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COMPARATIVE EFFECTIVENESS OF OPIOID-FREE ANESTHESIA AND OPIOID-BASED ANESTHESIA ON THE INCIDENCE OF POSTOPERATIVE NAUSEA AND VOMITING: A SYSTEMATIC REVIEW

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Abstract

Perioperative pain management commonly relies on opioids, which are associated with significant adverse effects, particularly postoperative nausea and vomiting (PONV), affecting up to 80% of high-risk surgical patients. This systematic review aimed to compare the effectiveness of opioid-free anesthesia (OFA) and opioid-based anesthesia (OBA) in reducing PONV incidence. This systematic review followed the PRISMA guidelines. A comprehensive literature search was conducted in PubMed, EuropePMC, and OpenAlex. Randomized controlled trials (RCTs) published between 2015 and 2025 that compared OFA and OBA in adult patients (>18 years) and reported PONV outcomes were included. Results of the 117 articles identified, five RCTs met the inclusion criteria. Although the limited number of studies limits the generalizability of the findings, this reflects the application of strict inclusion criteria that prioritize high-quality RCTs. Four studies (Clanet et al., 2024; Choi et al., 2022; Chen et al., 2023; Pratyusha et al., 2025) reported a statistically significant reduction in PONV in patients receiving OFA. In contrast, Yu et al. (2023) found no significant difference between OFA and OBA. Additionally, OFA was associated with reduced postoperative opioid consumption, which may contribute to lower PONV rates. Conclusion OFA demonstrates promising potential as a safe and effective alternative to OBA in reducing PONV. However, larger, well-designed randomized controlled trials are needed to confirm these findings and to further evaluate the impact of OFA on postoperative pain control and recovery quality.

Keywords : Anesthesia; OFA; OBA; Opioid; PONV.

INTRODUCTION

Perioperative pain management is a fundamental aspect of surgical care across a wide range of surgical procedures. In general, opioids provide the foundation for effective analgesia and can maintain intraoperative hemodynamic stability (1). However, prolonged use of opioids can lead to undesirable side effects, which can significantly impede recovery and patient satisfaction (2).

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One of the most common side effects of opioid use is postoperative nausea and vomiting (PONV). In evaluating the effectiveness of opioid-free anesthesia, PONV was chosen as the primary outcome due to its strong and direct relationship with intraoperative opioid use. Compared to other postoperative outcomes such as pain scores, quality of recovery, or length of hospital stay, PONV is the most consistently reported complication and has a significant impact on patient experience and anesthesia service efficiency. PONV is also often rated by patients as a more bothersome side effect than postoperative pain and is one of the main causes of delayed discharge from the post-anesthesia care unit (PACU) (3,4).

Epidemiologically, PONV is reported to occur in approximately 30% of surgical patients in general and can increase to 80% in high-risk patient groups (3,4) It is a major concern for patients and healthcare providers, as it can lead to delays in patient recovery, extended stays in the post-anesthesia care unit (PACU) and hospital, increased healthcare costs, and major patient dissatisfaction. Opioids can stimulate μ-opioid receptors in the postrema area of the medulla oblongata, which is part of the Chemoreceptor Trigger Zone (CTZ). CTZ activation triggers nausea and vomiting responses through the dopamine D2 and 5-HT_3 (serotonin) pathways. Besides PONV, opioids also carry risks such as respiratory depression, pruritus, opioid-induced hyperalgesia (OIH), and potential addiction (1).

Faced with these challenges, opioid-free anesthesia (OFA) has emerged as an alternative technique, aiming to minimize or completely eliminate the use of intraoperative opioids. OFA usually implements a multimodal analgesia strategy, combining various non-opioid agents that work synergistically to achieve adequate pain control and hemodynamic stability. (J11) Commonly used non-opioid components in OFA protocols include alpha-2 agonists such as dexmedetomidine, local anesthetics such as lidocaine, N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and esketamine, nonsteroidal anti-inflammatory drugs (NSAIDs), magnesium sulfate, and dexamethasone, often complemented by regional anesthesia techniques (4).

