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PERIOPERATIVE PAIN MANAGEMENT IN ADULT SURGICAL PATIENTS: A SYSTEMATIC REVIEW OF PHARMACOLOGIC AND ANESTHETIC STRATEGIES FOR OPIOID SPARING ANALGESIA

ABDULRAHMAN ABDULLAH ASEERI
Pharmacist, National Guard Hospital.

ABDULRAHMAN ABDULAZIZ BIN MOUSA
Pharmacy Technician, National Guard Hospital.

ABDULAZIZ HOMOUD ALKHATHAMI
Pharmacy Technician, National Guard Hospital.

MOHAMMED NAZAL ALSHAMMARI
Pharmacy Technician, National Guard Hospital.

YOUSEF ABDULRAHMAN ALZEER
Pharmacy Technician, National Guard Hospital.

SALEH JASEM MOHAMMED ALANIZI
Anesthesia Technician, National Guard Hospital.

Abstract

Effective perioperative pain management must balance timely analgesia with minimizing opioid-related harm. Pharmacologic and anesthetic strategies that deliberately reduce perioperative opioid exposure have expanded rapidly, including multimodal analgesia protocols, opioid-sparing and opioid-free anesthesia (OFA), and intravenous lidocaine or ketamine-based regimens. This systematic review synthesized randomized and comparative clinical studies evaluating opioid-sparing approaches in adult surgical patients. Electronic databases were searched to November 2025 for trials comparing multimodal or OFA strategies against conventional opioid-centered care, with outcomes including opioid consumption, pain scores, and recovery indices. Nine eligible studies were identified: eight randomized controlled trials and one retrospective cohort, spanning gynecologic laparoscopy and laparotomy, breast lumpectomy, major abdominal laparoscopy, orthopedic arthroscopy, and robotic prostatectomy. Enhanced recovery pathways and structured multimodal regimens consistently reduced postoperative opioid use while maintaining or improving pain scores and quality-of-recovery measures. OFA strategies using lidocaine, esketamine, and dexmedetomidine often achieved non-inferior analgesia with reduced intraoperative opioid requirements, though extubation time and sedative effects were sometimes increased. Intravenous lidocaine as an adjunct showed procedure- and context-dependent benefits. Overall, perioperative opioid-sparing strategies appear safe and feasible when integrated into multidisciplinary care pathways, but heterogeneity of regimens and outcomes limits firm procedural recommendations.

Keywords: Perioperative Pain; Opioid-Sparing; Multimodal Analgesia; Opioid-Free Anesthesia; Esketamine; Lidocaine; Adult Surgery.

INTRODUCTION

Acute postoperative pain remains one of the most frequent and distressing complications after surgery, and inadequate control is linked to delayed mobilization, cardiopulmonary complications, and persistent postsurgical pain [1,2]. For decades, systemic opioids have

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been the backbone of perioperative analgesia because of their rapid onset and potent effect, but they carry a substantial burden of adverse events, including respiratory depression, ileus, opioid-induced constipation, nausea, vomiting, pruritus, sedation, and potential for prolonged use and dependence [1–4]. These concerns have driven a global shift toward opioid-sparing perioperative pain management. Multimodal analgesia, defined as the concurrent use of several non-opioid agents and techniques targeting different pain pathways, has become a core component of enhanced recovery after surgery (ERAS) programs [5]. Scheduled acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentinoids, regional blocks, and wound infiltration are combined with judicious opioid rescue rather than high-dose background infusions. In laparoscopic cholecystectomy and gynecologic procedures, evidence-based pathways incorporating such components reduce pain scores, opioid consumption, and length of stay compared with traditional opioid-heavy regimens [6,7]. Intravenous lidocaine is another established adjunct in this context. A Cochrane review and subsequent consensus statement concluded that continuous perioperative lidocaine infusion can reduce early postoperative pain, opioid requirements, and ileus in selected abdominal procedures, albeit with variability across trials [8,9].

Esketamine and related N-methyl-D-aspartate antagonists have similarly been evaluated as components of perioperative multimodal analgesia; meta-analytic data suggest modest reductions in postoperative pain and opioid use when low-dose infusions are incorporated into balanced anesthesia [10]. More recently, opioid-free or opioid-reduced anesthesia (OFA) has emerged. These regimens rely on combinations of agents such as dexmedetomidine, lidocaine, and esketamine to avoid intraoperative opioids, while postoperative rescue often still includes small opioid doses. Randomized trials in gynecologic and noncardiac surgery report comparable pain scores and opioid consumption to opioid-based anesthesia, with differing profiles of hemodynamic instability and sedation [14,19]. However, the clinical literature remains fragmented by procedure type, drug combinations, and outcome measures. For anesthesiologists and clinical pharmacists charged with designing perioperative protocols, it is unclear which pharmacologic and anesthetic strategies offer meaningful opioid-sparing benefits without compromising analgesia or safety. This systematic review therefore focuses on adult surgical patients and synthesizes randomized and comparative clinical studies that explicitly evaluated perioperative opioid-sparing strategies, multimodal protocols, OFA, and intravenous lidocaine, against conventional opioid-centered care.

METHODS

This systematic review was planned in accordance with the PRISMA 2020 statement [20]. The protocol was developed a priori but not prospectively registered.

Eligibility Criteria

We included clinical studies that met the following criteria:

Population: adults (≥18 years) undergoing any elective or urgent surgical procedure under general or regional anesthesia.

