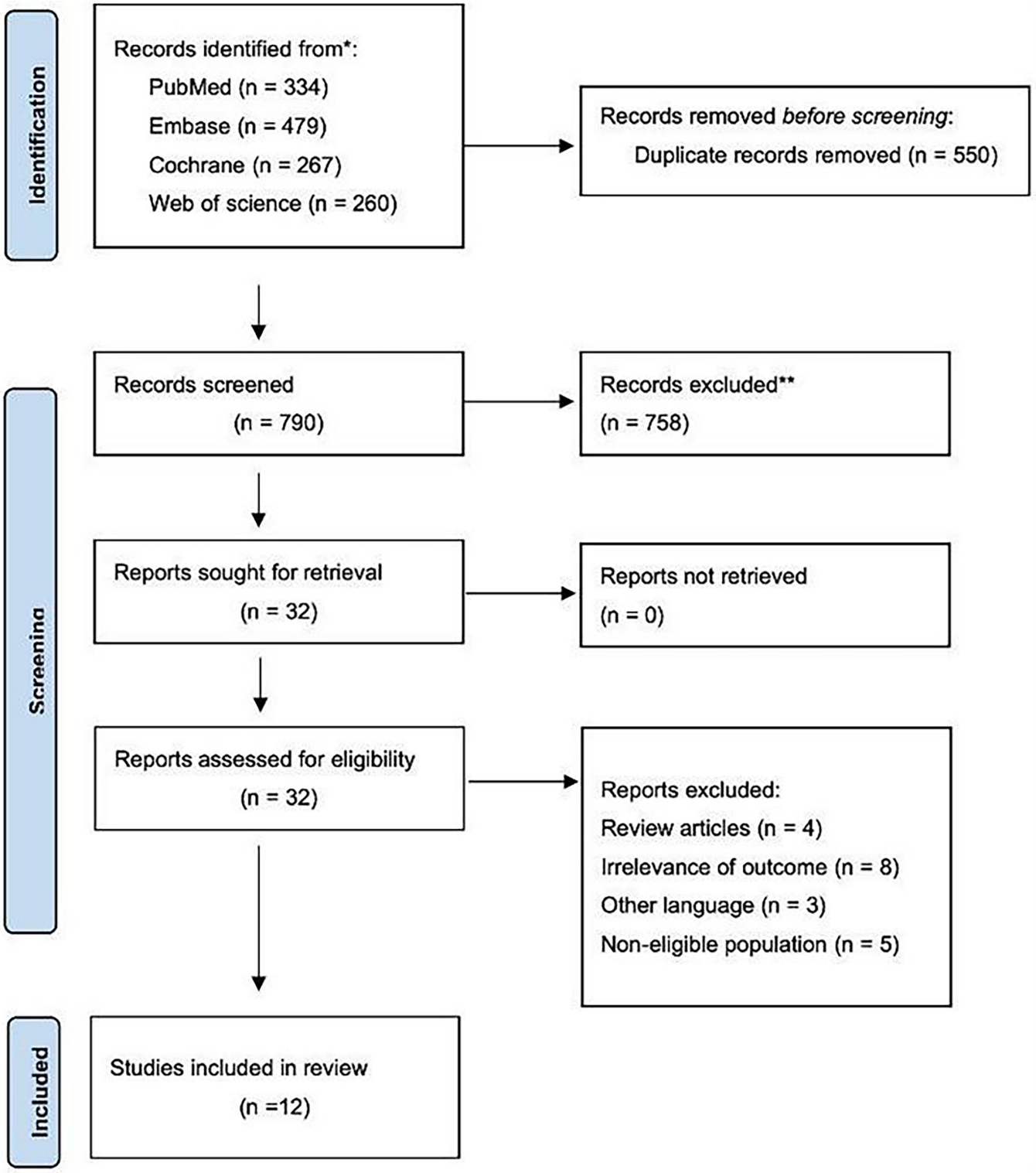

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart showing the results of the literature search.

generating the randomised sequence,[20 26 27 29 30 32–36] and 2 were unclear due to insufficient information.[28 31] Nine studies appropriately described the details of the allocation concealment method,[20 26 27 29 30 32 33 35 36] but the remaining three were assessed as having an unclear risk of bias.[28 31 34] The risk of blinding the patients, and of the trial staff, was unclear in two studies.[28 31] For blinding of outcome assessment, 11 studies were described and 1 was uncertain.[31] Only 1 study had a high risk of incomplete outcome data.[31] In selective reporting, 11 were judged to be low risk,[20 26–35] but 1 was high risk because not all prespecified outcomes were reported.[36] Of all the studies, we considered only seven to be free of bias from other