In the study of Mahrose et al., the group that received opioid-free pterygopalatine ganglion block (SPGB) showed a significantly lower incidence of nausea (6.6% vs. 22.2%) and vomiting (4.4% vs. 17.7%) compared to the opioid-based group. However, other factors remain debated regarding the benefits and risks of OFA, including hemodynamic lability, prolonged recovery time, and orientation. Therefore, a comprehensive systematic review is essential to synthesize the available evidence, identify patterns, and provide objective data to inform clinical decision-making and optimize perioperative and postoperative care. This review aims to clarify the comparative effectiveness of OFA and OBA, specifically regarding the crucial outcome of postoperative nausea.

Although previous systematic reviews and meta-analyses by Olausson et al. (2022) and Salomé et al. (2021) have evaluated the comparison between opioid-free anesthesia (OFA) and opioid-based anesthesia (OBA), this systematic review provides several important novelties that distinguish it from these previous studies and vomiting (5)

Temporal novelty and the recentness of the evidence are the main contributions of this review. This study exclusively included the most recent randomized controlled trials (RCTs) published through 2025, including studies by Clanet et al. (2024) and Pratyusha et al. (2025), which were not included in previous systematic reviews and meta-analyses. Therefore, this review provides the most up-to-date picture of OFA's effectiveness, particularly in the context of modern anesthesia practice.

METHOD

Our review employed a systematic review approach and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, encompassing both the preparation and reporting phases.

Search Strategy

To find relevant studies from inception to June 2025, we conducted an extensive literature search in electronic databases (PubMed, EuropePMC, OpenAlex). using the boolean (‘opioid-free anesthesia’ OR ‘OFA’) AND (‘opioid based anesthesia’ OR ‘OBA’) AND (‘Postoperative nausea and vomiting’ OR ‘PONV’). In addition, a filter

was also applied to include only full-text, English-language, human studies.

The authors further identified additional publications by reviewing the reference lists of eligible articles. Titles and abstracts of studies were assessed against the predefined inclusion/exclusion criteria after duplicates were removed. The target population for this trial consists of adult patients who underwent surgery and received opioid free anesthesia. The outcome of this study is to assess the criteria for postoperative nausea and vomiting with opioid free anesthesia. Inclusion criteria were met by a randomized clinical trial comparing the use of opioid free anesthesia with opioid based anesthesia on the incidence of postoperative nausea and vomiting in adult patients >18 years of age in 2015-2025.

Risk of Bias Assessment

The authors used established methods, including Joanna Briggs Institute tools, to assess risk of bias. The software examines bias in several areas, including the randomization of sequence generation, allocation concealment, blinding of participants and staff, and impartial evaluation of findings. The study also considered handling incomplete outcome data, selective reporting of results, and detection of other potential biases.

The authors categorized bias issues in each research area as “low, " "high, or “medium” based on the data provided. “Low” indicates a low likelihood that bias will affect the study findings; ‘high’ indicates a high likelihood that bias will affect the findings; and “moderate” indicates methodological aspects were well met, but there were some weaknesses, such as unclear blinding or lack of information on handling missing data. The authors used this method to thoroughly assess the quality of the evaluated papers, thereby improving the analysis and findings of the studies by ensuring a fair and consistent application of the Joanna Briggs Institute's bias assessment instrument.

Data Extraction

The authors cited full-text versions and additional sources while collecting relevant data from the included publications. Data collection for this investigation was thorough. Selected pertinent information was thoroughly extracted from the included papers. Important study population data, such as age, surgeries undergone, type of

anesthesia used, and incidence of postoperative nausea and vomiting, were collected, and no grey literature analysis was conducted in this study.

RESULTS AND DISCUSSION

Results

A total of 117 articles were retrieved from the database. The authors removed thirty-six articles due to duplicate articles (n=36). Furthermore, 81 articles are eligible for additional screening. After an abstract review, 56 articles were excluded. 25 articles were sought, but none were retrieved. The remaining 25 articles were further assessed. Twenty articles were excluded because they had 2 control groups (n=5), participant age <18 years (n=1), did not specify the incidence of postoperative nausea and vomiting (n=8), or were not RCTs (n=6). The last five RCT studies were eligible for this systematic review. (Figure 1).

