frontiers | Frontiers in Anesthesiology

TYPE Mini Review
PUBLISHED 04 November 2025
DOI 10.3389/fanes.2025.1714040

OPEN ACCESS

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RECEIVED 26 September 2025
ACCEPTED 16 October 2025
PUBLISHED 04 November 2025

CITATION
Pershad A, Elvir Lazo OL and Wong R (2025) Opioid-free anesthesia: a scoping review of efficacy, safety, and implementation challenges.
Front. Anesthesiol. 4:1714040.
doi: 10.3389/fanes.2025.1714040

Opioid-free anesthesia: a scoping review of efficacy, safety, and implementation challenges

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Background: Opioid-free anesthesia (OFA) is a multimodal strategy to avoid intraoperative opioids and minimize associated complications, though evidence remains variable.
Methods: A systematic search of PubMed and Google Scholar (2010–2025), supplemented by AI tools (Google Gemini) for earlier publications, summarized eligible studies (RCTs, cohorts, systematic reviews, and meta-analyses) comparing OFA to opioid-based anesthesia (OBA). Data were summarized following PRISMA-ScR guidelines.
Results: Across 23 randomized controlled trials and one cohort study, OFA consistently reduced PONV, while demonstrating analgesia and recovery outcomes comparable to OBA. Hemodynamic stability was variable, with dexmedetomidine-based OFA regimens sometimes associated with increased bradycardia and hypotension. PACU stay varied, ranging from 9 min shorter to 15–35 min longer with OFA. Long-term outcome data are limited.
Conclusion: OFA is a feasible approach that significantly reduces PONV while maintaining comparable analgesia and recovery. However, heterogeneous protocols, small sample sizes, and scarce long-term data limit external validity. Large, multicenter trials are needed to standardize OFA protocols and clarify long-term outcomes.

KEYWORDS

opioid-free anesthesia (OFA), multimodal analgesia, enhanced recovery after surgery (ERAS), postoperative pain, non-opioid analgesics, opioid crisis

1 Introduction

The perioperative period has become a critical juncture leading to long-term opioid use and dependence (1, 2). While intraoperative opioid administration is a cornerstone of general anesthesia due to its potent analgesia, sympatholytic properties, and synergistic effect with anesthetic agents, its widespread use is linked to both acute and chronic complications (3, 4).

Acute complications, known as Opioid-Related Adverse Drug Events (ORADEs), include postoperative nausea and vomiting (PONV), constipation, urinary retention, dry mouth, dizziness, drowsiness, sedation, pruritus, and, more severely, respiratory depression. Affecting 10%–14% of surgical patients (5). Another serious acute risk is opioid-induced hyperalgesia (OIH), a paradoxical state where opioid administration increases pain sensitivity (6–8). ORADEs can prolong hospitalization and increase healthcare costs (5).

Beyond the acute setting, perioperative opioid exposure can also lead to Persistent Postoperative Opioid Use (PPOU) and Chronic Postsurgical Pain (CPSP) or persistent

pain lasting over three months (2). The transition to CPSP is linked to central nervous system sensitization, which can be caused by poorly managed acute pain (9). The incidence of PPOU varies widely in different studies, from as low as 0.119% after caesarian delivery (10), 3% major elective surgery (11), 5%–54.4% after bariatric surgery (12–14), to 6% in some cohorts of adults undergoing both minor and major surgery (15). This highlights how perioperative opioid use could unintentionally lead to long-term dependence. In response to these risks, anesthesiologists are increasingly exploring opioid-free anesthesia (OFA) and opioid-sparing techniques. Given the diversity of OFA regimens and study designs, a scoping review was selected to synthesize its current evidence on the efficacy and safety and explore the practical challenges of its implementation.

2 Methods

A comprehensive literature review was conducted across PubMed and Google Scholar to identify relevant articles in patients undergoing abdominal, breast, gynecological, or orthopedic surgical procedures between January 2010 and August 2025. The search strategy included combinations of keywords such as "opioid-free anesthesia" OR "opioid-free anaesthesia", "opioid-sparing", "multimodal analgesia", "multimodal anesthesia", "non-opioid anesthesia", "dexmedetomidine", "ketamine", "lidocaine", "esmolol", "acetaminophen", "NSAID", "magnesium sulfate", "gabapentinoid", "enhanced recovery after surgery", "perioperative opioid", "postoperative opioid use", and "postsurgical pain." AI-powered tools such as Google Gemini were used to uncover interconnected and relevant publications, including studies performed prior to 2010. Searches were restricted to human studies.

Eligibility criteria included randomized controlled trials, cohort studies, meta-analyses, or systematic reviews that compared OFA with opioid-based anesthesia (OBA) and reported acute perioperative outcomes or long-term outcomes. OFA included protocols that excluded opioid medications intraoperatively. OBA included any regimens that included intraoperative opioid use. Exclusion criteria included case reports, studies with a small sample size (total sample size <20 patients), conference abstracts, and opinion pieces.

This scoping review was conducted and reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. A total of 23 randomized controlled trials and 1 retrospective cohort study were included. Screening and data extraction were performed independently by the first author and verified for consistency. From each study, we extracted sample size, anesthetic regimens, medication dosages, ORADEs, chronic complications, and postoperative pain. Table 1 summarizes the mechanisms and roles of specific pharmacological agents in anesthesia. Trial characteristics are presented in Table 2. No formal review protocol was preregistered.

3 Non-opioid targets and mechanisms in opioid-free anesthesia

OFA is a multimodal anesthesia approach that targets multiple points along the nociceptive (pain) pathway to provide analgesia and manage the surgical stress response. Instead of opioids, OFA uses a combination of non-opioid medications, including α2-adrenergic agonists (e.g., dexmedetomidine), NMDA receptor antagonists (e.g., ketamine), local anesthetics (e.g., IV lidocaine), non-steroidal anti-inflammatory drugs, magnesium, acetaminophen, glucocorticoids (dexamethasone), local infiltration analgesia, regional, and neuraxial blocks, and others (14–39). These agents and drug classes are described in Table 2 below.

Through synergistic interactions, these agents can prevent central sensitization, maintain hemodynamic stability, and provide effective pain control. This combined approach may reduce ORADEs and the risk of long-term opioid misuse. For example, perioperative use of lidocaine, ketamine, and gabapentinoids has been shown to reduce the risk of CPSP for up to 6 months (40), and perioperative gabapentin decreased the time to opioid cessation post-surgery (41). Additionally, individually ketamine and magnesium can maintain stability of blood pressure and heart rate, respectively (42). Esmolol was found to reduce pain and postoperative opioid consumption (43) and has shown to pose an opioid-sparing effect intraoperatively (44). The effectiveness and safety of OFA can differ based on the type of surgery (Table 1).

4 Acute clinical outcomes

4.1 Postoperative nausea and vomiting (PONV)

The most consistent benefit of OFA compared to opioid-based anesthesia (OBA) is a significant reduction in PONV. Numerous randomized-controlled trials across various surgical specialties, including bariatric (18), thoracic (33, 36), thyroid (38), and orthopedic surgery (30) have demonstrated lower PONV incidence rates with OFA. For instance, OFA offered a clinically and statistically significant reduction in PONV rates from 30%–32% to 14%–15% in video-assisted thoracic surgery (36) and from 40% to 13% in shoulder arthroscopy (30). Meta-analyses have also consistently shown a clinically meaningful reduction in PONV with OFA (54–57). While a few studies in patients undergoing gynecologic laparoscopy (28) and thoracic surgery (34) have found no clinically or statistically significant difference, the overall evidence overwhelmingly supports OFA as a highly effective strategy for PONV prevention.