Table 1 Study characteristics

No	Study	n	Surgery	Multimodal opioid-free regimens	Opioid regimens	Country
1	Bakan *et al*[30]	40/40	Laparoscopic cholecystectomy	Dexmedetomidine/lidocaine/midazolam dexamethasone /dexketoprofen/ paracetamol vecuronium/propofol wound infiltration with bupivacaine	Remifentanil/fentanyl/midazolam dexamethasone/dexketoprofen/ paracetamol vecuronium/propofol wound infiltration with bupivacaine	Turkey
2	Mulier *et al*[33]	23/22	Laparoscopic bariatric surgery	Dexmedetomidine/lidocaine/ketamine paracetamol/propofol+sevoflurano rocuronium	Sulfentanyl/paracetamol propofol+sevoflurano/rocuronium	Belgium
3	Toleska *et al* [31]	30/30	Laparoscopic cholecystectomy	Lidocaine/ketamine/magnesium sulfate paracetamol/dexamethasone/midazolam metamizole/propofol+sevoflurane/ rocuronium	Fentanyl/midazolam/metamizole propofol+sevoflurane/rocuronium	Macedonia
4	Hakim *et al*[26]	40/40	Gynaecological laparoscopic surgery	Dexmedetomidine/propofol/cisatracurium	Fentanyl/propofol/cisatracurium	Egypt
5	Luong *et al*[32]	47/47	Laparoscopic cholecystectomy	Lidocaine/ketamine/magnesium sulfate propofol/rocuronium/ketorolac paracetamol wound infiltration with ropivacaine 0.5%	Fentanyl/propofol/rocuronium	Vietnam
6	Massoth *et al*[20]	76/76	Gynaecological laparoscopy	Dexmedetomidine/esketamine dexamethasone/ondansetron propofol+sevoflurane/rocuronium	Sulfentanyl/dexamethasone/ondansetron propofol+sevoflurane/rocuronium	Germany
7	Ibrahim *et al*[34]	51/52	Sleeve gastrectomy	Propofol/cisatracurium/dexmedetomidine ketamine/lidocaine	Propofol/cisatracurium/remifentanil	Egypt
8	An *et al*[36]	51/50	Laparoscopic radical colectomy	Dexmedetomidine/sevoflurane ropivacaine/ketorolac/ propofol/ cisatracurium	Remifentanil/sevoflurane/propofol cisatracurium bilateral paravertebral blockade (0.5% ropivacaine 15 mL per side)	China
9	Choi *et al*[27]	37/38	Gynaecological laparoscopy	Dexmedetomidine/lidocaine propofol/ rocuronium	Remifentanil/propofol/rocuronium	Korea
10	Tochie *et al*[28]	18/18	Gynaecological surgery	Magnesium sulfate/lidocaine/ketamine dexamethasone/propofol/rocuronium isoflurane/a calibrated mixture of magnesium sulfate, ketamine and clonidine	Protocol/dexamethasone/diazepam fentanyl/propofol/ocuronium isoflurane/ saline as placebo	Cameroon
11	Ahmed *et al*[35]	40/40	Laparoscopic bariatric surgeries	Dexmedetomidine/ketamine/lidocaine magnesium	Fentanyl/magnesium/propofol/ rocuronium	Egypt
12	Chen *et al*[29]	39/38	Gynaecological laparoscopic surgery	Esketamine/dexmedetomidine midazolam/propofol/cisatracurium	Sufentanil/remifentanil midazolam/ propofol/cisatracurium	China

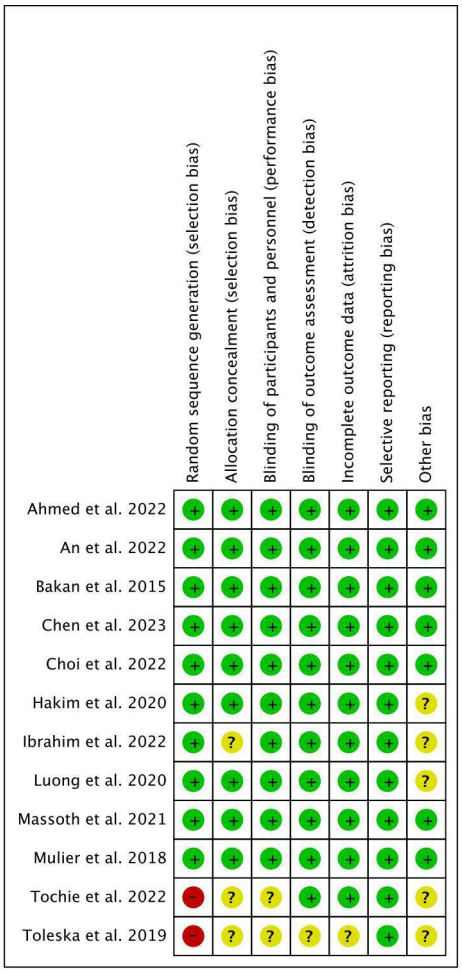

Figure 2 Risk-of-bias summary.

sources,[20 27 29 30 33 35 36] whereas the others were unclear risk because of insufficient evidence.[26 28 31 32 34]

Quality of evidence and sensitivity analysis

The certainty and quality of evidence for each outcome were evaluated using the GRADE method.[37] This method involves a systematic assessment of several factors, including study limitations, where we evaluated the risk of bias in each included study; inconsistency, by examining variations in findings across studies; indirectness, by determining the relevance of the evidence to our specific population, intervention and outcomes; imprecision, by reviewing CIs of the effect estimates; and publication bias, by considering the potential impact of unpublished studies on our results. Based on these criteria, we classified the quality of evidence for each outcome as high, moderate, low or very low, and summarised the GRADE assessments in table 2 to provide a transparent overview of the strength and certainty of our findings. To detect publication bias, Egger tests were performed for trials with more than 10 meta-analyses. Only for PONV was the Egger test performed, which showed publication bias (p<0.05). This suggests that the distribution of effect sizes may be biased. Publication bias was not tested for the other outcomes due to the small number of included studies. According to the GRADE assessment, the evidence quality for PONV, nausea and vomiting was deemed 'high quality'. The evidence quality for pain score (VAS/NRS) at 24 hours, total postoperative analgesic consumption, antiemetic use, extubation time and PACU discharge time was considered 'moderate quality'. Pain score (VAS/NRS) at 0–2 hours, shivering and pruritus were considered 'low quality', while other outcomes were deemed 'very low quality' (table 2).

The results of our meta-analysis showed a high degree of heterogeneity for pain scores 0–2 hours, pain scores 24 hours, analgesic consumption 0–2 hours and QoR-40. Sensitivity analysis by Stata showed that, after excluding any of the studies, the combined results of the remaining studies were not statistically significant and were consistent with the original combined results, indicating stable results (online supplemental figure A).

Primary outcome

Pain scores

There were four studies with a total of 288 patients who reported postoperative pain scores measured on an NRS or VAS ranging from 0 to 10 at 0–2 hours. Pooled results showed that the group receiving OFA had significantly lower 2-hour postoperative pain scores than the OA (MD −1.30; 95% CI −2.23 to −0.36; I^2=92%; p<0.001) (figure 3a). However, six studies with 554 patients reported no significant difference in OFA 24-hour pain scores compared with OA (MD −0.52; 95% CI −1.06 to 0.03; I^2=91.7%; p<0.001) (figure 3b).

