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Systematic Review

## Opioid-Free and Opioid-Sparing Anesthesia For Postoperative Pain Management: Systematic Review

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### Abstract

**Background:** Opioid-free anesthesia (OFA) and opioid-sparing anesthesia (OSA) reduce postoperative opioid exposure and maintain analgesia and recovery quality. **Methods:** We conducted a PRISMA guided systematic review of original comparative studies evaluating OFA, OSA versus opioid-based anesthesia. We searched major biomedical databases and trial registries for adult surgical patients receiving general anesthesia. Outcomes include, postoperative pain scores, opioid consumption, rescue analgesia, postoperative nausea and vomiting (PONV), and quality of recovery measures. Two reviewers screened studies, extracted data, and assessed risk of bias independently. **Results:** we include 6 randomized controlled trials in laparoscopic cholecystectomy, gynecologic laparoscopy, video assisted thoracic surgery, bariatric surgery, breast surgery, and hysterectomy. OFA, OSA regimens commonly incorporated dexmedetomidine with ketamine, esketamine and, or intravenous lidocaine, often

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within multimodal pathways. Compared with opioid based anesthesia, OFA, OSA reduced PONV or antiemetic requirements. Effects on pain intensity and postoperative opioid use were variable: several trials reported lower early rescue analgesia and, or reduced morphine equivalent consumption, whereas others showed no significant differences. **Conclusion:** OFA, OSA were reliable for reducing opioid related adverse effects, mainly PONV, and support faster functional recovery. Analgesic benefits are protocol dependent. Standardized regimens and outcome reporting are needed to identify patients and procedures most likely to benefit.

**Keywords:** OFA; Opioid-sparing anesthesia; Multimodal analgesia; Postoperative pain; Postoperative nausea and vomiting; Dexmedetomidine; Ketamine; Intravenous lidocaine; Enhanced recovery after surgery.

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## Introduction

Postoperative pain is common after surgery and is managed with perioperative opioids. While opioids provide effective analgesia, they are associated with opioid-related adverse effects that hinder early recovery, including postoperative nausea and vomiting (PONV), sedation, ileus, pruritus, and respiratory depression. These harms are relevant to enhance recovery pathways, where early oral intake, mobilization, and discharge are key targets.

Opioid free anesthesia (OFA) refers to general anesthesia delivered without intraoperative opioids, typically through a multimodal approach that substitutes non opioid agents (dexmedetomidine, ketamine, esketamine, intravenous lidocaine, and other adjuncts) and regional techniques. Opioid-sparing anesthesia (OSA) reduces, rather than eliminates, intraoperative opioids by combining smaller opioid doses with non-opioid adjuncts. OFA, OSA protocols vary in drug selection, dosing, timing, and co-interventions, which complicates interpretation and pooling in procedures and settings (1).

The most benefit of opioid-minimizing strategies is reduced PONV. A large meta-analysis comparing opioid inclusive versus OFA reported a lower rate of PONV in OFA groups (2). A later meta-analysis focused on PONV evaluated randomized studies and supported a PONV reduction with OFA compared with opioid anesthesia (3). Surgery-specific analyses

in gynecological procedures conclude that OFA is associated with lower PONV in that setting (4).

In a network meta-analysis of 42 randomized trials, comparisons between opioid-based anesthesia and multiple OFA regimens showed no clear difference in pain intensity at 24 hours, and certainty of evidence ranged from moderate to very low depending on regimen and comparison (5). Benefit risk assessing pain and opioid consumption at several times also found uncertainty in clinical improvements and note hemodynamic trade-offs with some OFA (6).

This systematic review synthesizes original studies of OFA and OSA to found impacts on postoperative pain, opioid consumption, PONV, and recovery outcomes.

## Methods

This systematic review was prepared according to PRISMA 2020. We searched PubMed, MEDLINE and the PubMed Central full text archive for original comparative studies evaluating OFA or OSA strategies intended to improve postoperative pain control and decrease opioid exposure. We also screened reference lists of included articles and related reviews to identify eligible studies with free full text. The search was run on articles published from 2019 to 2025.

Search concepts combined terms for OFA, OSA (opioid-free, opioid sparing, multimodal anesthesia), perioperative non-opioid agents

(dexmedetomidine, ketamine, esketamine, lidocaine, esmolol), and postoperative outcomes (pain, opioid consumption, nausea, vomiting, recovery). Records were de duplicated, and titles, abstracts were screened before full-text assessment for eligibility criteria.