4.2 Pain control

The impact of OFA on immediate postoperative pain is variable. Some studies in breast surgery, laparoscopic cholecystectomy,

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TABLE 1 Common non-opioid agents used in opioid-free anesthesia (OFA) and their characteristics.

Agents	Examples and dosage ranges	Target/ mechanism	Strengths	Limitations/risks
Acetaminophen (45–48)	• 1 g–2 g IV • 500–600 mg PO preoperatively	Central COX inhibition (weak prostaglandin block)	• Analgesia • Opioid-sparing	• Hepatotoxicity
NSAIDs (Ibuprofen, Ketorolac) and COX-2 inhibitors (celecoxib, parecoxib) (19, 25, 34, 35, 45, 49, 50)	• Ketorolac 30 mg • Diclofenac 75 mg	Peripheral COX inhibition	• Anti-inflammatory • Analgesia • ↓ opioid use	• Bleeding risk • Renal impairment • CV risks
Regional/Local Anesthetics (Bupivacaine, Ropivacaine, Lidocaine) (16, 27, 31, 33, 34, 45, 47)	• Ropivacaine 0.1875%–0.5% for blockade • Bupivacaine 0.25% for blockade • Ropivacaine 0.1875%–0.2% 4–10 ml/hr continuous infusion	Nerve/plexus/ neuraxial sodium channel block)	• Robust analgesia • ↓ opioids • improved recovery	• Limited duration unless catheter • Local Anesthetic Systemic Toxicity (LAST) • Risk of motor block, nerve injury
IV Lidocaine (16, 19, 21, 22, 27, 28, 33, 34, 39, 45, 47)	• 1–1.5 mg/kg pre-induction bolus • 1.5–2 mg/kg/h infusion	Sodium channel blockade (peripheral & central)	• ↓ postoperative pain • ↓ ileus in abdominal surgery • ↓ postoperative opioid use	• Modest benefit • Toxicity risk with higher dose • Effect variable across surgeries
NMDA Antagonist (Ketamine, Esketamine) (16, 18–22, 24, 28–30, 33, 37–39, 42, 45, 51)	• Ketamine 0.15–0.5 mg/kg induction bolus • Ketamine 0.15–0.25 mg/kg/h infusion • Esketamine 0.15–0.3 mg/kg induction bolus • Esketamine 0.1–0.125 mg/kg maintenance boluses	NMDA receptor antagonist	• Prevents central sensitization • Useful in opioid-tolerant pts • ↓ acute opioid needs	• Dysphoria, hallucinations • ↑ sympathetic tone • Less effective for PONV Increased salivation
α2-Agonists (Dexmedetomidine, Clonidine) (16, 18–20, 22–26, 29, 30, 33, 34, 36–39, 45, 51, 52)	• Clonidine 1–4 mcg/kg loading dose • Dexmedetomidine 0.5–1 mcg/kg loading dose → 0.2–1.2 mcg/kg/h maintenance	α2-adrenergic agonists	• Sedation • Analgesia • Lowered intraoperative and postoperative opioid need • ↓ PONV	• Bradycardia, hypotension • Delayed recovery at higher doses
Gabapentinoids[a] (Gabapentin, pregabalin) (40, 41, 45, 51)	• Gabapentin 1200 mg preoperatively • Gabapentin 150–300 mg preoperatively	α2δ calcium channel subunit modulators	• Helpful for neuropathic pain; reduce central sensitization; modest opioid-sparing	• Sedation, dizziness • ↑ risk of respiratory depression esp. with opioids/ OSA
Glucocorticoid (Dexamethasone) (16, 18–21, 26, 29, 30, 34, 36–38, 45, 47, 52)	• Dexamethasone 5–10 mg IV	Glucocorticoid; anti-inflammatory, antiemetic	• Strong antiemetic and anti-inflammatory • Prolongs regional block duration • Single-dose safe in most	• Hyperglycemia • Immunosuppression with repeated use
Magnesium sulfate (16, 21, 27, 32, 42, 47, 51–53)	• Varied, typically: • 30–50 mg/kg pre-induction and 8–10 mg/kg/h maintenance • 5–10 mg/kg pre-induction • 1.5 g infusion	NMDA antagonism calcium channel modulation	• Modest ↓ in pain and opioid use • Generally safe at moderate doses • Prolongs regional block duration	• Hypotension • Flushing at high doses
β-blocker (Esmolol) (20, 32, 43, 44)	• 0.5–1 mg/kg at induction	β1 blockade ↓ sympathetic tone	• Stabilizes hemodynamics • Reduces sympathetic response • May reduce opioid use intra-op	• Bradycardia • Hypotension • Reduced postoperative pain and opioid consumption

[a]Gabapentinoids were included to illustrate commonly used non-opioid adjuvants within multimodal anesthesia pathways, even though they are not always components of intraoperative OFA regimens and were not components of OFA in the studies we selected as a part of this review.

laparoscopic colectomy, pancreatic resection, and spine surgery have reported improved early pain scores and reduced postoperative analgesic use (23–25, 27, 29, 44). A meta-analysis by Cheng et al. (56) supported these findings, reporting a reduced need for rescue analgesia in OFA groups undergoing laparoscopic surgery.

In contrast, other studies in bariatric surgery, gynecologic laparoscopy, and shoulder arthroscopy found no significant reduction in 24 h opioid consumption with OFA (19, 20, 22, 28, 30). Studies in thoracic surgery have also reported similar postoperative pain scores and opioid use between OFA and OBA groups (31, 34).

TABLE 2 Study characteristics and key findings of recent trials comparing opioid-free (OFA) and opioid-based anesthesia (OBA) regimens.