Postoperative analgesic consumption

For studies that did not report total opioid consumption, the opioid consumption reported over the longest time frame was analysed. Three studies used morphine,[20 33 35] and three studies used fentanyl as postoperative analgesics.[30 32 34]

Four studies reported 0–2-hour postoperative analgesic consumption (measured in mg), as shown in the meta-analysis (MD −0.90; 95% CI −1.44 to −0.35; I^2=83.3%; p<0.001) (figure 4a). Six studies reported total postoperative analgesic consumption (measured in mg), as shown in the meta-analysis (MD −0.43; 95% CI −0.60 to −0.26; I^2=1.8%; p=0.405) (figure 4b). The results showed that the use of OFA reduced the amount of postoperative analgesics.

Quality of recovery

A total of five studies using the QoR-40 were included. The results of the meta-analysis showed an association of OFA with improved postoperative quality of recovery scores compared with OA (MD 1.37; 95% CI 0.36 to 2.39; I^2=94.2%; p<0.001) (figure 5). QoR-40 scores range from 40 to 200, with higher scores indicating better quality of recovery.

Table 2 GRADE assessment

Outcomes	No of participants (studies)	Certainty assessment					Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias		
Pain score (VAS/NRS) 0–2 hours	288 (4 RCTs)	Not serious*	Serious†	Not serious	Serious‡	None	MD −1.29; 95% CI −2.23 to −0.36	⊕⊕◯◯ Low
Pain score (VAS/NRS) 24 hours	701 (7 RCTs)	Not serious*	Serious†	Not serious	Not serious	None	MD −0.52; 95% CI −1.06 to 0.03	⊕⊕⊕◯ Moderate
Postoperative analgesic consumption 0–2 hours	380 (4 RCTs)	Not serious	Serious§†	Not serious	Serious‡	None	MD −0.72; 95% CI −1.21 to −0.22	⊕◯◯◯ Very low
Postoperative analgesic consumption total	554 (6 RCTs)	Not serious	Serious§	Not serious	Not serious	None	MD 0.39; 95% CI −0.56 to −0.22	⊕⊕⊕◯ Moderate
QoR-40	339 (5 RCTs)	nNot serious	Serious†	Not serious	Serious‡¶	None	MD 1.37; 95% CI 0.36 to 2.39	⊕◯◯◯ Very low
Postoperative PONV or unspecified	842 (10 RCTs)	Not serious	Not serious	Not serious	Not serious	Strong association	OR 0.38; 95% CI 0.24 to −0.59	⊕⊕⊕⊕ High
Postoperative nausea	481 (5 RCTs)	Not serious	Not serious	Not serious	Not serious	Strong association	OR 0.49; 95% CI 0.32 to 0.74	⊕⊕⊕⊕ High
Postoperative vomiting	481 (5 RCTs)	Not serious	Not serious	Not serious	Not serious	Strong association	OR 0.42; 95% CI 0.20 to 0.90	⊕⊕⊕⊕ High
Antiemetic use	343 (4 RCTs)	Not serious	Not serious	Not serious	Serious‡	None	MD 0.29; 95% CI 0.14 to 0.61	⊕⊕⊕◯ Moderate
Extubation time	649 (8 RCTs)	Not serious	Serious†	Not serious	Not serious	None	MD −0.03; 95% CI −0.56 to 0.50	⊕⊕⊕◯ Moderate
PACU discharge time	490 (5 RCTs)	Not serious	Serious†	Not serious	Not serious	None	MD 0.24; 95% CI −0.48 to 0.97	⊕⊕⊕◯ Moderate
Shivering	280 (4 RCTs)	Not serious	Not serious	Not serious	Serious‡¶	None	OR 0.45; 95% CI 0.20 to 1.03	⊕⊕◯◯ Low
Bradycardia	321 (5 RCTs)	Not serious	Serious§†	Not serious	Serious‡¶	None	OR 0.69; 95% CI 0.18 to 2.72	⊕◯◯◯ Very low
Hypotension	219 (3 RCTs)	Not serious	Serious§†	Not serious	Serious‡¶	None	OR 0.33; 95% CI 0.03 to 3.32	⊕◯◯◯ Very low
Pruritus	212 (3 RCTs)	Not serious	Not serious	Not serious	Serious‡¶	None	OR 0.12; 95% CI 0.01 to 1.08	⊕⊕◯◯ Low

*The risk-of-bias judgements were rated as 'high', but we estimate that this does not represent a serious risk of bias for this outcome.
†The quality of evidence was downgraded by one level for inconsistency due to moderate or high heterogeneity (I^2>50%) among studies.
‡The quality of the evidence was downgraded one level for imprecision because the total number of participants is less than the threshold for continuous outcomes (<400).
§The quality of the evidence was downgraded one level because of inconsistent definition of the reported outcome.
¶The quality of the evidence was downgraded by one level because of the wide IsCIs.
NRS, Numerical Rating Scale; PACU, post-anaesthesia care unit; PONV, postoperative nausea and vomiting; QoR, quality of recovery; RCT, randomised controlled trial; VAS, Visual Analogue Scale.