We included RCTs and comparative observational studies including adults ( $\geq 18$  years) undergone surgery with general anesthesia. Eligible comparisons were OFA that avoided intraoperative opioids by using non-opioid systemic agents with or without regional techniques, or OSA designed to minimize perioperative opioid dose, compared with an opioid-based anesthetic regimen (fentanyl, remifentanyl, sufentanyl) or an alternative OSA. Studies were required to report at least one postoperative outcome of interest with extractable data. We excluded pediatric studies, case series without a comparator, protocols, editorials, and conference abstracts lacking a full text report.

Primary outcomes were postoperative pain intensity and postoperative opioid consumption within the early postoperative period, reported as fentanyl dose, morphine use, or morphine equivalents. Secondary outcomes included PONV, recovery profiles, hemodynamic adverse effects, and additional recovery indicators.

For each included study we extracted country, setting, design, sample size, procedure type, detailed anesthetic, analgesic protocols, and outcomes at each reported time point. Risk of bias was assessed using RoB 2 for randomized trials and ROBINS-I for nonrandomized studies. We performed qualitative synthesis and structured tabulation of study characteristics and main findings rather than quantitative metaanalysis.

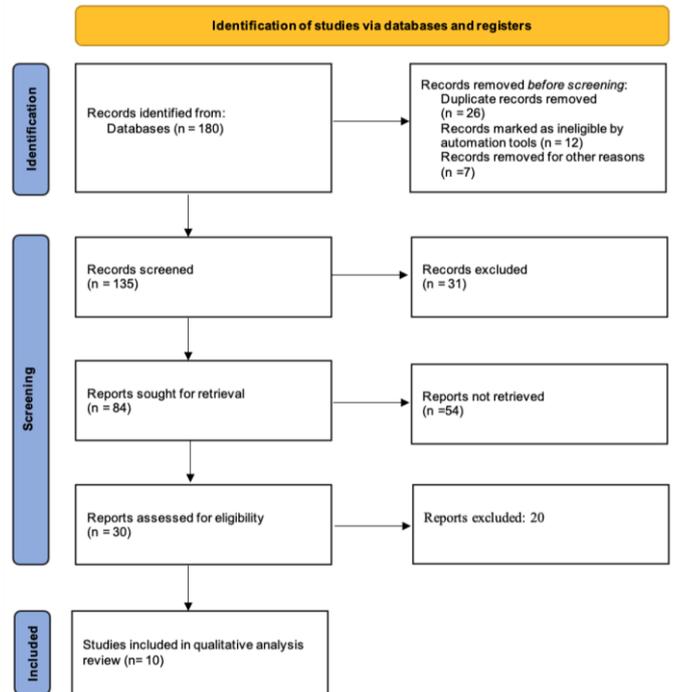


Fig 1: PRISMA flow chart

## Results

Six randomized trials met the eligibility criteria.

Procedures included laparoscopic cholecystectomy, gynecologic laparoscopic surgery and total laparoscopic hysterectomy, video assisted thoracoscopic surgery (VATS) lobectomy, and laparoscopic sleeve gastrectomy. In studies, OFA protocols combined dexmedetomidine with ketamine, esketamine, or lidocaine, sometimes alongside regional techniques (TAP blocks), while opioid based comparators used intraoperative fentanyl, remifentanyl, or sufentanyl.

Vishnuraj et al. (2024) randomized 88 patients to OFA (ketamine plus dexmedetomidine) or fentanyl based anesthesia. Fentanyl use for rescue analgesia was lower during the first 2 h after extubation ( $61.4 \pm 17.4$  vs  $79.0 \pm 19.4$   $\mu\text{g}$ ;  $P < 0.001$ ) but was similar by 6 h ( $152 \pm 28.2$  vs  $164 \pm 33.4$   $\mu\text{g}$ ;  $P = 0.061$ ); moderate PONV occurred less often with OFA (4.5%

vs 34%). In an OSA, Bajracharya et al. (2019) found intraoperative esmolol was similar to lidocaine for 24-h morphine-equivalent consumption after laparoscopic cholecystectomy (median 1.0 vs 1.5 mg;  $P = 0.27$ ), with greater early PACU sedation in the lidocaine group.