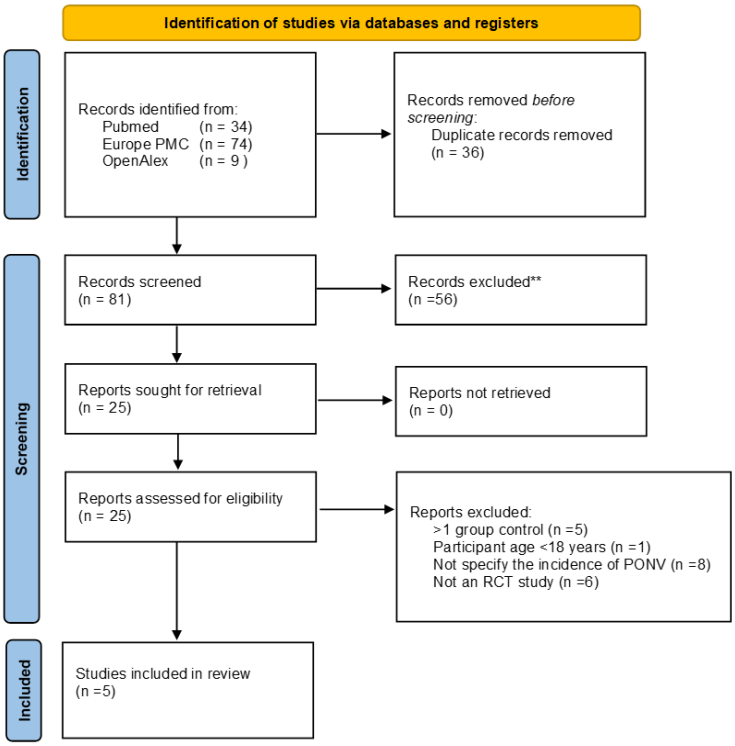

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram

The authors categorized these studies by their level of evidence (Table 1), and all the research used is Randomized Controlled Trial research.

Table 1. Studies Level of Evidence

Study	Journal	Study Design	Level of Evidence
(Matthieu Clanet, *et al*,. 2024)	British Journal of Anaesthesia	Randomized Controlled Trial	I
(Hoon Choi, *et al*., 2022)	Journal of Pain Research	Randomized Controlled Trial	I
(Liang Chen, *et al.,* 2023)	BMC Anesthesiology	Randomized Controlled Trial	I
(A Chaitanya Pratyusha, *et al*., 2025)	BMC Anesthesiology	Randomized Controlled Trial	I
(Jun-Ma Yu, *et al*., 2023)	Journal of Pain Research	Randomized Controlled Trial	I

To assess the methodological quality and risk of bias of the included RCTs, we used the revised Joanna Briggs Institute (JBI) Critical Appraisal Tool for RCTs. Each item was scored as "Yes," "No," or "Unclear," and the 13-question survey included 5 selected studies with a low risk of bias. (Table 2).

Table 2. Risk of Bias Assessment for Included Studies

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Risk
Matthieu Clanet, et al,. 2024	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	U	✓	Low
Hoon Choi, *et al*., 2022	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Low
Liang Chen, *et al.,* 2023	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	Low
A Chaitanya Pratyusha, *et al*., 2025	✓	U	✓	-	✓	✓	✓	✓	✓	U	✓	U	✓	Moderate
Jun-Ma Yu, *et al*., 2023	✓	U	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Low

Abberviation : ✓, Yes; -, No; U, Unclear

Q1. Was true randomization used for assignment of participants to treatment groups?

Q2. Was allocation to treatment groups concealed?

Q3. Were treatment groups similar at the baseline?

Q4. Were participants, those delivering treatment, and outcome assessors blinded?

Q5. Were treatment groups treated identically other than the intervention of interest?

Q6. Was follow-up complete, and were participants analyzed in the groups they were assigned to?

Q7. Were outcomes measured in the same way for treatment groups?

Q8. Were outcomes measured in a reliable and valid way?

Q9. Was appropriate statistical analysis used?

Q10. Was the study sufficiently powered to detect a clinically important effect?

Q11. Are outcomes measured clinically important?

Q12. Is there no conflict of interest or evidence of potential bias?

Q13. Are the conclusions of the study supported by the results and applicable in practice?