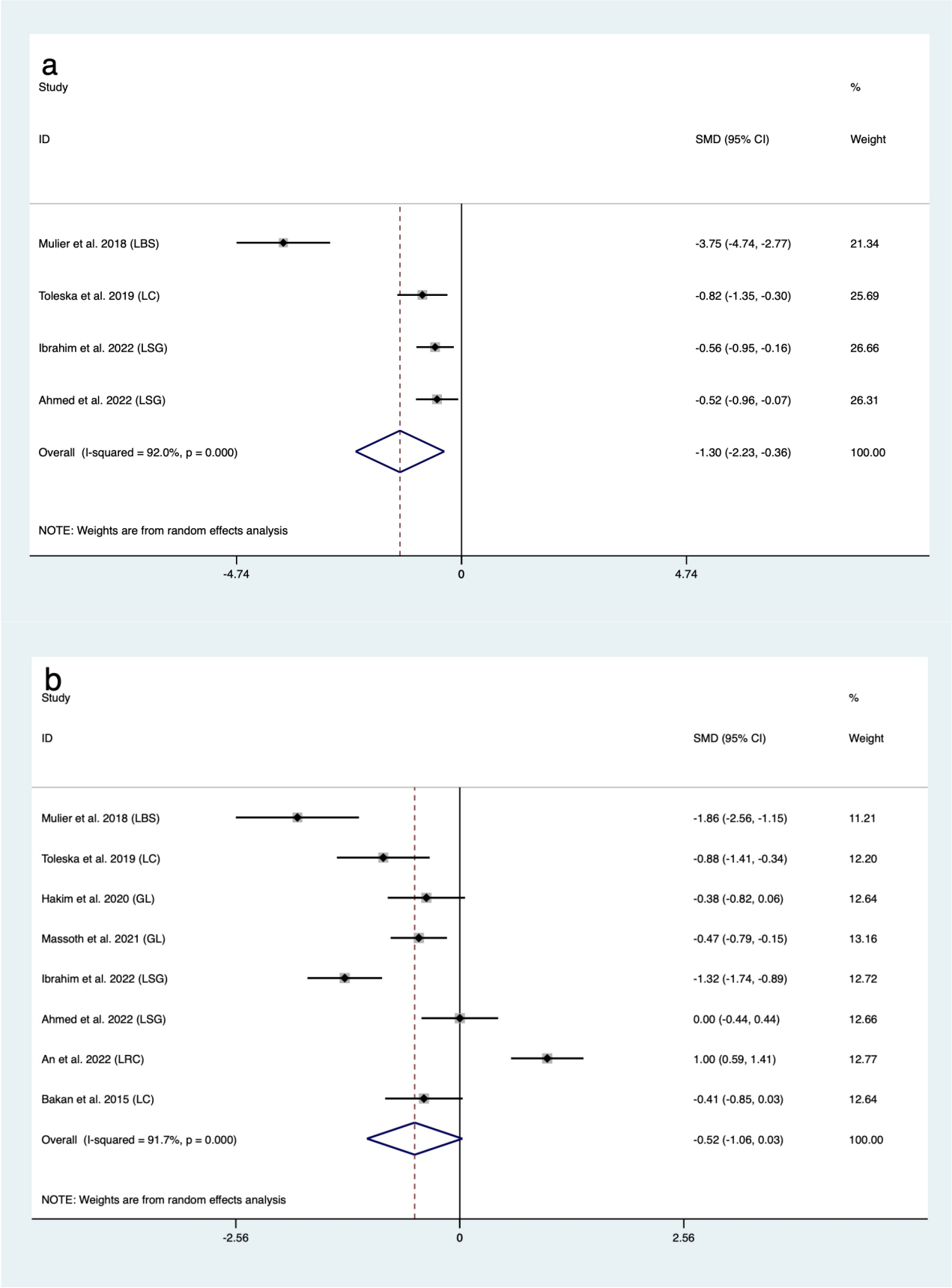

Figure 3 (a) Forest plot of postoperative pain VAS/NRS 0–2 hours. I^2 (95% CI), 92.0% (82.7% to 96.3%). (b) Forest plot of postoperative pain VAS/NRS 24 hours. I^2 (95% CI), 91.7% (86.1% to 95.1%). GL, gynaecological laparoscopy; LBS, laparoscopic bariatric surgery; LC, laparoscopic cholecystectomy; LRC, laparoscopic radical colectomy; LSG, laparoscopic sleeve gastrectomy; NRS, Numerical Rating Scale; SMD, standardised mean difference; VAS, Visual Analogue Scale.