Study	Surgery type	Study type	Sample	OFA regimen	OBA comparator regimen	OFA findings
Ziemann-Gimmel et al. (18)	Bariatric (laparoscopic bariatric)	Randomized Controlled Trial	119	Dexmetedomidine 0.5 mcg/kg loading dose over 10 min Maintenance with Dexmetedomidine 0.1–0.3 mcg/kg/h alongside propofol-based TIVA Single dose of ketamine 0.5 mg/kg prior to incision	IV fentanyl 0.5–1 mcg/kg prior to induction of general anesthesia Maintenance with intermittent fentanyl, morphine, or hydromorphone boluses per discretion of anesthesia provider alongside general anesthesia with inhalational anesthetics	Decreased PONV and antiemetic use
Clanet et al. (19)	Bariatric (laparoscopic sleeve/gastric bypass)	Randomized Controlled Trial	172	100 ml infusion bag over 10 min: Dexmedetomidine 0.5 mcg/kg Magnesium 40 mg/kg Maintenance with 50 ml syringe at 0.2–0.4 ml/kg/h: Dexmetedomidine 2 mcg/ml 50 ml syringe containing Lidocaine 980 mg and Ketamine 50 mg infused at 2 ml/kg/h until completion of surgical methylene blue test, followed by 1 ml syringe containing 0.9% NaCl then resume at 1 ml/kg/h	100 ml infusion bag over 10 min: Magnesium 40 mg/kg Maintenance with 50 ml syringe at 0.2–0.4 ml/kg/h: Remifentanil 60 mcg/ml 50 ml syringe containing 0.9% NaCl at 2 ml/kg/h until completion of surgical methylene blue test, followed by 1 ml syringe containing Morphine 10 mg then resumed at 1 ml/kg/h:	Decreased PONV. Did not reduce opioid consumption in 24 h postoperative. Comparable QoR-40 scores
Perez et al. (20)	Bariatric (laparoscopic/ robotic)	Randomized Controlled Trial	181	Dexmedetomidine 1 mcg/kg bolus over 10 min and ketamine 0.5 mg/kg at induction Maintenance with dexmedetomidine 0.4 mcg/kg/h (titrated between 0.3–0.5 mcg/kg/h) and lidocaine 2 mcg/kg/h Esmolol bolus as needed for HR and systolic BP > 20% above baseline	Fentanyl 50 mcg at induction. Maintenance with fentanyl boluses as needed for HR and systolic BP > 20% above baseline	Did not reduce opioid consumption in 24 h postoperative. Comparable ORADEs, hospital length of stay, patient satisfaction, and opioid consumption at 1- and 3-months post-discharge.
Dagher et al. (21)	Bariatric	Randomized Controlled Trial	58	After induction and intubation: Lidocaine 1.5 mg/kg bolus followed by 1.5 mg/kg/h continuous infusion Ketamine 0.2 mg/kg bolus followed by 0.15 mg/kg/h infusion Magnesium sulfate 50 mg/kg administered over 30 min followed by 8 mg/kg/h infusion Dexmedetomidine 0.2–0.5 mcg/kg/h, adjusted based on BP and HR Dexamethasone 8 mg	At induction, fentanyl 1 mcg/kg, increased to 3–4 mcg/kg at incision. Fentanyl 0.5–1 mcg/kg boluses as needed to maintain hemodynamic stability	Reduced postoperative opioid consumption Improved pain management Maintained hemodynamic stability. Provided higher patient satisfaction scores. Comparable PONV Did not increase sedation
Barakat et al. (22)	Bariatric (Laparoscopic sleeve gastrectomy)	Randomized controlled trial	83	Dexmedetomidine 0.5 mcg/kg and Lidocaine 1 mg/kg over 10 min pre-induction. Ketamine 0.15 mg/kg at induction Maintenance with dexmedetomidine 0.3 mcg/kg/h, lidocaine 1.5 mg/kg/h and ketamine. 0.15 mg/kg/h	Fentanyl 2 mcg/kg, ketamine 0.15 mg/ kg bolus at induction Maintenance with Remifentanil 0.2–0.3 mcg/kg/min and ketamine 0.15 mg/kg/h	Comparable pain scores at 24 h and 48 h Comparable opioid consumption, PONV, and need for antiemetics. Higher antihypertensives requirement
Qian et al. (24)	Breast (lumpectomy)	Randomized Controlled Trial	80	Dexmetedomidine 0.5 mcg/kg loading dose over 10 min, esketamine 0.1 mg/kg, and lidocaine 1.5 mg/kg pre-induction. Midazolam 0.03–0.04 mg/kg at induction Maintenance with Dexmetedomidine 0.1–0.2 mcg/kg/h, esketamine 0.1–0.2 mg/kg/h, and lidocaine 1–1.5 mg/kg/h	Sufentanil 0.2–0.4 mcg/kg and midazolam 0.03–0.04 mg/kg Maintenance with remifentanil 0.1–0.3 mg/kg/min	Delayed need for postoperative opioid use Comparable postoperative analgesia Maintained hemodynamic stability. Decreased PONV
An et al. (25)	Colorectal (laparoscopic radical colectomy)	Randomized Controlled Trial	102	Paravertebral block: 15 ml per side of solution of 0.5% Ropivacaine and dexmedetomidine 0.2 mcg/kg Dexmedetomidine 0.6 mcg/kg and 0.5 mg atropine infusion for 10 min pre-induction	Paravertebral block: 15 ml per side of 0.5% Ropivacaine Sufentanil 0.5 mcg/kg at induction. Maintenance with remifentanil 200–500 mcg/h	Reduced postoperative rescue NSAID analgesic Comparable intra-operative analgesia index. Higher intra-op glucose Comparable PONV, urinary

(*Continued*)

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TABLE 2 Continued

Study	Surgery type	Study type	Sample	OFA regimen	OBA comparator regimen	OFA findings
				Ketorolac 30 mg and dexmedetomidine 0.5 mcg/kg/h at induction Maintenance with dexmedetomidine 0.5 mcg/kg/h GA Recovery with palonosetron 0.25 mg, neostigmine ≤ 2 mg, and atropine 0.2–1 mg PCA containing Dexmedetomidine 6 mcg/kg and ketorolac 180 mg	GA Recovery with nalmefene 0.05 mg, palonosetron 0.25 mg, neostigmine (≤ 2 mg), and atropine (0.2–1 mg) PCA containing dezocine 0.5 mg/kg and ketorolac 180 mg	retention, intestinal paralysis, and pruritus
Zhang et al. (26)	Elective colorectal cancer resection (under ERAS)	Randomized controlled trial	96	Thoracic epidural with 0.25% Ropivacaine and 0.5% lidocaine Dexmedetomidine loading dose over 30 min before induction Midazolam 0.05 mg/kg and lidocaine 1.5 mg/kg at induction Maintenance with dexmedetomidine 0.3 mcg/kg/h infusion, stopped at colorectal dissection	Bilateral transversalis fascia plane block with 50 ml 0.25% Ropivacaine Midazolam 0.05 mg/kg and sufentanil 0.3–0.5 mcg/kg at induction Maintenance with remifentanil infusion, titrated to maintain BIS between 40 and 60.	Comparable postoperative QoR-40 scores, PONV, time to first meal, and postoperative drainage tube removal. Comparable postoperative opioid consumption and pain scores at 24 h Increased time of sedation
Luong et al. (27)	General surgery (laparoscopic cholecystectom)	Randomized Controlled Trial	94	Magnesium 30 mg/kg and lidocaine 2 mg/kg pre-induction Ketogesic 30 mg at induction Ketamine 0.5 mg/kg intravenous bolus and ropivacaine 0.5% at edge of incision right after induction Maintenance with lidocaine 1.5 mg/kg/h and magnesium 1.5 g 1 g paracetamol at gallbladder resection	Fentanyl 5 mcg/kg at induction Intraoperative fentanyl 1.5 mcg/kg every 30 min	Associated with lower intraoperative hypotension Reduced PONV Reduced postoperative opioid consumption Increased risk of hypersalivation
López-Álvarez et al. (44)	General surgery (laparoscopic cholecystectomy)	Randomized Controlled Trial	60	Midazolam 0.3 mg/kg premedication Esmolol 0.5 mg/kg at induction. Maintenance with esmolol 5–15 mcg/kg/min Port insertions infiltrated with 0.5% levobupivacaine at end of procedure.	Midazolam 0.3 mg/kg premedication. Ketamine 0.5 mg/kg and remifentanil 0.5 mcg/kg at induction. Maintenance with remifentanil 0.1–0.5 mcg/kg/min infusion. Port insertions infiltrated with 0.5% levobupivacaine at end of procedure.	Reduced postoperative opioid consumption Comparable PONV and sedation
Hu et al. (28)	Gynecologic laparoscopic surgery	Randomized controlled trial	74	Lidocaine 1.5 mg/kg and esketamine 0.15 mg/kg infusion over 5 min pre-induction Maintenance with lidocaine 1.5 mg/kg/h and esketamine 0.1 mg/kg/h	Sufentanil 0.3 mcg/kg and saline infusion over 5 min pre-induction Maintenance with sufentanil 0.1 mcg/kg/h and saline infusion	Comparable 48 h time-weighted average pain scores, postoperative opioid consumption, gastrointestinal recovery, and patient satisfaction scores Decreased time to extubation
Katz et al. (59)	Total Abdominal Hysterectomy	Randomized Controlled Trial	45	Midazolam 0.05 mg/kg at induction and thiopentone 3–5 mg/kg at induction.	Two Groups: Group 2: Midazolam 0.05 mg/kg, Alfentanil 30 mcg/kg, and thiopentone 3–5 mg/kg at induction. Maintenance with alfentanil 10–20 mcg/kg boluses every hour. Group 3: Midazolam 0.05 mg/kg and alfentanil 100 mcg/kg at induction. Maintenance with continuous infusion of alfentanil 1–2 mcg/kg/min, adjusted by 0.25–0.5 mcg/kg/min and with alfentanil 10–20 mcg/kg bolus to maintain hemodynamic variables within 20% of pre-operative values.Bolus	Morphine consumption and VAS pain scores were lowest in the group receiving continuous alfentanil infusion. Alfentanil boluses offered improved VAS scores and morphine consumption compared to OFA. No statistically significant difference in pain at 6-month post-surgery.