Study	Number of Subject		Post Operative Nausea and Vomiting		
	OFA	OBA	OFA	OBA	p value
Matthieu Clanet, *et al*,. 2024	86	86	37%	59%	(P=0.005)
Hoon Choi, *et al*., 2022	37	38	2.7%	23.7%	(P=0.014)
Liang Chen, *et al*., 2023	39	38	10.1%	28.9%	(P = 0,027)
A Chaitanya Pratyusha, *et al*., 2025	24	24	0%	16.6%	(p = 0.037)
Jun-Ma Yu, *et al*., 2023	75	75	14.7%	13.3%	(p = 0.814)

Table 3. Characteristic and Outcome of Studies

*Opioid Free Anesthesia = OFA, Opioid Based Anesthesia = OB

The studies included in this analysis exhibit clinical heterogeneity in terms of sample size, surgical type, and anesthesia protocols. The number of samples per study varied, ranging from 48 to 172 patients. The types of surgery studied also varied, including gynecological, abdominal, thoracic, and bariatric surgery. In addition, the opioid-free anesthesia (OFA) protocols applied were not uniform, with combinations of various non-opioid agents such as dexmedetomidine, ketamine or esketamine, lidocaine, magnesium sulfate, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and regional anesthesia techniques

Given these variations, the results of this study were interpreted using a narrative synthesis approach rather than an integrated quantitative analysis (meta-analysis). The interpretation of the results focused on the direction and consistency of OFA's effects on postoperative nausea and vomiting (PONV), rather than on estimating the magnitude of the combined effect. This approach is considered most appropriate given the

differences in clinical and methodological characteristics between studies.

Of the five randomized controlled trials (RCTs) analyzed, four studies reported a statistically significant reduction in PONV incidence in the OFA group compared to the opioid-based anesthesia (OBA) group. One other study found no significant difference between the two groups.

The study by (6) involved 86 subjects in both the OFA and OBA groups. The OFA group received sevoflurane combined with dexmedetomidine and etomidate, along with continuous infusions of lidocaine and ketamine. In contrast, the OBA group was maintained with sevoflurane and remifentanil, followed by morphine postoperatively. Both groups underwent induction with magnesium sulfate, lidocaine, ketamine, paracetamol, diclofenac, and dexamethasone, and received 4 mg ondansetron for PONV prophylaxis. The study found a significantly lower incidence of PONV in the OFA group (37%) compared with the OBA group (59%). This difference was statistically significant ($p = 0.005$), indicating that the opioid-free regimen was associated with a substantial reduction in PONV (6)

In the study by (3), a total of 75 patients were randomized into two groups, with 37 receiving opioid-free anesthesia (OFA) and 38 receiving opioid-based anesthesia (OBA). The OFA group was administered dexmedetomidine, beginning with a bolus dose prior to induction, followed by a continuous infusion throughout the procedure, in place of intraoperative opioids. In contrast, the OBA group received remifentanil via continuous intravenous infusion, titrated to maintain a targeted effect-site concentration to provide intraoperative analgesia. The results showed a markedly lower incidence of postoperative nausea and vomiting (PONV) in the OFA group, with only 2.7% of patients experiencing symptoms, compared to 23.7% in the OBA group. This difference was statistically significant ($p = 0.014$), indicating that the use of OFA with dexmedetomidine may provide a substantial benefit in reducing the risk of PONV compared to conventional opioid-based anesthesia (3)

In the study by (7) 39 participants were in the OFA group and 38 in the OBA group.

The OFA group received intravenous esketamine and dexmedetomidine, while the OBA group received sufentanil for induction and a continuous remifentanil infusion intraoperatively. All patients in both groups also received bilateral ultrasound-guided transversus abdominis plane (TAP) blocks with ropivacaine, along with intravenous flurbiprofen axetil for preventive analgesia. The incidence of PONV was significantly lower in the OFA group (10.1%) compared to the OBA group (28.9%), with a p-value of 0.027, supporting the effectiveness of OFA in reducing postoperative nausea and vomiting (7)

In the study by (8) , 48 patients were equally divided between the opioid-free anesthesia (OFA) and opioid-based anesthesia (OBA) groups. Patients in the OFA group received a thoracic paravertebral block with ropivacaine prior to induction of general anesthesia. Anesthesia was induced with dexmedetomidine infusion, followed by continuous maintenance throughout the procedure. Ketamine was administered at the time of skin incision, with additional doses given as needed to manage hemodynamic responses. For postoperative analgesia, patients received intermittent doses of ropivacaine through a paravertebral catheter over 72 hours. In the OBA group, patients were premedicated with a transdermal fentanyl patch several hours before surgery (9).