For gynecologic laparoscopy under ERAS, Chen et al. (2023) reported better postoperative analgesia with an esketamine dexmedetomidine OFA regimen versus sufentanil, remifentanil, with lower PONV, but longer awakening and orientation recovery. In total laparoscopic hysterectomy, Li et al. (2025) found faster postoperative bowel recovery with OFA: median time to first bowel movement was 42 h (IQR 38–48) versus 49 h (42–56) with opioid anesthesia ( $p < 0.01$ ), and time to flatus was also

shorter (30 vs 35 h;  $p = 0.02$ ); postoperative ileus was lower (6.8% vs 14.5%;  $p = 0.07$ ).

An et al. (2021) found lower PONV with OFA (4.3% vs 41.7%;  $p < 0.001$ ) and less dizziness, but longer recovery and extubation times (13.2 vs 9.5 min and 12.5 vs 9.7 min, respectively). In bariatric surgery, two sleeve gastrectomy trials reported mixed OSA effects. Barakat et al. (2025) found no significant difference in PACU morphine use ( $5.55 \pm 3.48$  vs  $6.38 \pm 3.79$  mg;  $p = 0.255$ ) or pain at discharge. Song et al. (2025) reported better recovery quality and lower postoperative pain Table 1. Characteristics of included studies

related burden with OFA: OBAS scores were lower at 6 h, 24 h, and 48 h (all  $p < 0.001$ ) and PCA use was reduced ( $3.5 \pm 1.5$  vs  $9.5 \pm 5.4$  presses), with fewer hemodynamic adverse events.

**Table 1: characteristics of the included studies**

Study	Country	Design	Surgery and population	N	Intervention (OFA, opioid-sparing)	Comparator	Key outcomes, follow-up
Vishnuraj et al., 2024 (7)	India	RCT, double-blind	Elective laparoscopic cholecystectomy (ASA I-II, 18–60 y)	88 (44, 44)	Ketamine 0.35 mg/kg IV bolus + dexmedetomidine 0.5 mcg/kg/h infusion (no intraop opioids)	Fentanyl-based anesthesia	Primary: cumulative fentanyl via PCA in first 6 h; Secondary: PONV, vitals (0–6 h)
Bajracharya et al., 2019 (8)	Nepal	RCT, noninferiority	Elective laparoscopic cholecystectomy	86 (43, 43)	Esmolol infusion (opioid-sparing; no remifentanyl)	Lidocaine infusion (opioid-sparing comparator)	Primary: 24-h morphine-equivalent consumption; Secondary: pain, sedation, PONV (0–24 h)
Chen et al., 2023 (9)	China	RCT, noninferiority; ERAS	Gynecological laparoscopic surgery	77 (39, 38)	Esketamine + dexmedetomidine opioid-free regimen	Sufentanil, remifentanyl opioid-based anesthesia	Primary: AUC of VAS pain scores postop; Secondary: recovery times, PONV
An et al., 2021 (10)	China	Prospective RCT	VATS lobectomy	97 (46, 51)	OFA with dexmedetomidine + paravertebral block	Opioid anesthesia with sufentanil + paravertebral block	Primary: QoR-15 at 6 h; Secondary: recovery times, PONV, hospital stay
Barakat et al., 2025 (11)	Egypt	Single-center RCT	Laparoscopic sleeve gastrectomy	83 (40, 43)	Dexmedetomidine + lidocaine + ketamine infusions	Fentanyl bolus + remifentanyl infusion (opioid-based)	Primary: PACU morphine consumption; Secondary: VAS at discharge, 0–48 h opioids, antiemetics
Song et al., 2025 (12)	China	Double-blind RCT	Laparoscopic sleeve gastrectomy	76 (38, 38)	OFA regimen (esketamine + dexmedetomidine; opioid-free)	Opioid anesthesia regimen (OBA)	Primary: QoR-15 (24 & 48 h); Secondary: VAS, OBAS, Rhodes N&V index, hemodynamics