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TABLE 2 Continued

Study	Surgery type	Study type	Sample	OFA regimen	OBA comparator regimen	OFA findings
Hublet et al. (29)	Pancreatic resection	Retrospective cohort	77	Magnesium 30–40 mg/kg, dexamethasone 10 mg, and diclofenac 75 mg pre-induction. Dexmetedomidine infusion 0.5 mcg/kg/h 10 min prior to induction Lidocaine 1.5 mg/kg and IV esketamine bolus 0.25 mg/kg at induction Maintenance: IV lidocaine 1.5 mg/kg/h, IV esketamine 0.125 mg/kg/h, and dexmetedomidine 0.4–0.7 mcg/kg/h	Magnesium 30–40 mg/kg, dexamethasone 10 mg, diclofenac 75 mg, and morphine 4 mcg/kg pre-induction Lidocaine 1.5 mg/kg and target-controlled infusion (TCI) of remifentanil 3 −5 ng/ml at induction Maintenance with remifentanil 2 −5 ng/ml	Reduced postoperative pain and opioid consumption Reduced the comprehensive complication index Shortened length of stay by 4 days
Xue et al. (30)	Shoulder arthroscopy	Randomized controlled trial	60	Interscalene brachial plexus block with 20 ml of 0.375% ropivacaine TIVA dexmedetomidine 0.8–1 mcg/kg infusion for 10 min followed by continuous infusion of dexmedetomidine of 0.3–0.5 mcg/kg/h Esketamine 0.3 mg/kg prior to incision followed by esketamine 0.15 mg/kg infusion	Interscalene brachial plexus block with 20 ml of 0.375% ropivacaine TIVA Propofol 2 mg/kg, cisatracurium 0.2 mg/kg, fentanyl 3–4 mcg/kg at induction. Maintenance with remifentanil 5–10 mcg/kg/h	Decreased PONV incidence and severity in the first 24 h. Shortened PACU stay Comparable pain scores and postoperative analgesia (NSAIDs and opioids consumption) Comparable incidence of hallucinations, nightmares, bradycardia, or excessive oral secretions
Barakat et al. (23)	Spine (multilevel fusion)	Randomized Controlled Trial	48	Dexmedetomidine 0.5 mcg/kg/h and lidocaine 1 mg/kg/h continuous IV infusion over 10 min before induction. Induction: ketamine 0.15 mg/kg. Maintained: dexmedetomidine 0.3 mcg/kg/h, lidocaine 1.5 mg/kg/h, ketamine 0.15 mg/kg/h infusion.	Fentanyl 2 mcg/kg, ketamine 0.15 mg/kg Maintenance: remifentanil 0.2–0.3 mcg/kg/min, ketamine infusion 0.15 mg/kg/h.	Reduced postoperative opioid consumption Decreased PONV in the first 24 h postoperatively. Higher antihypertensive requirement Longer PACU stay
An et al. (31)	Thoracic (VATS/ thoracoscopic lung)	Randomized Controlled Trial	100	Thoracic Paravertebral Block: 15 ml of 0.5% Ropivacaine Dexmedetomidine 1 mcg/kg loading dose 10 min Dexmedetomidine 0.5 mcg/kg/h, ketorolac 30 mg, and etomidate 0.2–0.3 mg/kg at induction Maintenance with dexmedetomidine 0.5 mcg/kg/h	Thoracic Paravertebral Block: 15 ml of 0.5% Ropivacaine Sufentanil 0.5 mcg/kg, etomidate 0.2–0.3 mg/kg at induction Maintenance with remifentanil 200–500 mcg/h	Comparable intraoperative analgesia index Higher depth of sedation and blood glucose levels.
Wang et al. (32)	Thoracic (VATS/ thoracoscopic lung)	Randomized Controlled Trial	124	Epidural 10 ml of 0.1875% Ropivacaine followed by 4–5 ml/hr continuous infusion Lidocaine 40 mg and magnesium sulfate 5–10 mg/kg and esmolol 0.5–1 mg/kg at induction. Maintenance with lidocaine 1 mg/kg/h (maximum 300 mg)	TCI of remifentanil (3–5 ng/ml), sufentanil 10–20 mcg, epidural hydromorphone 0.3–0.5 mg in 3–5 ml 10 min prior to incision Maintenance with Epidural 10 ml of 0.1875% Ropivacaine followed by 4–5 ml/hr continuous infusion after lung resection	Decreased severity of motion-pain and incidence of PCEA-related adverse events on postoperative at 24 h
Feng et al. (33)	Thoracic (VATS/ thoracoscopic lung)	Randomized Controlled Trial	120	Dexmedetomidine 0.6 mcg/kg over 10 min and esketamine 0.3 mg/kg at induction Maintenance with dexmedetomidine 0.2–1.0 mcg/kg/h infusion and esketamine 0.1 mg/kg boluses surgical pleth index (SPI)-guided	Sufentanil 0.3 mcg/kg at induction Maintenance with sufentanil 0.1 mcg/kg boluses SPI-guided	Halved the incidence of PONV Longer PACU stay.
Kim et al. (34)	Thoracic (VATS/ thoracoscopic lung)	Retrospective cohort (propensity-score matching)	196	Dexmedetomidine 0.6 mcg/kg infusion over 10 min pre-induction Maintenance with dexmedetomidine 0.5 mcg/kg/h infusion adjusted in increments of 0.1 mcg/kg/h until completion of intercostal block Thoracoscopic intercostal block	TCI of remifentanil (effect-site concentration 3–4 ng/ml) at induction Maintenance with remifentanil via TCI (effect-site concentration 1–4 ng/ml) Thoracoscopic intercostal block	Comparable QoR-15, pain, PONV, opioid consumption, opioid-related adverse events. Hypotension/bradycardia were numerically more frequent (not significant).