General anesthesia was induced using fentanyl, propofol, and atracurium, with supplemental intraoperative fentanyl administered based on hemodynamic changes. Notably, the incidence of postoperative nausea and vomiting (PONV) was 0% in the OFA group, compared to 16.6% in the OBA group. This difference was statistically significant ($p = 0.037$), suggesting a strong antiemetic benefit of the opioid-free regimen in this patient population (8).

Lastly, the study by Jun-Ma Yu et al.(8) involved 75 patients in both the OFA and OBA groups. The OFA group received a pre-induction infusion of dexmedetomidine, followed by induction with propofol, lidocaine (continued intraoperatively), cisatracurium, and a pre-incision dose of esketamine (10). Local infiltration with dexmedetomidine and ropivacaine was also administered. In contrast, the OBA group

received a placebo saline infusion before induction with propofol, remifentanil (maintained intraoperatively), and cisatracurium, along with the same local infiltration technique. The incidence of PONV was similar between the two groups, 14.7% in the OFA group and 13.3% in the OBA group, with no statistically significant difference ($p = 0.814$), suggesting neither technique had a distinct advantage in this population.

The lack of significant differences in this study is thought to be related to the use of multimodal analgesia and extensive local infiltration in both groups, thereby reducing the differences in effects that can be attributed solely to opioid avoidance (11).

Meanwhile, across the studies analyzed, there was clinical heterogeneity, including variations in sample size, surgical type, and anesthesia protocols. Therefore, formal statistical heterogeneity assessments, such as I^2 calculations and subgroup analyses by surgery type, were not performed, given the narrative review design and the limited number of studies, which could potentially undermine the validity of subsequent statistical analyses. However, a qualitative comparison between studies shows that the reduction in PONV incidence in the OFA group is relatively consistent, especially in studies with higher intraoperative opioid exposure in the control group.

Furthermore, because the OFA protocols applied are multimodal and vary between studies, this study does not allow for the identification of the specific contribution of each non-opioid component to the reduction in PONV. Thus, the existing findings support the concept that the reduction or avoidance of opioids within the framework of multimodal analgesia as a whole plays a role in reducing the risk of PONV, with clinical benefits likely resulting from the synergistic effects of various non-opioid agents, rather than from a single pharmacological intervention.

Discussion

Opioids are conventional analgesics used for intraoperative pain relief in general anesthesia, but they have many potential side effects, including respiratory depression, postoperative nausea and vomiting (PONV), ileus, and hyperalgesia. The main strategy of OFA is to eliminate the use of opioids intraoperatively. By not using opioids, the

main cause of PONV is eliminated, thereby reducing the incidence of postoperative nausea and vomiting (3,8). This systematic review evaluated the comparative effectiveness of opioid-free anesthesia (OFA) and opioid-based anesthesia (OBA) on postoperative nausea and vomiting (PONV) across five randomized controlled trials (RCTs). Overall, the findings demonstrated variability but predominantly favored OFA as a strategy to reduce PONV incidence (12,13).

Four of the studies provided strong evidence supporting the superiority of OFA, reporting statistically significant reductions in PONV incidence. Clanet et al. (2024) observed a substantial decrease in PONV rates when employing an OFA protocol comprising dexmedetomidine, etomidate, lidocaine, and ketamine, compared to conventional opioid-based regimens involving remifentanil and morphine (37% vs. 59%, p = 0.005). This statistically robust outcome underscores the premise that avoidance of opioids during anesthesia may substantially mitigate opioid-induced emetogenic side effects.

Consistent with these findings (3) documented a significant reduction in PONV incidence with dexmedetomidine-based OFA compared to remifentanil-based OBA (2.7% vs. 23.7%, p = 0.014). The pronounced difference highlights the potential antiemetic benefits associated with dexmedetomidine, attributable to its alpha-2 adrenergic receptor agonist properties, providing sedation and analgesia devoid of the gastrointestinal disturbances frequently associated with opioids Additionally, (7) supported these outcomes by reporting significantly lower PONV incidence in patients administered OFA regimens consisting of esketamine and dexmedetomidine relative to OBA protocols utilizing sufentanil and remifentanil (10.1% vs. 28.9%, p = 0.027). Given that both study arms included ultrasound-guided transversus abdominis plane (TAP) blocks, the observed difference is likely attributable predominantly to opioid omission (3).