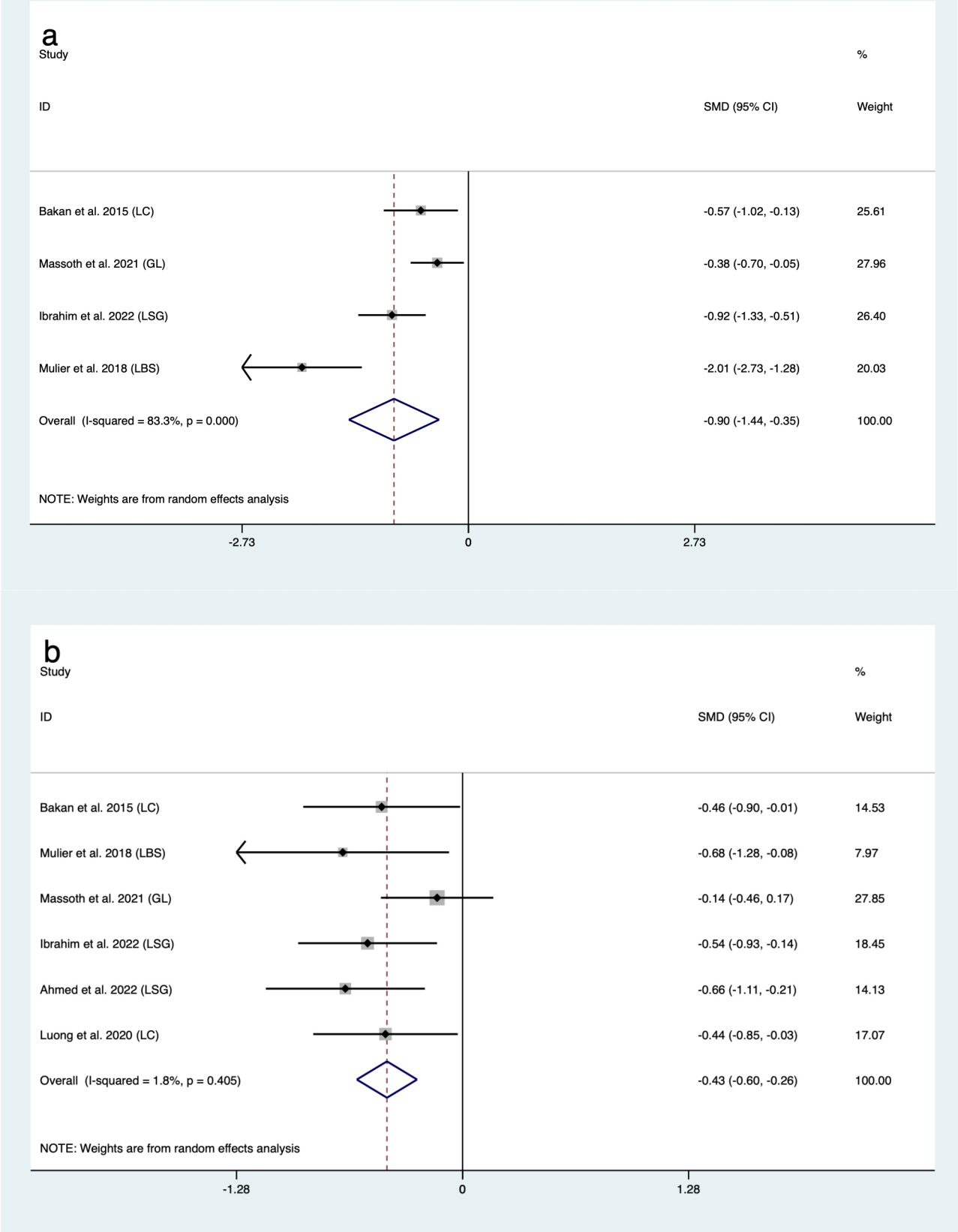

Figure 4 (a) Forest plot of postoperative analgesic consumption 0–2 hours. I^2 (95% CI), 83.3% (57.5% to 93.4%). (b) Forest plot of postoperative analgesic consumption total. I^2 (95% CI), 1.8% (0% to 18.2%). GL, gynaecological laparoscopy; LBS, laparoscopic bariatric surgery; LC, laparoscopic cholecystectomy; LRC, laparoscopic radical colectomy; LSG, laparoscopic sleeve gastrectomy; SMD, standardised mean difference.

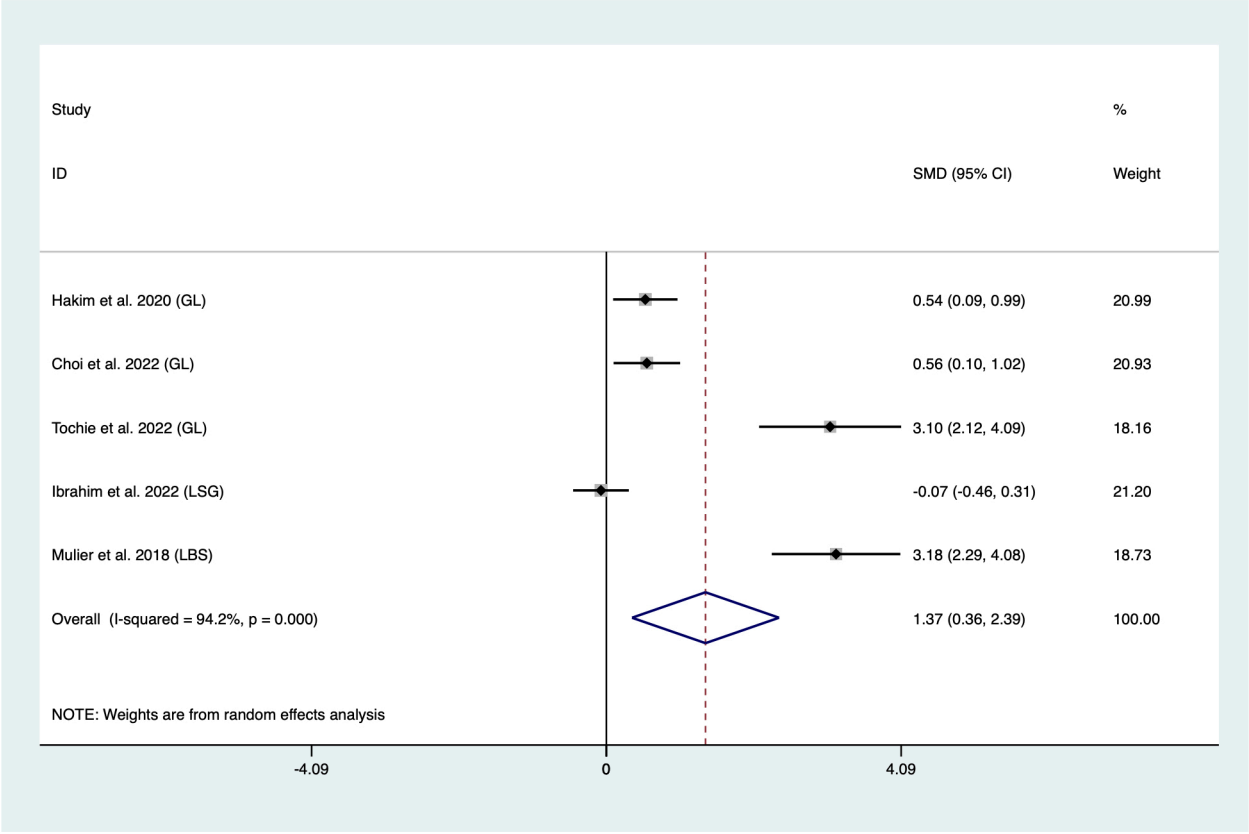

Figure 5 Forest plot of quality of recovery. I^2 (95% CI), 94.2% (89.1% to 96.7%). GL, gynaecological laparoscopy; LBS, laparoscopic bariatric surgery; LSG, laparoscopic sleeve gastrectomy; SMD, standardised mean difference.

Secondary outcomes

PONV/nausea/vomiting/antiemetic use

The inclusion of 10 studies eligible to report PONV in the meta-analysis showed an association of OFA with a reduced incidence of PONV events in patients undergoing laparoscopic surgery compared with conventional OA (OR 0.38; 95% CI 0.25 to 0.57; I^2=28.5%; p=0.183) (figure 6a). Five of the trials reported nausea and vomiting separately, and the meta-analysis results suggest that OFA could reduce nausea (OR 0.49; 95% CI 0.32 to 0.74; I^2 =0%; p=0.447) (figure 6b) and vomiting (OR 0.42; 95% CI 0.20 to 0.90; I^2 =23.2%; p=0.267) (figure 6c).

Four studies reported on antiemetic use. The results of the meta-analysis suggest that OFA could reduce the use of antiemetics compared with conventional OA (MD 0.29; 95% CI 0.14 to 0.61; I^2 = 0%; p=0.473) (figure 6d).