(*Continued*)

TABLE 2 Continued

Study	Surgery type	Study type	Sample	OFA regimen	OBA comparator regimen	OFA findings
Yan et al. (35)	Thoracic (VATS/ Thoracoscopic lung)	2 centers Randomized Controlled Trial	159	Thoracic epidural Dexmedetomidine 0.5–1 μg/kg IV before induction Induction: esketamine 0.125 mg/kg Maintenance: if needed esketamine 0.125 mg/kg Before the incision: Epidural administration 10 ml 0.2% ropivacaine + esketamine 0.25 mg/kg then intermittent bolus of 0.2% ropivacaine (5 ml/h) Postoperative PCEA: ropivacaine 0.15% with esketamine 25 mg	Thoracic Epidural Induction: Fentanyl 4 μg/kg Maintenance: if needed fentanyl 1 μg/kg Before the incision: Epidural administration morphine 2 mg then intermittent bolus of 0.2% ropivacaine (5 ml/h) Postoperative PCEA: ropivacaine 0.15% with morphine10 mg	Reduced PONV and pruritus. Reduced incidence of pain, at 24 h and mild chronic pain at 3- and 6-months post-surgery. Comparable acute postoperative pain at 48 h.
Yan et al. (36)	Thoracic (VATS/ thoracoscopic lung)	Randomized controlled trial	165	Thoracic paravertebral block 20 ml of 0.5% ropivacaine Dexmedetomidine 0.5 mcg/kg for 15 min pre-induction Lidocaine 1.5 mg/kg at induction Maintenance with dexmedetomidine 0.5 mcg/kg/h and lidocaine 1.5 mg/kg/h	Thoracic paravertebral block 20 ml of 0.5% ropivacaine Sufentanil 0.3–0.4 mcg/kg at induction. Maintenance with remifentanil 0.1–0.2 mcg/kg/min	Decreased 24 h PONV and had lower incidence of postoperative complications (including respiratory depression, hypoxemia, pulmonary embolism, hypotension, pruritus, drowsiness, dizziness, fatigue, constipation, and uroschesis) Comparable QoR-15 scores, pain, and 6-min walk test.
Selim et al. (37)	Thoracic (VATS/ thoracoscopic lung)	Retrospective cohort (propensity-score matching)	81	Dexmetedomidine 0.5 mcg/kg 20 min pre-induction then 0.3–1.0 μg/kg/h Ketamine bolus 0.15–0.40 mg/kg and lidocaine bolus 1.5 mg/kg at induction Maintenance with dexmedetomidine 0.3–1 mcg/kg/h, ketamine 0.25 mg/kg/h, and lidocaine 2 mg/kg/h	Remifentanil TCI (target of 3–5 ng/ml) Maintenance with TCI of remifentanil (target of 2–4 ng/ml)	Reduced postoperative pain and opioid consumption at 48 h post-surgery
Wang et al. (38)	Thyroid/ Parathyroid	Double Blinded Randomized Controlled Trial	394	Esketamine 0.3 mg/kg and lidocaine 1 mg/kg at induction Maintenance with esketamine 0.1 mg/kg boluses	sufentanil 0.3 mcg/kg and saline (volume matched to lidocaine) at induction. Maintenance with sufentanil 0.1 mcg/kg boluses	Decreased incidence of PONV Lowered rates of hypotension and desaturation after tracheal extubation. Higher rates of patient satisfaction. Comparable length of PACU stay, postoperative pain scores at PACU discharge, 24 h, and 48 h post-surgery. Comparable incidence of 30-d major complications.
Beloeil et al. (39)	Mixed major noncardiac surgery	Randomized Controlled Trial	312	Lidocaine 1.5 mg/kg, ketamine 0.5 mg/kg and dexmedetomidine 0.4–1.4 mcg/kg at induction Maintenance with lidocaine 1.5 mg/kg/h, ketamine 0.25 mg/kg/h, and dexmedetomidine 0.4–1.4 mcg/kg/h	Lidocaine 1.5 mg/kg, ketamine 0.5 mg/kg and TCI of remifentanil (target 3–5 ng/ml) Maintenance with lidocaine 1.5 mg/kg/h, ketamine 0.25 mg/kg/h, and TCI of remifentanil (target 2–5 ng/ml)	Decreased PONV and postoperative opioid use. Prolonged sedation and time to extubation Longer PACU stays Trial was terminated early due to higher rates of adverse events in the OFA group, including bradycardia and hypoxemia.

Meta-analyses have also concluded that OFA provides little to no consistent improvement in postoperative pain requirements (54, 55). The effectiveness of OFA in managing pain appears highly dependent on the specific protocol and its meticulous execution. Nevertheless, the consensus is that OFA is not inferior to OBA in terms of postoperative pain control.

4.3 Postoperative recovery

Quality of Recovery (QoR), a composite score that assesses physical comfort, emotional state, pain, and other factors, has been used to evaluate the overall benefits of OFA (58). Some studies have demonstrated comparable QoR outcomes between OFA and OBA.

Clanet et al. (19) reported similar QoR-40 scores at both 24 h and 30 days postoperatively in bariatric surgery patients. Kim et al. (34) and Yan et al. (36) found nearly identical QoR-15 scores between OFA and OBA groups in patients undergoing video-assisted thoracic surgery. However, a meta-analysis by Liu et al. (49) reported a clinically meaningful improvement in QoR-40 scores among OFA patients, primarily driven by enhanced pain control and physical comfort. This improvement was not reflected in QoR-15 scores, highlighting the sensitivity of different QoR instruments. The evidence suggests that, at a minimum, OFA is comparable to OBA in terms of overall postoperative recovery.

4.4 Intraoperative hemodynamic stability

Maintaining hemodynamic stability with OFA is a potential challenge due to the variety of regimens used and their pharmacodynamics, contributing to notable discrepancies in the literature. Two systematic reviews noted a higher incidence of bradycardia (14, 55), and some studies noted hypotension requiring increased use of vasopressors (52) or hypertension needing more antihypertensive agents (23), particularly with dexmedetomidine-based regimens. A large multicenter trial by Beloeil et al. (39) was even halted prematurely due to a higher incidence of severe bradycardia and hypoxemia in the dexmedetomidine-based OFA group. This study was criticized, however, by Mieszczański et al. (14) due to the high average doses of dexmedetomidine (1.2 mcg/kg/h) and long average anesthetic time of 268 min. Regardless, the possibility of increased intraoperative hemodynamic instability is clinically meaningful when comparing OFA and OBA.

Conversely, other research suggests OFA can lead to comparable hemodynamic stability (21, 29, 30). In a trial of patients undergoing lumpectomy, the OFA group experienced statistically and clinically significant lower rates of hypotension (5% vs. 38%) and bradycardia (8% vs. 32%) (24). Lower rates of intraoperative hypotension were also seen in laparoscopic cholecystectomy (1% vs. 8%) (27) and thyroid surgery (1% vs. 5%) (38). However, it remains unclear whether these differences translate into meaningful clinical consequences.