A particularly compelling outcome was reported by (7), in which patients receiving OFA had no PONV (0%) compared with a significantly higher incidence (16.6%) in the OBA group (p = 0.037). This result underscores the pronounced antiemetic

efficacy achievable through opioid avoidance combined with multimodal analgesic strategies, including regional anesthesia and dexmedetomidine administration.

However, contradictory findings were reported (12) in a study of laparoscopic cholecystectomy involving 150 participants, in which no significant difference in PONV incidence was observed between the OFA and OBA groups. This may occur because ondansetron (an antiemetic agent) was given to both groups after the start of surgery, potentially introducing bias into this study (12,14).

These findings are consistent with recent randomized controlled trials beyond the five core studies included in this review. For instance, (3) compared opioid-free anesthesia (OFA) with opioid-sparing anesthesia (OSA) and observed a significantly lower incidence of PONV within the first hour postoperatively in the OFA group (4.4%) compared to the OSA group (19.6%). This highlights the superior antiemetic benefit of complete opioid avoidance, even over reduced-opioid techniques. Similarly, (10) reported a notable reduction in PONV within 24 hours among patients receiving OFA (14.6%) versus those receiving OBA (30.1%), yielding a statistically significant relative risk reduction (RR = 0.49; 95% CI: 0.26–0.90; p = 0.017). (12) also found a significant difference in PONV incidence on the first postoperative day, 13.3% in the OFA group versus 40% in the OBA group (p = 0.02, asymptotic; p = 0.039, exact), further reinforcing OFA's advantage.

Aligned with these recent findings, this systematic review also supports the conclusions of prior systematic reviews and meta-analyses by by (15) and (16), both of which affirmed the antiemetic benefits of OFA. Olausson et al. demonstrated a significant reduction in adverse postoperative events, primarily driven by decreases in nausea (OR 0.27) and vomiting (OR 0.22). Analyzing 33 RCTs, reported that OFA was associated with reduced PONV (RR 0.46 in PACU; RR 0.34 at 24 hours), as well as lower rates of sedation and shivering, although improvements in pain and opioid use were modest. Together, these findings consolidate the growing body of evidence supporting OFA as an effective approach to reduce PONV, while also highlighting the need for

continued investigation into the long-term safety and optimal clinical applications of opioid-free strategies.

As for the advantages of this study, the use of a systematic review approach allowed a thorough and systematic screening of the literature, so that the results obtained were based on strong and reliable evidence, also the studies included are only randomized controlled trials, enhancing the internal validity of the analysis and the presence of clear inclusion and exclusion criteria helped ensure that only relevant and high-quality studies were included in the analysis. Nonetheless, our findings should be interpreted with caution due to major limitations in the included studies; some had relatively small sample sizes, limiting the power to detect subtle differences. Moreover, the heterogeneity in OFA protocols, surgical procedures, and PONV evaluation criteria complicates direct comparisons and pooled analyses. Larger randomized controlled trials are needed to confirm these findings. In addition, future studies should aim to explore the use of opioid-free anesthesia in managing postoperative pain, postoperative nausea and vomiting, and the quality of postoperative recovery, among others.

The findings of this systematic review suggest that the use of opioid-free anesthesia (OFA) is a safe and effective approach in various types of surgical procedures, with a lower risk of opioid side effects. Therefore, OFA can be considered as an alternative in modern anesthesia practice, especially in patients with a high risk of opioid complications such as postoperative nausea and vomiting.

CONCLUSION

In summary, Opioid free anesthesia shows potential as an effective option to reduce postoperative complications such as postoperative nausea and vomiting. From almost all studies reviewed, it was found that opioid free anesthesia was associated with significantly lower incidence of postoperative nausea and vomiting, while opioid based anesthesia showed significantly higher incidence of postoperative nausea and vomiting. Despite the heterogeneity of the studies, it was concluded that opioid free anesthesia is considered safe and well-tolerated. However, inconsistencies in study design and the need for larger, prospective

randomized controlled trials. Future research should aim to explore the use of OFA and outcomes such as postoperative pain, postoperative nausea and vomiting, and quality of postoperative recovery.

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