Extubation time and PACU discharge time

The results of the meta-analysis of eight studies suggest that OFA is not associated with a shorter time to extubation in patients (measured in minutes; MD −0.03; 95% CI −0.56 to 0.50; I^2=90.8%; p<0.001) (figure 7a). Additionally, five studies reported PACU discharge time (measured in minutes), showing no significant difference between the OFA group and the OA group (MD 0.24; 95% CI −0.48 to 0.97; I^2=93.4%; p<0.001) (figure 7b).

Other adverse events

Shivering was reported in four studies, as the results of the meta-analysis showed (OR 0.45; 95% CI 0.20 to 1.03; I^2 =27.1%; p=0.249) (figure 8a). Five studies reported bradycardia (OR 0.69; 95% CI 0.18 to 2.72; I^2=69.5%; p=0.020) (figure 8b). Hypotension was reported in three studies (OR 0.33; 95% CI 0.03 to 3.32; I^2=79.6%; p=0.007) (figure 8c). Pruritus was reported in three studies (OR 0.12, 95% CI 0.01 to 1.08; I^2 =0%; p=0.406) (figure 8d).

DISCUSSION

In this systematic review and meta-analysis, the results suggest that OFA is associated with lower pain scores in patients within 0–2 hours after surgery compared with OA. However, at 24 hours following the operation, there was no significant difference in pain score between the two groups. These findings align with prior studies.[17 18 38]

This meta-analysis found that OFA is associated with lower overall consumption of postoperative analgesics, both within 0–2 hours after surgery and throughout the postoperative period, compared with OA. These results indicate that patients who receive OFA may require fewer postoperative analgesics for pain management than those who receive OA. These findings suggest that OFA could be associated with a reduced need for analgesics after surgery, potentially leading to improved postoperative recovery

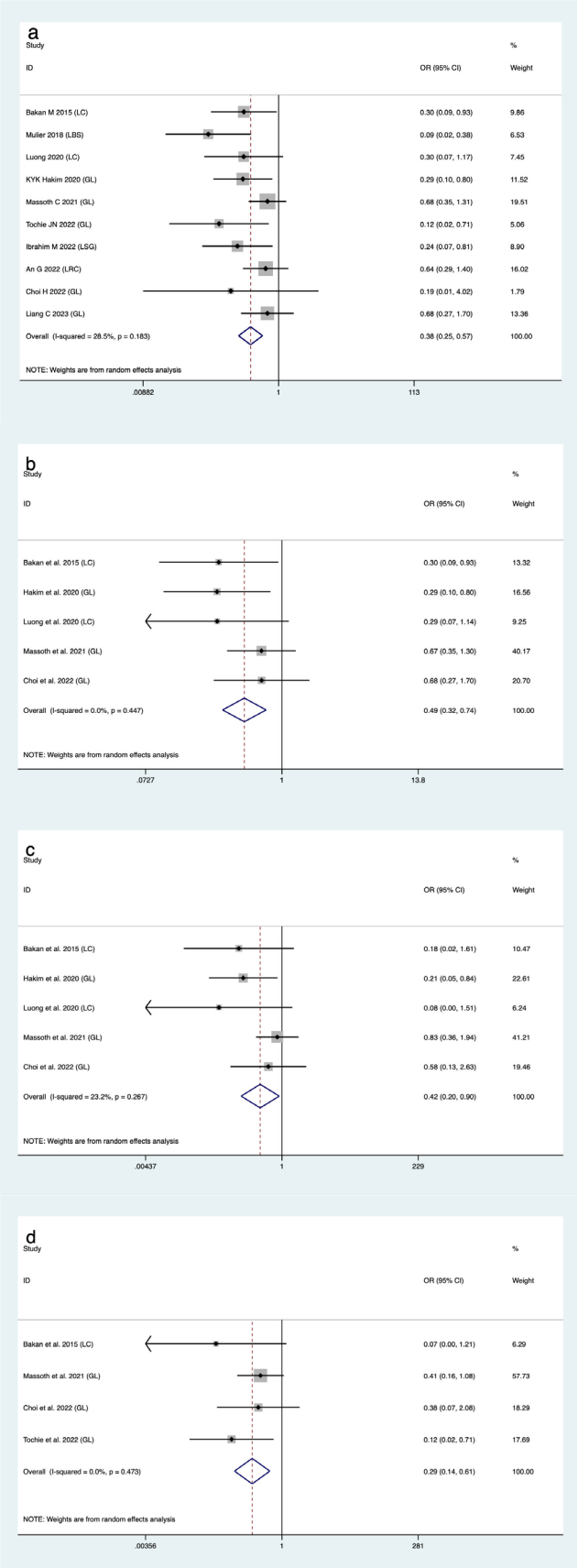

Figure 6 (a) Forest plot of PONV. I^2 (95% CI), 28.5% (0% to 65.7%). (b) Forest plot of nausea. I^2 (95% CI), 0% (0% to 79.2%). (c) Forest plot of vomiting. I^2 (95% CI), 0% (0% to 68.5%). (d) Forest plot of antiemetic use. I^2 (95% CI), 0% (0% to 84.7%). GL, gynaecological laparoscopy; LBS, laparoscopic bariatric surgery; LC, laparoscopic cholecystectomy; LRC, laparoscopic radical colectomy; LSG, laparoscopic sleeve gastrectomy; PONV, postoperative nausea and vomiting.