The discrepancy in outcomes highlights the critical need for developing robust, standardized protocols and providing comprehensive education to enhance clinician understanding and effective management of the unique pharmacodynamics of non-opioid agents.

4.5 Length of post-anesthesia care unit (PACU) stay

OFA may prolong PACU stays, a trade-off worth considering against reduced opioid-related complications. Studies in major spine (23), thoracic surgery (33), and mixed major non-cardiac surgery (39) have reported a longer PACU duration (15.5–35 min) for OFA patients, often attributed to the sedative effects of dexmedetomidine even in the absence of pain or nausea.

In contrast, other studies have found either **no significant difference** or even a **shorter PACU stay** with OFA protocols. A study on shoulder arthroscopy found a statistically significant reduction in PACU stay by 9.3 min (30). Similarly, a trial in thyroid and parathyroid surgery and a meta-analysis on laparoscopic surgery demonstrated comparable PACU stays between OFA and OBA (38, 56).

The differences in length of PACU stay are likely influenced by surgical complexity and the sedative profile of dexmedetomidine. An absolute reduction of 9.3 min with OFA for shoulder arthroscopy may not be clinically meaningful. However, an increased length of stay by 35 min with an opioid-free approach may negatively impact efficiency and resource use. This underscores the need to balance depth of sedation with the possible benefits of OFA.

5 A critical knowledge gap: the long-term impact of OFA

A critical knowledge gap in the OFA literature is the lack of robust, high-level evidence on long-term patient outcomes, particularly regarding PPOU and CPSP. The central hypothesis that OFA reduces these risks remains largely unproven. Only a handful of studies have assessed long-term outcomes, with mixed results. While one thoracic trial found a reduction in CPSP with a non-opioid epidural pathway (35), other studies found no difference in chronic pain incidence at six months (58, 59).

Crucially, no randomized controlled trials were found to have reported PPOU as a primary or secondary outcome, despite this being a key public health objective of OFA. The absence of data on opioid prescription fulfillment beyond the immediate postoperative period is a major limitation. Interestingly, some retrospective data have paradoxically suggested that higher intraoperative fentanyl doses may be associated with a lower incidence of PPOU, potentially by preventing inadequate pain control and subsequent central sensitization (60). This paradox underscores the complexity of the pain-anesthesia-dependence relationship and the urgent need for targeted, long-term investigation. Taken together, the scarcity of long-term data and the inconsistency of existing findings mirror the broader methodological issues in OFA literature, as discussed below.

6 Limitations of the evidence base and future directions

As summarized in Table 1, most available studies on OFA consist of small, single-center randomized controlled trials with heterogeneous anesthetic protocols and patient populations. Many trials included fewer than 100 participants and were powered to detect short-term outcomes such as PONV, postoperative pain, and quality-of-recovery scores, rather than long-term outcomes. It is possible that several trials that noted comparable findings for pain, hemodynamic stability, postoperative opioid use, or other ORADEs may be reflecting Type II error rather than true equivalence. Guo et al. (61) and Gricourt et al. (16) agree that there is a critical need for large, multicenter trials to

improve the generalizability and external validity of findings across diverse surgical settings and patient demographics.

The marked heterogeneity among OFA regimens further complicates comparison across trials. Protocols varied in drug combinations, dosing, and timing. Several studies do not clearly outline titration or monitoring strategies. The inconsistency between blinding strategies across studies also introduces a source of bias and increases the difficulty of comparing across trials. Shanthanna and Joshi (62) emphasize that future studies should develop procedure- and patient-specific combinations with standardized dosing and administration.

As noted earlier, only a few studies assessed CPSP after discharge. PPOU was not outlined as an endpoint in any of the studies that we reviewed. Most studies that we reviewed had short observation periods, making it challenging to evaluate long-term opioid-related complications as they relate to OFA. This is compounded by the fact that inappropriate postoperative prescribing and a lack of discharge stewardship programs may lead to persistent opioid use, potentially offsetting the intraoperative benefits of OFA (2, 63). More studies are needed to clarify the long-term impact of OFA on CPSP and PPOU, which is a core rationale for its adoption.

The cost-effectiveness of OFA remains largely unexplored. While OFA may reduce complications and hospital stays, its higher upfront costs, driven by multi-agent regimens and increased monitoring, pose a barrier to widespread adoption (21). Further research is needed to evaluate the economic impact of OFA to guide its broader implementation.

7 Conclusion

Opioid-free anesthesia (OFA) offers a valuable strategy to reduce perioperative opioid exposure. The most consistent and immediate benefit reported is a significant reduction in PONV. While short-term pain control and recovery outcomes appear comparable to opioid-based approaches, substantial limitations remain. However, the long-term impact of OFA on PPOU and CPSP remains largely unknown. To advance the clinical utility of this technique, future research must prioritize robust, multicenter, well-powered trials with standardized protocols, established safety metrics, and sufficient longitudinal follow-up to definitively assess PPOU and CPSP. Furthermore, cost-effectiveness analyses are crucial for determining the broader economic and clinical implications of OFA and its appropriate role in mitigating the opioid crisis.

Author contributions

AP: Conceptualization, Investigation, Writing – original draft. OE: Conceptualization, Writing – review & editing, Project administration, Supervision. RW: Conceptualization, Writing – review & editing, Supervision.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

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References

1. Egan TD. Are opioids indispensable for general anaesthesia? *Br J Anaesth.* (2019) 122:e127–35. doi: 10.1016/j.bja.2019.02.018

2. Shanthanna H, Ladha KS, Kehlet H, Joshi GP. Perioperative opioid administration. *Anesthesiology.* (2021) 134:645–59. doi: 10.1097/ALN.0000000000003572

3. Ferry N, Hancock LE, Hendrix JM, Dhanjal ST. *Opioid Anesthesia*. Treasure Island, FL: StatPearls Publishing (2025).

4. Glass PSA, Gan TJ, Howell S, Ginsberg B. Drug interactions: volatile anesthetics and opioids. *J Clin Anesth.* (1997) 9:18S–22. doi: 10.1016/S0952-8180(97)00122-0

5. Yiu CH, Gnjidic D, Patanwala A, Fong I, Begley D, Khor KE, et al. Opioid-related adverse drug events in surgical patients: risk factors and association with clinical outcomes. *Expert Opin Drug Saf.* (2022) 21:1211–23. doi: 10.1080/14740338.2022.2049230

6. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician.* (2011) 14:145–61. doi: 10.36076/ppj.2011/14/145

7. Yu EHY, Tran DHD, Lam SW, Irwin MG. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia.* (2016) 71:1347–62. doi: 10.1111/anae.13602

8. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth*. (2014) 112:991–1004. doi: 10.1093/bja/aeu137

9. Moka E, Aguirre JA, Sauter AR, Lavand'homme P. Chronic postsurgical pain and transitional pain services: a narrative review highlighting European perspectives. *Reg Anesth Pain Med*. (2025) 50:205–12. doi: 10.1136/rapm-2024-105614

10. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA Intern Med*. (2016) 176:1286–93. doi: 10.1001/jamainternmed.2016.3298

11. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *Br Med J*. (2014) 348:g1251. doi: 10.1136/bmj.g1251

