Signa Vitae

SYSTEMATIC REVIEW

Application of opioid-free general anesthesia in laparoscopy: a meta-analysis of randomized controlled studies

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Abstract

Applying opioid-free general anesthesia (OFGA) in laparoscopy was controversial. A systematic review and meta-analysis were conducted to investigate the efficacy and safety of employing OFGA in laparoscopy. Relevant clinical trials to include in this systematic review and meta-analysis were scrutinized through electronic databases such as Embase, PubMed, Cochrane Library and Web of Science. The quality of selected randomized controlled trials (RCTs) was assessed by Cochrane Collaboration's bias risk assessment tool. The meta-analysis was conducted on Review Manager 5.3. The quality of evidence was assessed in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The analysis in this study included 14 RCTs involving 1042 patients. No notable variation examined in 24-hour postoperative pain score between the opioid-based and OFGA groups (mean difference = -0.43, 95% confidence interval (-1.08, 0.22); $p = 0.19$). However, OFGA application reduced the postoperative analgesic needs and the incidence of postoperative nausea and vomiting. The meta-analysis and systematic review findings indicated that OFGA could be effectively and safely used in laparoscopy.

Keywords

Opioid-free general anesthesia; Laparoscopy; Meta-analysis

1. Introduction

Laparoscopy has replaced several conventional open surgeries because of reduced surgical trauma, lower postoperative pain, and rapid postoperative recovery. Laparoscopy is applied in operations [1] such as laparoscopic cholecystectomy [2], laparoscopic splenectomy [3], laparoscopic bariatric surgery [4], laparoscopic gynecological surgery [5], and laparoscopic urology surgery [6]. Opioid-based general anesthesia (OBGA) is often employed in laparoscopy. However, opioid-related postoperative complications including postoperative nausea and vomiting (PONV), itching, urinary retention and respiratory depression prolong the hospital stay [7–9]. Moreover, excessive legal and illegal opioids usage can increase the mortality rates [10].

The strategy of enhanced recovery after surgery (ERAS) combines the evidence-based multimodal approaches during perioperative period. This strategy reduces the postoperative complications and accelerates patient recovery [11]. Opioid-free general anesthesia (OFGA) has thus been proposed. OFGA is a multimodal anesthesia combining the multiple non-opioid drugs to reduce or even avoid the opioids usage while achieving high-quality anesthesia [12]. Several studies have reported OFGA in laparoscopy. However, its efficacy and safety have been controversial [13–16]. In addition, the current evidence lacks strict opioid-free strategies employed during anesthesia, and the subsequent maintenance stages [17–19].

Studies strictly following the OFGA strategy were thus included. The systematic review and meta-analysis were conducted to explore the efficacy and safety of this strategy in laparoscopic procedures.

2. Materials and methods

The systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations. This research study was registered in International Prospective Register of Systematic Reviews with registration number, CRD 42023434751.

2.1 Systematic literature search

The electronic databases like PubMed, Cochrane Library, Embase and Web of Science were searched in the period from database inception till 31 July 2023, with no language restriction. The systematic search strategies had been described in **Supplementary material**. Moreover, the references corresponding to eligible studies were searched.

2.2 Selection criteria

The study inclusion criteria (PICOS) were as follows: (1) Participants (P): individuals undergone laparoscopy; (2) Intervention (I): trials utilizing OFGA; (3) Comparison (C): trials employing OBGA; (4) Outcome (O): trials reporting the OFGA efficacy; and (5) Study design (S): randomized controlled trials (RCTs).

Exclusion criteria from this study were as follows: (1) studies reporting the usage of OFGA wherein opioids were still administered during anesthesia, anesthesia maintenance, or before emergence; (2) studies with no tangible outcomes; (3) incomplete studies including conference abstracts or ongoing works; (4) non-RCTs; and (5) animal studies.