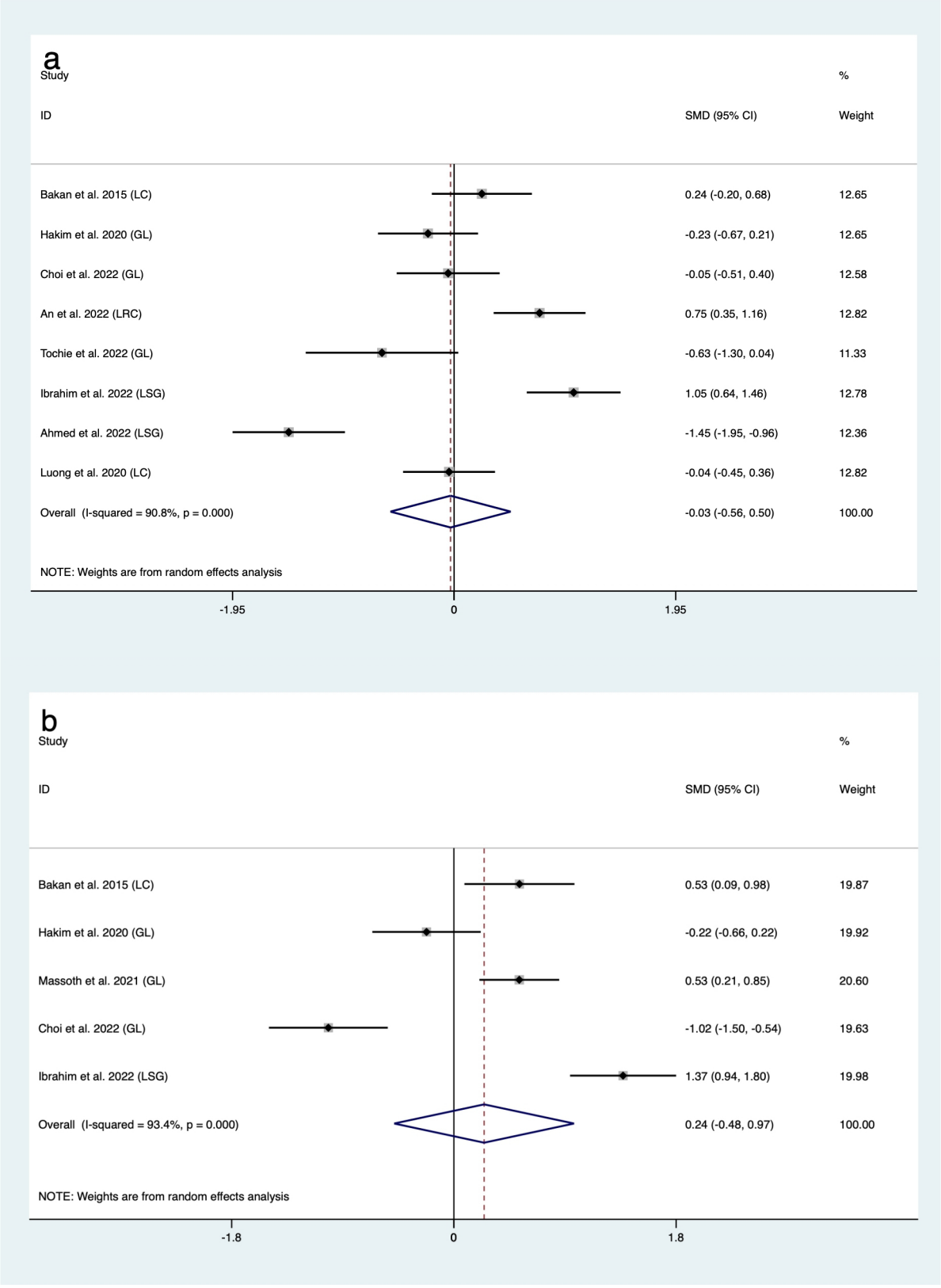

Figure 7 (a) Forest plot of extubation time. I^2 (95% CI), 90.8% (84.4% to 94.6%). (b) Forest plot of PACU discharge time. I^2 (95% CI), 93.4% (87.6% to 96.5%).GL, gynaecological laparoscopy; LC, laparoscopic cholecystectomy; LRC, laparoscopic radical colectomy; LSG, laparoscopic sleeve gastrectomy; PACU, post-anaesthesia care unit; SMD, standardised mean difference.