12. Gribsholt SB, Pedersen AM, Svensson E, Thomsen RW, Richelsen B. Prevalence of self-reported symptoms after gastric bypass surgery for obesity. *JAMA Surg*. (2016) 151:504–11. doi: 10.1001/jamasurg.2015.5110

13. Pierik AS, Coblijn UK, de Raaff CAL, van Veen RN, van Tets WF, van Wagensveld BA. Unexplained abdominal pain in morbidly obese patients after bariatric surgery. *Surg Obes Relat Dis*. (2017) 13:1743–51. doi: 10.1016/j.soard.2017.05.027

14. Mieszczański P, Kołacz M, Trzebicki J. Opioid-Free anesthesia in bariatric surgery: is it the one and only? A comprehensive review of the current literature. *Healthcare*. (2024) 12:1094. doi: 10.3390/healthcare12111094

15. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, et al. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg*. (2017) 152:e170504. doi: 10.1001/jamasurg.2017.0504

16. Gricourt Y, Cuvillon P, Forget P. Opioid-free anaesthesia as a valuable alternative to opioid-based practices: evidence and future challenges. *Pain Manag*. (2025) 15:721–31. doi: 10.1080/17581869.2025.2542719

17. Forget P. Opioid-free anaesthesia. Why and how? A contextual analysis. *Anaesth Crit Care Pain Med*. (2019) 38:169–72. doi: 10.1016/j.accpm.2018.05.002

18. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. *Br J Anaesth*. (2014) 112:906–11. doi: 10.1093/bja/aet551

19. Clanet M, Touihri K, El Haddad C, Goldsztejn N, Himpens J, Fils JF, et al. Effect of opioid-free versus opioid-based strategies during multimodal anaesthesia on postoperative morphine consumption after bariatric surgery: a randomised double-blind clinical trial. *BJA Open*. (2024) 9:100263. doi: 10.1016/j.bjao.2024.100263

20. Perez JJ, Strunk JD, Preciado OM, DeFaccio RJ, Chang LC, Mallipeddi MK, et al. Effect of an opioid-free anesthetic on postoperative opioid consumption after laparoscopic bariatric surgery: a prospective, single-blinded, randomized controlled trial. *Reg Anesth Pain Med*. (2024) 50:699–705. doi: 10.1136/rapm-2024-105632

21. Dagher C, Mattar R, Aoun M, Tohme J, Naccache N, Jabbour H. Opioid-free anesthesia in bariatric surgery: a prospective randomized controlled trial. *Eur J Med Res*. (2025) 30:320. doi: 10.1186/s40001-025-02565-9

22. Barakat H, Gholmieh L, Nader JA, Karam VY, Albaini O, Helou ME, et al. Opioid-free versus opioid-based anesthesia in laparoscopic sleeve gastrectomy: a single-center, randomized, controlled trial. *Perioper Med*. (2025) 14:16. doi: 10.1186/s13741-024-00486-5

23. Barakat H, Al Nawwar R, Abou Nader J, Aouad M, Yazbeck Karam V, Gholmieh L. Opioid-free versus opioid-based anesthesia in major spine surgery: a prospective, randomized, controlled clinical trial. *Minerva Anestesiol*. (2024) 90:482–90. doi: 10.23736/S0375-9393.24.17962-X

24. Qian XL, Li P, Chen YJ, Xu SQ, Wang X, Feng SW. Opioid free total intravenous anesthesia with dexmedetomidine-esketamine-lidocaine for patients undergoing lumpectomy. *J Clin Med Res*. (2023) 15:415–22. doi: 10.14740/jocmr5000

25. An G, Wang G, Zhao B, Zhang X, Li Z, Fu J, et al. Opioid-free anesthesia compared to opioid anesthesia for laparoscopic radical colectomy with pain threshold index monitoring: a randomized controlled study. *BMC Anesthesiol*. (2022) 22:241. doi: 10.1186/s12871-022-01747-w

26. Zhang L, Yu X-H, Zhang H-M, Wang S, Chen J-L, Li X-S, et al. Efficacy of opioid-free anesthesia in short-term recovery following laparoscopic-assisted colorectal tumor resection: a randomized trial. *Front Oncol*. (2025) 15:1588623. doi: 10.3389/fonc.2025.1588623

27. Luong NV. Evaluation of efficacy of free opioid anesthesia for laparoscopic cholecystectomy: a prospective, randomized double-blinded study. *Open Anesth J*. (2000) 14:73–9. doi: 10.2174/2589645802014010073

28. Hu Y, Zhang QY, Qin GC, Zhu GH, Long X, Xu JF, et al. Balanced opioid-free anesthesia with lidocaine and esketamine versus balanced anesthesia with sufentanil for gynecological endoscopic surgery: a randomized controlled trial. *Sci Rep*. (2024) 14:11759. doi: 10.1038/s41598-024-62824-3

29. Hublet S, Galland M, Navez J, Loi P, Closset J, Forget P, et al. Opioid-free versus opioid-based anesthesia in pancreatic surgery. *BMC Anesthesiol*. (2022) 22:9. doi: 10.1186/s12871-021-01551-y

30. Xue Z, Yan C, Liu Y, Yang N, Zhang G, Qian W, et al. Opioid-free anesthesia with esketamine-dexmedetomidine versus opioid-based anesthesia with propofol-remifentanil in shoulder arthroscopy: a randomized controlled trial. *BMC Surg*. (2024) 24:228. doi: 10.1186/s12893-024-02518-9

31. An G, Zhang Y, Chen N, Fu J, Zhao B, Zhao X. Opioid-free anesthesia compared to opioid anesthesia for lung cancer patients undergoing video-assisted thoracoscopic surgery: a randomized controlled study. *PLoS One*. (2021) 16:e0257279. doi: 10.1371/journal.pone.0257279

32. Wang S, Li Y, Liang C, Han X, Wang J, Miao C. Opioid-free anesthesia reduces the severity of acute postoperative motion-induced pain and patient-controlled epidural analgesia-related adverse events in lung surgery: randomized clinical trial. *Front Med*. (2023) 10:1243311. doi: 10.3389/fmed.2023.1243311

33. Feng C, Xu Y, Chen S, Song N, Meng X, Liu H, et al. Opioid-free anaesthesia reduces postoperative nausea and vomiting after thoracoscopic lung resection: a randomised controlled trial. *Br J Anaesth*. (2024) 132:267–76. doi: 10.1016/j.bja.2023.11.008

34. Kim M, Huh J, Choi H, Hwang W. No difference in postoperative recovery outcomes between opioid-free and opioid-sparing anesthesia under multimodal analgesic protocol for video-assisted thoracoscopic surgery: a propensity score matching cohort study. *J Clin Med*. (2024) 13:6581. doi: 10.3390/jcm13216581

35. Yan H, Chen W, Chen Y, Gao H, Fan Y, Feng M, et al. Opioid-Free versus opioid-based anesthesia on postoperative pain after thoracoscopic surgery: the use of intravenous and epidural esketamine. *Anesth Analg*. (2023) 137:399–408. doi: 10.1213/ANE.0000000000006547

36. Yan X, Liang C, Jiang J, Ji Y, Wu A-S, Wei C-W. Effects of balanced opioid-free anesthesia on post-operative nausea and vomiting in patients undergoing video-assisted thoracic surgery: a randomized trial. *BMC Anesthesiol*. (2025) 25:62. doi: 10.1186/s12871-025-02938-x