Table 2. Main findings of included studies

Study	Pain, recovery quality	Post-op opioid use	PONV, antiemetic use	Other key findings
Vishnuraj et al., 2024 (7)	Early rescue analgesia lower with OFA (first 2 h).	Fentanyl (0–2 h): 61.4±17.4 vs 79.0±19.4 µg; 0–6 h: 152±28.2 vs 164±33.4 µg (ns).	Moderate PONV: 4.5% vs 34%.	Demographics similar; PCA fentanyl used for rescue.
Bajracharya et al., 2019 (8)	Pain scores comparable; higher postoperative sedation with lidocaine group.	24-h morphine equivalents: 1.5±2.3 (esmolol) vs 1.0±2.1 mg (lidocaine), p=0.27 (noninferior).	PONV: 16% (esmolol) vs 14% (lidocaine).	Esmolol was non-inferior to lidocaine for 24-h opioid requirement.
Chen et al., 2023 (9)	Non-inferior AUC of VAS pain scores (mean difference -6.12; 95% CI -11.66 to -0.58; noninferiority margin 10).	OFA avoided intraop opioids; rescue opioid use not higher than opioid group.	PONV: 10.1% vs 28.9%.	Awakening 4.1 vs 3.3 min; orientation recovery 6.0 vs 5.2 min (both longer with OFA).
An et al., 2021 (10)	QoR-15 at 6 h higher with OFA; less dizziness.	OFA avoided intraop opioids (both groups received paravertebral block).	PONV: 4.3% vs 41.7% (p<0.001).	Longer recovery and extubation times (13.2 vs 9.5 min; 12.5 vs 9.7 min).
Barakat et al., 2025 (11)	VAS at PACU discharge similar (0.58±0.87 vs 0.47±0.8).	PACU morphine: 5.55±3.48 vs 6.38±3.79 mg (p=0.255); no difference in morphine up to 48 h.	Nausea medication: 20% vs 27.9% (ns); antiemetic doses 0–24 h: 72.5% vs 83.7% (ns).	More intra-op antihypertensive use in OFA (37.5% vs 13.95%).
Song et al., 2025 (12)	Lower OBAS at 6, 24, 48 h (6.6 vs 9.6; 4.3 vs 6.3; 3.0 vs 4.1; all p<0.001). QoR-15 higher at 24 & 48 h (p<0.001).	Fewer PCA activations: 3.5±1.5 vs 9.5±5.4 (p<0.001).	Rhodes nausea, vomiting index lower with OFA at 6, 24, 48 h (p<0.001).	Shorter PACU Aldrete>9 time with OFA (7.8 vs 23.4 min); less hypotension (5.3% vs 21.1%).

## Discussion

In systematic reviews and meta-analyses, the most reproducible signal for OFA is a reduction in opioid-related adverse effects, especially PONV, rather than superior analgesia. The meta-analysis by Frauenknecht et al. (2019) (2) found high quality evidence that PONV is lower in OFA compared with opioid inclusive approaches. Recent articles reinforce this finding in broader surgical populations (3) and in gynecological surgery (4).

The direction and magnitude of postoperative pain and opioid consumption effects differ in protocols and surgeries. Tripodi et al. (2025) (5) used a

network meta-analysis of 42 RCTs (4666 participants) and reported no clear difference in pain intensity at 24 hours between opioid based anesthesia and diverse OFA regimens, with certainty ranging from moderate to very low in comparisons. This aligns with benefit-risk evaluations that used co-primary outcomes of pain and morphine consumption at early and later time points (2, 24, and 48 hours). Analgesic advantages are uncertain and must be weighed against potential harms (6). For your discussion, this supports that OFA does not automatically mean better analgesia, and that protocol components, rescue analgesia rules, and outcome timing affect outcomes.

Safety is central when opioids are removed from anesthesia, some OFA rely on  $\alpha_2$  agonists and NMDA antagonists, which increase risks of bradycardia, hypotension. This is illustrated in bariatric surgery evidence: a network metaanalysis comparing OFA versus OSA for laparoscopic bariatric procedures found that OFA reduced early PONV more than OSA but is associated with increased bradycardia, while pain intensity and postoperative opioid consumption were similar between strategies (13). A dedicated systematic review, metaanalysis reported associations with lower postoperative complications and reduced opioid demand, but also noted a heterogeneity for several pooled outcomes, underscoring that estimates not generalize in institutions and protocols (14).

Patient centered recovery is increasingly prioritized, a meta-analysis found that OFA improve quality of recovery at 24 hours, but the authors highlighted significant heterogeneity and moderate to low certainty evidence (15). According to literature, OFA and OSA were

reliable for reducing PONV, variable for analgesia, and requiring careful attention to hemodynamics, recovery profiles, and multimodal postoperative analgesia pathways (1).

### **Conclusion**

OFA and OSA reduce opioid exposure and opioidrelated adverse effects, mainly postoperative nausea and vomiting, in several surgical settings. Analgesic benefits are not uniform: postoperative pain scores and opioid requirements differ by procedure, protocol components, and rescue analgesia pathways. Regimens rely on dexmedetomidine with ketamine and intravenous lidocaine and require closer hemodynamic monitoring and, in some studies, are associated with longer emergence or recovery times.

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