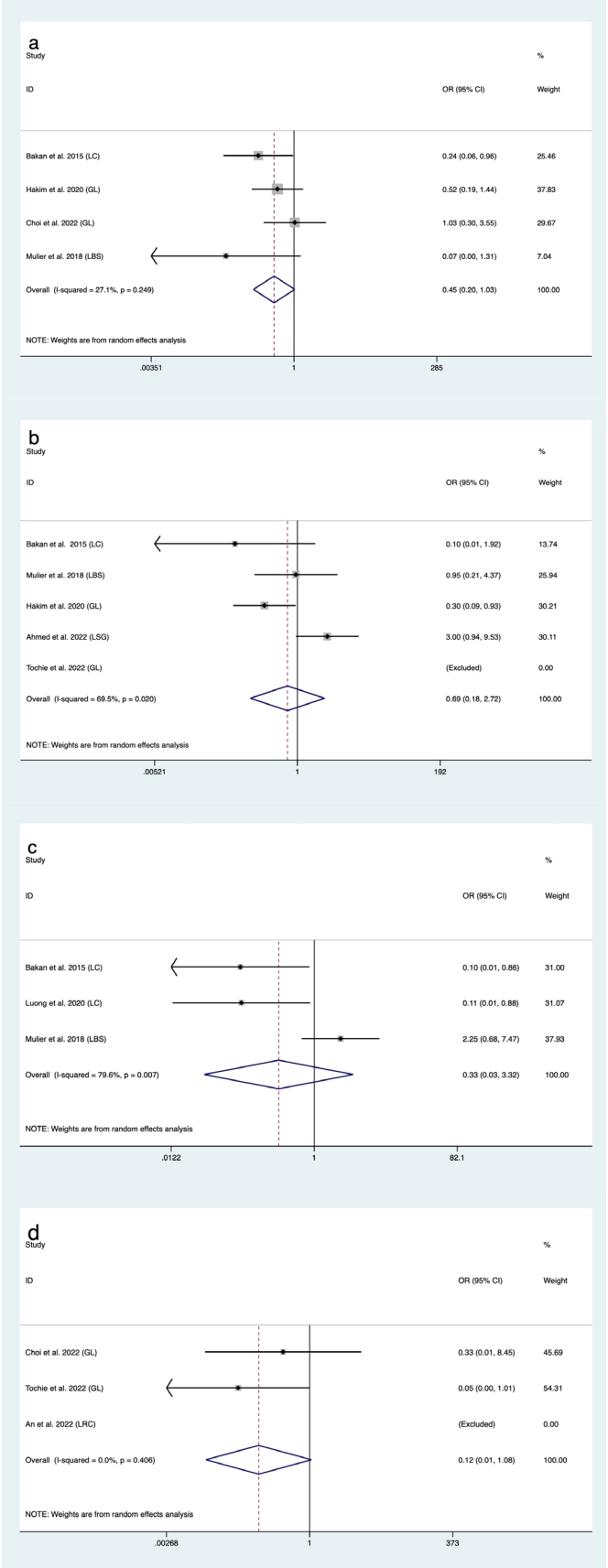

Figure 8 (a) Forest plot of shivering. I^2 (95% CI), 27.1% (94.0% to 72.7%). (b) Forest plot of bradycardia. I^2 (95% CI), 69.5% (12.1% to 89.5%). (c) Forest plot of hypotension. I^2 (95% CI), 79.6% (35.1% to 93.6%). (d) Forest plot of pruritus. I^2 (95% CI), 0% (0% to 89.6%). GL, gynaecological laparoscopy; LC, laparoscopic cholecystectomy; LBS, laparoscopic bariatric surgery; LSG, laparoscopic sleeve gastrectomy.

by mitigating side effects. A meta-analysis conducted by Alexander Olausson *et al*[17] indicated that postoperative total opioid consumption was significantly lower in the opioid-free anaesthesia group compared with the opioid group. This finding suggests that OFA may be associated with reduced opioid requirements and potentially superior pain management.

Significant heterogeneity was observed in the results, which may be attributed not only to variability in study design and anaesthetic application but also potentially to differences in surgical indications. For instance, bariatric surgeries tend to be more complex than cholecystectomies, potentially leading to varying postoperative analgesic requirements and outcomes. This complexity may influence both the types of analgesics used and the overall effectiveness of pain management strategies.

Although performing a subgroup analysis was not deemed appropriate in this context, we acknowledge that further investigation into the impact of surgical indications on analgesic consumption could yield valuable insights. Furthermore, current evidence primarily pertains to short-term follow-up studies and necessitates confirmation through long-term follow-up data. Additional research with extended follow-up durations is necessary to compare the effects of OFA with opioids in managing postoperative pain and opioid consumption. Such studies can provide comprehensive information, thereby establishing a more reliable basis for clinical practice and decision-making.

For the analysis of postoperative quality of recovery, this meta-analysis found that OFA significantly improved patients' postoperative quality of recovery scores compared with OA according to the QoR-40 Quality of Recovery Scale, which aligns with previous findings.[39 40]

Moreover, the use of an OFA was associated with a decrease in the occurrence of PONV, and the quality of evidence for PONV, as well as nausea and vomiting, has been deemed of 'high quality', particularly in laparoscopic surgeries. The potential benefits of OFA may be attributed to its avoidance of the common side effects associated with opioids, which can enhance patient well-being. The medications employed in OFA, such as dexmedetomidine, propofol, ketamine, lidocaine and magnesium, have been shown to reduce PONV. This aligns with the fourth edition of the consensus guidelines for preventing and treating PONV, which recommend the implementation of multimodal analgesic approaches to minimise the reliance on opioids during the perioperative period of laparoscopic surgery.[6]

The postoperative prophylactic use of an antiemetic regimen is not clear to us, and some studies have used ondansetron and/or dexamethasone as prophylaxis, which may also reduce the occurrence of PONV and the use of antiemetic drugs.[18] However, Ziemann-Gimmel[41] found a significant reduction in PONV in the OFA group, even with triple PONV prophylaxis for both groups. Thus, OFA appears to be associated with a reduced risk of PONV, which may correlate with lower use of antiemetics.

In terms of PACU discharge time, no significant difference was observed between the two groups, which is consistent with previous studies.[17 18] Although PACU recovery time can indirectly reflect the effectiveness of anaesthetic modalities, it cannot be used alone to judge the superiority of OFA versus opioid anaesthesia. For PACU discharge time, other factors, such as the type of surgery and patient characteristics, need to be considered.

In summary, OFA is a widely studied technique globally, continually undergoing refinement and improvement in clinical practice. Nevertheless, compared with opioids, there is less experience and knowledge regarding the specific drugs and their combinations in OFA.[10] Several controversies persist, warranting further research to optimise its therapeutic effectiveness and safety in anaesthesia practice. The meta-analysis provides new evidence and best practices for pain management and adverse events in multimodal OFA during laparoscopic surgery. However, due to the small number of literature included in the study, there is still a limited understanding of the advantages and disadvantages of opioid-free multimodal anaesthesia in surgery. Therefore, randomised trials with larger sample sizes are urgently needed to further support our conclusions, as well as to further investigate aspects such as long-term postoperative effects, quality of recovery and patient satisfaction.

Strengths and limitations

This systematic review and meta-analysis validated that OFA is safer and more effective than traditional OA in laparoscopic surgery, reducing postoperative adverse effects. However, it is important to acknowledge the limitations of this study, including the inclusion of only English-language studies for accurate analysis, which may limit the generalisability of findings from non-English studies. Additionally, our literature review was restricted to studies published from 2015 onwards, which may impact the generalisability of our findings by excluding earlier studies that could provide valuable information. The primary outcomes may also be affected by the absence of a standardised analgesic regimen for the drugs studied. Practical concerns regarding OFA, such as the selection, combination and dosages of adjuvants, as well as potential interactions, were noted. Furthermore, the lack of a reliable method for monitoring analgesia and the relatively small sample size to evaluate rare adverse events suggest the need for larger follow-up studies targeting complications and adverse events. One limitation of this study is that the literature search was conducted approximately 18 months prior to the finalisation of this manuscript. While we have made efforts to include key studies published during this period through manual updates, it is possible that some recent developments may not have been fully captured. Future research should aim to incorporate more up-to-date literature to ensure the findings reflect the latest advancements in the field.

CONCLUSION

Our meta-analysis provides evidence supporting the effectiveness and safety of multimodal OFA in managing postoperative pain and promoting recovery after laparoscopic surgery according to the GRADE assessment. This approach not only reduces the occurrence of PONV and other complications but also offers a promising alternative to traditional anaesthesia methods for minimally invasive procedures. However, further research is necessary to optimise the selection and dosage of anaesthetics in multimodal OFA protocols. Future studies should also focus on specific patient populations and include long-term follow-up to evaluate the sustained analgesic effects of this approach.

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