37. Selim J, Jarlier X, Clavier T, Boujibar F, Dusséaux M-M, Thill J, et al. Impact of opioid-free anesthesia after video-assisted thoracic surgery: a propensity score study. *Ann Thorac Surg*. (2022) 114:218–24. doi: 10.1016/j.athoracsur.2021.09.014

38. Wang D, Sun Y, Zhu Y-J, Shan X-S, Liu H, Ji F-H, et al. Comparison of opioid-free and opioid-inclusive propofol anaesthesia for thyroid and parathyroid surgery: a randomised controlled trial. *Anaesthesia*. (2024) 79:1072–80. doi: 10.1111/anae.16382

39. Beloeil H, Garot M, Lebuffe G, Gerbaud A, Bila J, Cuvillon P, et al. Balanced opioid-free anesthesia with dexmedetomidine versus balanced anesthesia with remifentanil for major or intermediate noncardiac surgery. *Anesthesiology*. (2021) 134:541–51. doi: 10.1097/ALN.0000000000003725

40. Doleman B, Mathiesen O, Sutton AJ, Cooper NJ, Lund JN, Williams JP. Non-opioid analgesics for the prevention of chronic postsurgical pain: a systematic review and network meta-analysis. *Br J Anaesth*. (2023) 130:719–28. doi: 10.1016/j.bja.2023.02.041

41. Hah J, Mackey SC, Schmidt P, McCue R, Humphreys K, Trafton J, et al. Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort: a randomized clinical trial. *JAMA Surg*. (2018) 153:303–12. doi: 10.1001/jamasurg.2017.4915

42. Forget P, Cata J. Stable anesthesia with alternative to opioids: are ketamine and magnesium helpful in stabilizing hemodynamics during surgery? A systematic review and meta-analyses of randomized controlled trials. *Best Pract Res Clin Anaesthesiol*. (2017) 31:523–31. doi: 10.1016/j.bpa.2017.07.001

43. Ozturk T, Kaya H, Aran G, Aksun M, Savaci S. Postoperative beneficial effects of esmolol in treated hypertensive patients undergoing laparoscopic cholecystectomy. *Br J Anaesth*. (2008) 100:211–4. doi: 10.1093/bja/aem333

44. López-Álvarez S, Mayo-Moldes M, Zaballos M, Iglesias BG, Blanco-Dávila R. Esmolol versus ketamine-remifentanil combination for early postoperative analgesia after laparoscopic cholecystectomy: a randomized controlled trial. *Can J Anesth Can Anesth*. (2012) 59:442–8. doi: 10.1007/s12630-012-9684-x

45. Kianian S, Bansal J, Lee C, Zhang K, Bergese SD. Perioperative multimodal analgesia: a review of efficacy and safety of the treatment options. *Anesthesiol Perioper Sci*. (2024) 2:9. doi: 10.1007/s44254-023-00043-1

46. Gerriets V, Anderson J, Patel P, Nappe TM. *Acetaminophen*. Treasure Island, FL: StatPearls Publishing (2025).

47. Wu CL, King AB, Geiger TM, Grant MC, Grocott MPW, Gupta R, et al. American society for enhanced recovery and perioperative quality initiative joint consensus statement on perioperative opioid minimization in opioid-naive patients. *Anesth Analg*. (2019) 129:567–77. doi: 10.1213/ANE.0000000000004194

48. Simpson JC, Bao X, Agarwala A. Pain management in enhanced recovery after surgery (ERAS) protocols. *Clin Colon Rectal Surg*. (2019) 32:121–8. doi: 10.1055/s-0038-1676477

49. Liu Y, Ma W, Zuo Y, Li Q. Opioid-free anaesthesia and postoperative quality of recovery: a systematic review and meta-analysis with trial sequential analysis. *Anaesth Crit Care Pain Med*. (2025) 44:101453. doi: 10.1016/j.accpm.2024.101453

50. Ghlichloo I, Gerriets V. *Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)*. Treasure Island, FL: StatPearls Publishing (2025).

51. Kaye AD, Urman RD, Rappaport Y, Siddaiah H, Cornett EM, Belani K, et al. Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. *J Anaesthesiol Clin Pharmacol*. (2019) 35:S40–5. doi: 10.4103/joacp.JOACP_51_18

52. Mieszczański P, Górniewski G, Ziemiański P, Cylke R, Lisik W, Trzebicki J. Comparison between multimodal and intraoperative opioid free anesthesia for laparoscopic sleeve gastrectomy: a prospective, randomized study. *Sci Rep*. (2023) 13:12677. doi: 10.1038/s41598-023-39856-2

53. Hicks MA, Tyagi A. *Magnesium Sulfate*. Treasure Island, FL: StatPearls Publishing (2025).

54. Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. *Anaesthesia*. (2019) 74:651–62. doi: 10.1111/anae.14582

55. Feenstra ML, Jansen S, Eshuis WJ, van Berge Henegouwen MI, Hollmann MW, Hermanides J. Opioid-free anesthesia: a systematic review and meta-analysis. *J Clin Anesth*. (2023) 90:111215. doi: 10.1016/j.jclinane.2023.111215

56. Cheng L, Liu J, Qin S, Geng X, Jing L, Fang S. Safety and effectiveness of multimodal opioid-free anaesthesia for pain and recovery after laparoscopic surgery: a systematic review and meta-analysis. *BMJ Open*. (2025) 15:e085988. doi: 10.1136/bmjopen-2024-085988

57. Zhang Z, Li C, Xu L, Sun X, Lin X, Wei P, et al. Effect of opioid-free anesthesia on postoperative nausea and vomiting after gynecological surgery: a systematic review and meta-analysis. *Front Pharmacol*. (2024) 14:1330250. doi: 10.3389/fphar.2023.1330250

58. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology*. (2013) 118:1332. doi: 10.1097/ALN.0b013e318289b84b

59. Katz J, Clairoux M, Redahan C, Kavanagh BP, Carroll S, Nierenberg H, et al. High dose alfentanil pre-empts pain after abdominal hysterectomy. *Pain*. (1996) 68:109–18. doi: 10.1016/S0304-3959(96)03172-7

60. Santa Cruz Mercado LA, Liu R, Bharadwaj KM, Johnson JJ, Gutierrez R, Das P, et al. Association of intraoperative opioid administration with postoperative pain and opioid use. *JAMA Surg*. (2023) 158:854–64. doi: 10.1001/jamasurg.2023.2009

61. Guo Z, Shan Z, Wang F. Research trends and knowledge mapping of opioid-free anesthesia: a global bibliometric analysis. *J Multidiscip Healthcare*. (2025) 18:4145–57. doi: 10.2147/JMDH.S533687

62. Shanthanna H, Joshi GP. Opioid-free general anesthesia: considerations, techniques, and limitations. *Curr Opin Anesthesiol*. (2024) 37:384. doi: 10.1097/ACO.0000000000001385

63. Allen ML, Silva APD, Braat S, Jones K, Chia A, Hucker TR, et al. Post-surgical discharge opioid prescribing, use and handling after introduction of a stewardship program. *Anaesth Intensive Care*. (2023) 51:239–53. doi: 10.1177/0310057X231160800