2.3 Data extraction and assessment of outcomes

Two of the authors employed EndNote to identify and eliminate duplicates. A subsequent evaluation determined if RCTs satisfied the eligibility criteria as per the title and abstract. The complete texts of screened studies were comprehensively reviewed to ascertain the inclusion criteria. The data were extracted from the selected studies. Two authors independently acquired and validated the information: names of authors, publication year, surgical procedure type, sample size, age demographics, and specifics of general anesthesia and postoperative pain control.

The primary outcome of this study revolved around the pain score recorded within 24 hours following the surgery. In studies where pain scores were gauged under distinct conditions such as during rest and coughing, only the latter scores were included in the meta-analysis. Secondary outcomes included the postoperative consumption of analgesics, number of individuals requiring rescue analgesia, and incidence of complications (hypotension, bradycardia and PONV).

2.4 Quality and risk evaluation

Cochrane Collaboration tool was employed to gauge potential bias in the studies. Bias risk evaluation included factors such as selection bias (random sequence generation and allocation concealment), performance bias (participant and personnel blinding), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other potential biases. Each trial was assessed as high risk, having some concerns or low risk. The confidence level was determined through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The certainty levels were classified as very low, low, moderate or high.

2.5 Statistical analysis

Review Manager (version 5.3, Nordic Cochrane Centre, Copenhagen, Denmark) was utilized for the meta-analysis. The combined risk ratio (RR) and 95% confidence intervals (CIs) were computed for the dichotomous outcomes. The mean differences (MDs) and 95% CIs were assessed for the continuous data in same units, however the standardized mean difference (SMD) was reported. The cases where continuous data were defined as medians (interquartile ranges or medians minimum-maximum), the values were transformed to corresponding means and standard deviations, adhering to previous methods. p values of < 0.05 were considered statistically significant. Pain scores presented *via* visual, verbal or numeric rating scales were converted to standardized analog scale of 0 to 10, facilitating the quantitative assessment.

Heterogeneity among the trials was evaluated by employing I^2 statistic with threshold of $I^2 > 50\%$ indicating "highly heterogeneous". Clinical and methodological factors were the primary causes of high clinical heterogeneity. Studies with low I^2 values were subjected to random-effects model for catering this variability.

3. Results

3.1 Search results

Initially, 528 relevant studies were extracted from electronic databases. By employing exclusion criteria, 128 duplicate publications and 369 studies were excluded after reading the titles and abstracts. The complete texts of remaining 31 studies were scrutinized to align with the study inclusion criteria. Further 17 studies were excluded because of the following reasons: non-laparoscopic surgeries (n = 2) [20, 21], non-adherence to RCT design (n = 12) [13–16, 22–29], and absence of tangible outcomes (n = 3) [30–32]. Finally, 14 studies fulfilling the inclusion criteria were included into meta-analysis [33–46]. Fig. 1 depicted the literature screening process.

3.2 Study characteristics

The publications era was from 2017 to 2023, and sample size of 30–101. The information of included studies was given in Table 1.

3.3 Bias risk

Fig. 2 summarized the bias risk of included studies. One RCT failed to clearly report the randomization method [42], while another did not report the allocation concealment [45]. Three studies did not adopt the double blinding [42, 45, 46], whereas the outcome assessors were not blinded in four studies [42, 44–46]. One RCT had an "unclear risk" of "selective reporting" [47]. Three studies had "other bias" because of the absence of sample size calculations, thus having an "unclear risk" [36, 43, 45].

3.4 Outcomes

3.4.1 Primary outcome

24-hour postoperative pain score. Seven RCTs presented data on 24-hour postoperative pain score. The forest plot indicated no significant variations between OFGA and OBGA groups (MD = −0.43, 95% CI (−1.08, 0.22); $p = 0.19$, $I^2 = 91\%$), having high heterogeneity (Fig. 3).

3.4.2 Secondary outcomes

3.4.2.1 Postoperative analgesics consumption

Consumption of postoperative analgesics was assessed in 10 RCTs. The forest plot indicated lower analgesics consumption
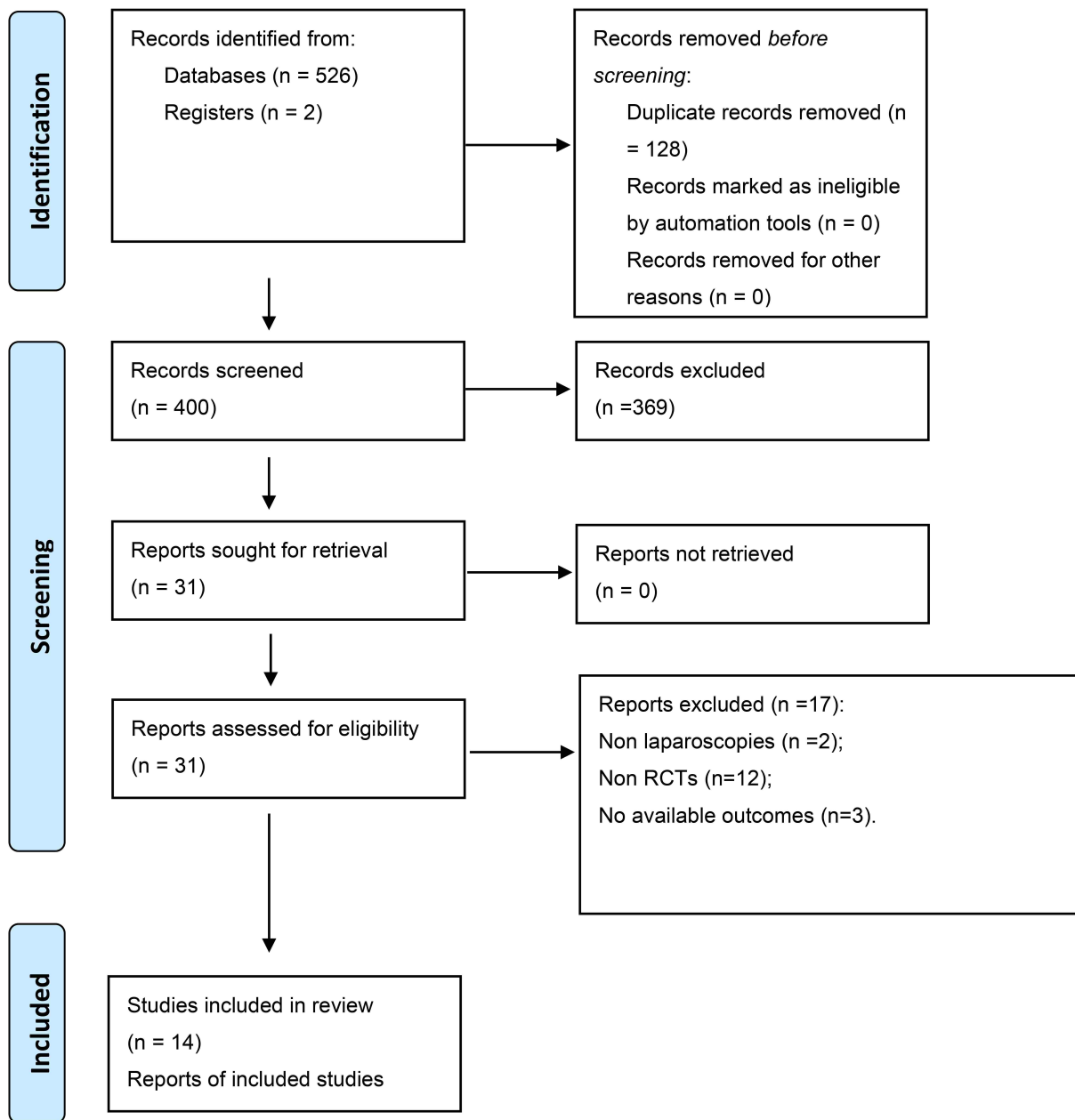
F I G U R E 1. The inclusion process of literature search. RCT: randomized controlled trial.

in OFGA group compared to the OBGA (SMD = −0.98, 95% CI (−1.51, −0.45); $p < 0.05$, $I^2 = 91\%$) (Fig. 4).

3.4.2.2 Patients requiring rescue analgesia

Six RCTs had recorded the number of patients requiring rescue analgesia. The forest plot indicated no significant variation in this number between OFGA and OBGA groups (RR = 0.76, 95% CI (0.54, 1.06); $p = 0.10$, $I^2 = 83\%$) (Fig. 5).

3.4.3 Adverse effects

Nine RCTs reported the PONV incidence. The forest plot indicated that OFGA reduced the PONV occurrence (RR = 0.42, 95% CI (0.31, 0.58); $p < 0.05$, $I^2 = 28\%$) (Fig. 6). The hypertension was recorded in 3 RCTs, and no considerable variation was observed between OFGA and OBGA groups (RR = 1.33, 95% CI (0.19, 9.34); $p = 0.77$, $I^2 = 78\%$)

(**Supplementary Fig. 1**). Three RCTs reported bradycardia, and higher occurrence was recorded in OFGA group compared to the OBGA (RR = 2.33, 95% CI (1.13, 4.80); $p < 0.05$, $I^2 = 0\%$) (**Supplementary Fig. 2**).

3.4.4 GRADE results

The evidence quality was rated from moderate to high. Table 2 portrayed the summary of GRADE assessment.

4. Discussion

Meta-analysis in this study investigated the safety and efficacy of OFGA in laparoscopy. The outcomes suggested that OFGA had similar postoperative pain relief outcomes to those of OBGA in laparoscopy patients, alongside the minimal need for postoperative analgesics and lowered PONV incidence.
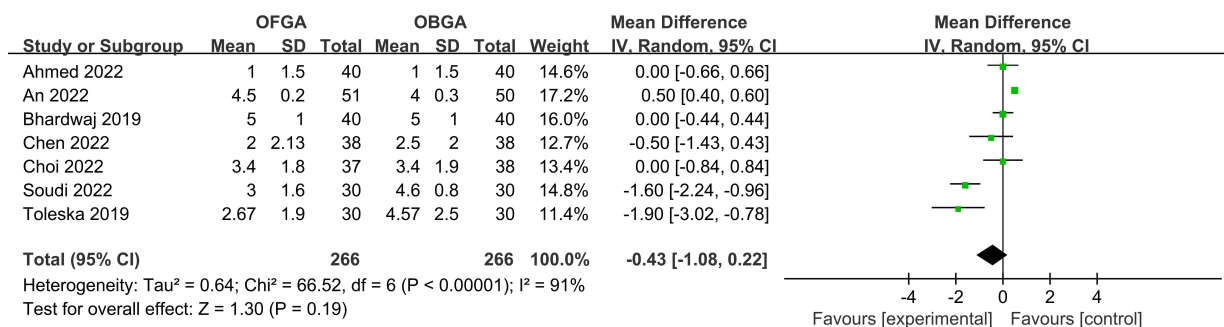
TABLE 1. The details of included studies.

| Study	Sample size		Type of size	Anesthesia induction		Anesthesia maintenance		Postoperative analgesia
	OFGA	OBGA		OFGA	OBGA	OFGA	OBGA	
Ahmed, 2022	40	40	Laparoscopic sleeve gastrectomy or gastric bypass	Dexmedetomidine, ketamine, lidocaine, magnesium, propofol, rocuronium.	Fentanyl, propofol, rocuronium.	Sevoflurane	Sevoflurane	Acetaminophen
An, 2022	51	50	Laparoscopic radical colectomy	Dexmedetomidine, ketorolac, propofol, cisatracurium.	Sufentanil, propofol, cisatracurium.	Dexmedetomidine, cisatracurium, sevoflurane.	Remifentanil, atracurium, sevoflurane.	PCIA
Bhardwaj, 2019	40	40	Laparoscopic urological surgery	Dexmedetomidine, propofol, atracurium, lidocaine, ketamine.	Fentanyl, propofol, atracurium.	Propofol, dexmedetomidine.	Propofol, fentanyl.	Diclofenac, paracetamol, tramadol.
Chen, 2022	38	38	Laparoscopic gynecological surgery	Dexmedetomidine, lidocaine, propofol 6, rocuronium.	Sufentanil, propofol 6, rocuronium.	Propofol, dexmedetomidine, lidocaine, rocuronium.	Propofol, remifentanil, rocuronium.	PCIA
Chen, 2023	39	38	Laparoscopic hysterectomy	Dexmedetomidine, midazolam, propofol, cisatracurium.	Midazolam, propofol, cisatracurium.	Dexmedetomidine, esketamine, propofol.	Remifentanil, propofol.	PCIA
Choi, 2022	37	38	Gynecological laparoscopy	Dexmedetomidine, propofol, rocuronium, lidocaine.	Propofol, rocuronium, remifentanil 3.5.	Dexmedetomidine, desflurane.	Remifentanil, desflurane.	PCIA
Greiss, 2022	41	41	Laparoscopic surgery	Dexmedetomidine, propofol, atracurium.	Fentanyl, propofol, atracurium.	Isoflurane, atracurium	Isoflurane, atracurium	Paracetamol
Hakim, 2019	40	40	Gynecological laparoscopic surgery	Dexmedetomidine, propofol, cisatracurium.	Fentanyl, propofol, cisatracurium.	Propofol, dexmedetomidine.	Propofol, fentanyl	Ketorolac acetaminophen
Ibrahim, 2022	51	52	Sleeve gastrectomy	Dexmedetomidine, propofol, ketamine, cisatracurium, ketamine, lidocaine.	Propofol, fentanyl, cisatracurium.	Sevoflurane	Sevoflurane	Paracetamol
Jebaraj, 2017	15	15	Robotic urological surgery	Dexmedetomidine, propofol, atracurium.	Fentanyl, propofol, atracurium.	Propofol, dexmedetomidine.	Propofol, fentanyl	Not mentioned
Luong, 2020	47	47	Laparoscopic cholecystectomy	Lidocaine, magnesium, propofol, ketogesic, rocuronium.	Propofol, fentanyl, rocuronium.	Propofol, lidocaine, magnesium.	Propofol	Not mentioned
Soudi, 2022	30	30	Laparoscopic bariatric surgery	Dexmedetomidine, ketamine, propofol, rocuronium.	Fentanyl, propofol, rocuronium.	Isoflurane, dexmedetomidine, ketamine.	Isoflurane, fentanyl	Paracetamol, diclofenac
Toleska, 2019	30	30	Laparoscopic cholecystectomy	Midazolam, lidocaine, propofol, rocuronium.	Midazolam, fentanyl, propofol, rocuronium.	Ketamine, lidocaine, magnesium sulphate, sevoflurane.	Sevoflurane	Not mentioned
Van Loocke, 2022	22	20	Laparoscopic bariatric surgery	Dexmedetomidine, esketamine, magnesium, propofol rocuronium.	Sufentanil, propofol, rocuronium.	Sevoflurane	Sevoflurane	Paracetamol

Abbreviations: OFGA: opioid free general anesthesia; OBGA: opioid-based general anesthesia; PCIA: patient controlled intravenous analgesia.
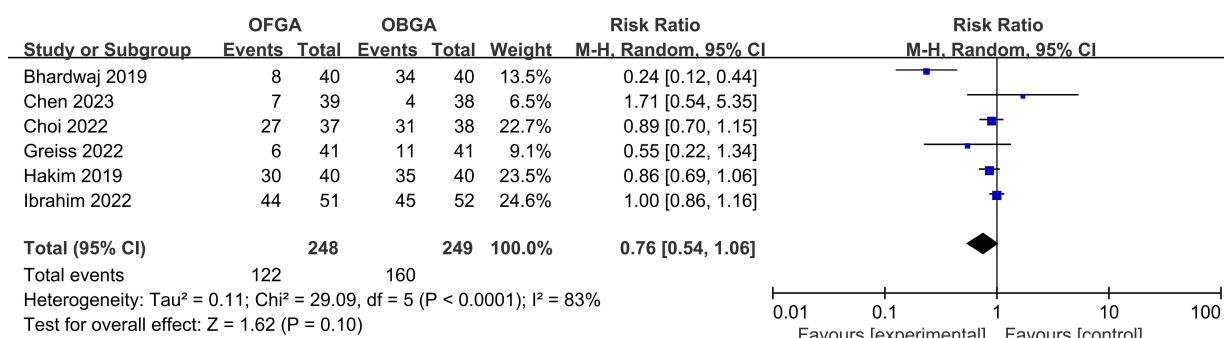
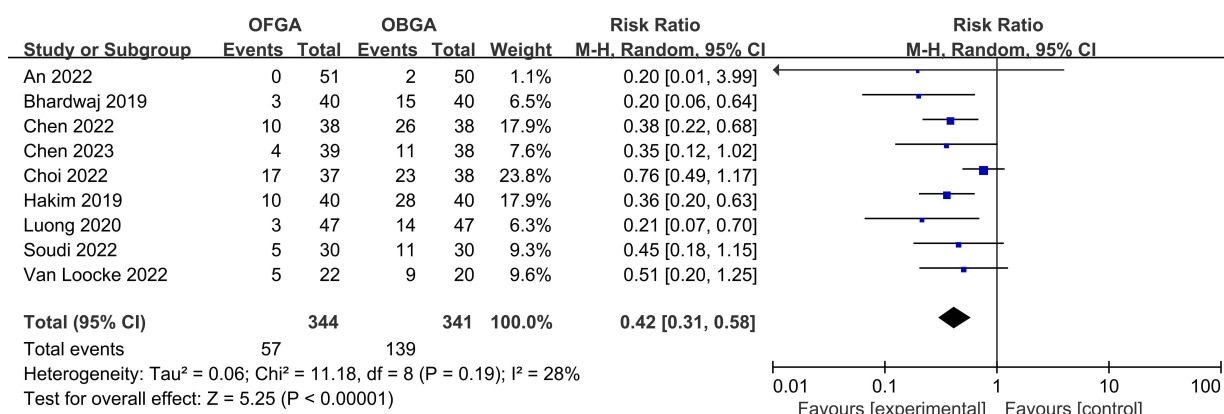**F I G U R E 2. Bias risk assessment of included studies.**

FIGURE 3. Forest plot of 24-hour postoperative pain scores. OFGA: opioid free general anesthesia; OBGA: opioid-based general anesthesia; CI: confidence interval; SD: standard deviation.
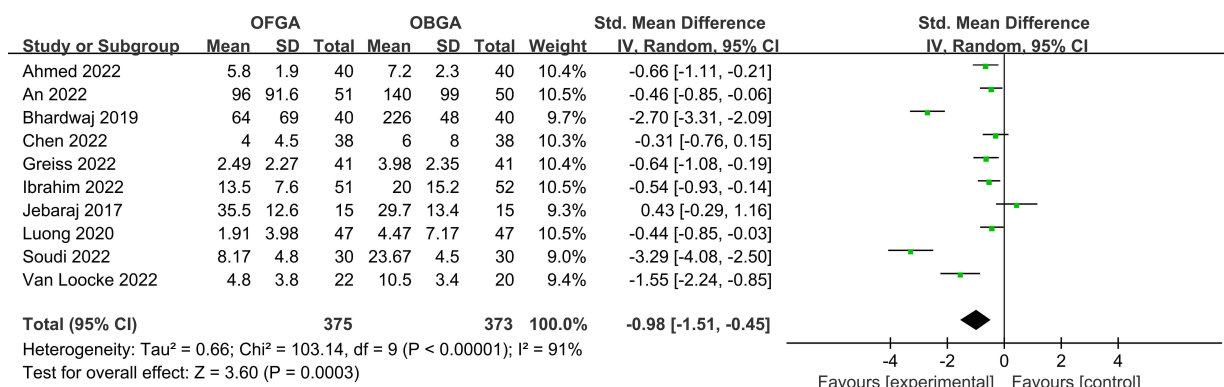
FIGURE 4. Forest plot of postoperative analgesics consumption. OFGA: opioid free general anesthesia; OBGA: opioid-based general anesthesia; CI: confidence interval; SD: standard deviation.

FIGURE 5. Forest plot of the number of individuals requiring rescue analgesia. OFGA: opioid free general anesthesia; OBGA: opioid-based general anesthesia; CI: confidence interval.

FIGURE 6. Forest plot of the occurrence of postoperative nausea and vomiting. OFGA: opioid free general anesthesia; OBGA: opioid-based general anesthesia; CI: confidence interval.

TABLE 2. GRADE summary.

Outcome	Included studies (n)	Patients (n)	Evidence quality	Reasons
Pain score at postoperative 24-hour	7	532	⊕⊕⊕◯ MODERATE	"Inconsistency" downgraded to "serious"
Postoperative analgesics consumption	10	748	⊕⊕⊕◯ MODERATE	"Inconsistency" downgraded to "serious"
Number of rescue analgesia	6	497	⊕⊕⊕◯ MODERATE	"Inconsistency" downgraded to "serious"
PONV incidence	9	685	⊕⊕⊕⊕ HIGH	NONE
Hypotension incidence	3	234	⊕⊕⊕◯ MODERATE	"Imprecision" downgraded to "serious"
Bradycardia incidence	3	220	⊕⊕⊕◯ MODERATE	"Imprecision" downgraded to "serious"

Abbreviation: PONV: postoperative nausea and vomiting.

Laparoscopy had been the mainstream method in abdominal surgery regarding ERAS strategy, however, postoperative pain was a challenge in perioperative management [48–50]. The traditional OBGA could not meet ERAS requirements. Hence, OFGA had gradually been in focus for anesthesiologists. A recent clinical trial depicted that OFGA had lower morphine requirement than OBGA during the first 24 hours of bariatric surgery [25]. Moreover, OFGA elicited better recovery in gynecological laparoscopy patients [38]. A previous meta-analysis exhibited that decreased perioperative opioid consumption was linked with decreased PONV incidence [51].

The meta-analysis in this study revealed that the OFGA patients had similar 24-hour postoperative pain scores which verified the findings of previous meta-analyses [29, 51]. Moreover, the analysis depicted similar requirements for rescue analgesia following the surgery for both OFGA and OBGA groups. However, considerable variation was observed in the consumption of postoperative analgesics, with the former exhibiting reduced consumption compared to the latter. This could be related to opioid-induced hyperalgesia, a phenomenon where opioids increased the patient sensitivity to pain stimuli [52]. A meta-analysis showed that intraoperative use of remifentanil increased the postoperative acute pain intensity, leading to enhanced morphine usage [53]. The latest animal study revealed that astrogliosis was involved in the pathogenesis of opioid-induced hyperalgesia [54]. Consequently, various analgesic techniques including medications and nerve blocks were employed during general anesthesia to reduce or even avoid opioid consumption [55, 56].

This meta-analysis reflected that OFGA reduced the PONV incidence owing to reduced opioid consumption. The fourth consensus guideline for PONV management indicated that long-acting opioids were the only postoperative factor for PONV occurrence [57]. Moreover, the bradycardia incidence was greater in OFGA group compared to OBGA which could be attributed to dexmedetomidine usage as opioid substitute in most studies [33–42, 44, 46].

This study had some limitations. Firstly, the scope of meta-analysis conducted herein was restricted to 24-hour postoperative pain scores owing to inadequate available data. Further research could provide more accurate assessment of pain scores at different time points following the surgery. Secondly, the use of various analgesic drugs and measures led to clinical heterogeneity because of the lack of relatively unified standards for OFGA strategy. Furthermore, no subgroup analyses were performed to differentiate between various types of surgeries or patient groups.

5. Conclusions

The meta-analysis conducted in this study demonstrated that OFGA could effectively and safely be employed in laparoscopy.

AVAILABILITY OF DATA AND MATERIALS

The datasets supporting the conclusions of this article are supplemented along with the article.

AUTHOR CONTRIBUTIONS

MHG—Conceptualization, Methodology and Writing–original draft; JM—Project administration, Resources and Supervision; XMH and JL—Formal analysis, Investigation and Validation.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at `https://??`.

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