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Intervention: perioperative pharmacologic and/or anesthetic strategies designed to reduce opioid exposure (e.g., multimodal analgesia protocols, OFA or opioid-reduced anesthesia, intravenous lidocaine or esketamine infusions). Interventions could be preoperative, intraoperative, and/or immediate postoperative.

Comparator: conventional opioid-centered care or less intensive multimodal regimens.

Design: randomized controlled trials (parallel-group) and prospective or retrospective comparative cohort studies.

Outcomes: at least one of the following, postoperative opioid consumption (dose or need for rescue), validated pain scores, quality-of-recovery indices, postoperative nausea and vomiting (PONV), or length of stay. We excluded pediatric studies, chronic pain or palliative cohorts, studies lacking a comparator group, and non-surgical or purely diagnostic procedures.

Search Strategy and Study Selection

MEDLINE, Embase, Cochrane CENTRAL, and Web of Science were searched from inception to 30 November 2025 using combinations of controlled vocabulary and keywords related to “opioid-free anesthesia,” “opioid-sparing,” “multimodal analgesia,” “lidocaine infusion,” “esketamine,” “dexmedetomidine,” and “surgery.” Search strategies were informed by prior reviews on multimodal analgesia, intravenous lidocaine, and S-ketamine [5,7–10]. Reference lists of relevant trials and reviews were hand-searched. Titles and abstracts were screened by two reviewers, followed by full-text assessment of potentially eligible articles. Disagreements were resolved by discussion without formal adjudication.

Data Extraction and Risk of Bias

From each included study we extracted design, surgical population, details of the opioid-sparing regimen, comparator, primary and secondary outcomes, and key findings related to opioid consumption, pain, and recovery. Risk of bias for randomized trials was assessed using domains analogous to the Cochrane RoB 2 tool (randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting). Comparative cohort studies were appraised for confounding, selection bias, and outcome assessment consistency, similar in scope to ROBINS-I.

Data Synthesis

Because of substantial heterogeneity in surgical procedures, anesthetic regimens, and endpoints, quantitative meta-analysis was not attempted. Instead, we undertook a narrative synthesis, grouping studies into:

(1) ERAS or multimodal analgesia protocols,

(2) OFA or opioid-reduced anesthesia using lidocaine, esketamine, and/or dexmedetomidine, and

(3) Regimens emphasizing intravenous lidocaine as a perioperative adjunct. Postoperative multimodal opioid-sparing prescribing protocols were considered within the first group [17,18].

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RESULTS

Study Selection and Overall Characteristics

The search identified nine eligible studies: eight randomized controlled trials and one retrospective cohort study, published between 2015 and 2025. Surgeries included laparoscopic gynecologic procedures, open gynecologic oncology laparotomy, hysteroscopy, major abdominal laparoscopy, breast lumpectomy, knee or shoulder arthroscopy, and robotic-assisted radical prostatectomy [11–18]. Most trials were single-center, with sample sizes typically in the tens to low hundreds. Risk of bias was generally low for randomization and outcome measurement, though several trials had unclear allocation concealment and limited blinding of postoperative caregivers [11–15,17–19]. The included studies are summarized in Table 1.

ERAS and Multimodal Analgesia Protocols

Laparoscopic Gynecologic Surgery ERAS Multimodal Analgesia

In a randomized trial of women undergoing laparoscopic gynecologic surgery, Geng et al. compared an ERAS-style multimodal analgesia protocol with conventional care [11]. The ERAS group received scheduled non-opioid analgesics and local anesthetic infiltration as part of a broader pathway, whereas the control group relied more heavily on titrated intravenous opioids and as-needed analgesics. The authors reported higher quality-of-recovery scores and lower early postoperative pain in the multimodal group, together with reduced opioid requirements for rescue analgesia in the first 24 hours [11]. Importantly, these benefits were observed without increases in PONV or other adverse events, suggesting that replacing background opioids with non-opioid combinations can improve both comfort and recovery.

Gynecologic Oncology Laparotomy Preemptive Multimodal Analgesia

A subsequent randomized trial by the same group evaluated preemptive multimodal analgesia in gynecologic oncology patients undergoing open laparotomy [12]. The intervention regimen combined preoperative administration of oral agents with intraoperative local anesthetic techniques and scheduled non-opioid postoperative analgesia, while the control arm received standard institutional practices with more opioid-centric dosing. Preemptive multimodal treatment reduced morphine consumption in the first 24 hours and improved early quality-of-recovery scores compared with controls, with no increase in major complications [12]. These two studies illustrate that structured, protocolized multimodal strategies can achieve meaningful opioid-sparing effects in both minimally invasive and open gynecologic surgery.

Breast Lumpectomy Postoperative Multimodal Protocol

Morin et al. implemented a multimodal, opioid-sparing regimen for outpatient lumpectomy, including preoperative non-opioid medications, intraoperative local anesthetic infiltration, and a standardized postoperative prescription favoring non-opioid analgesics [17]. Compared with a traditional regimen, the multimodal protocol produced superior pain control and substantially reduced postoperative opioid use, without an increase in

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unplanned healthcare contacts [17]. Patients reported high satisfaction, supporting the acceptability of such regimens in ambulatory oncologic surgery.

Knee and Shoulder Arthroscopy – Opioid-Sparing Prescribing Protocol

A large randomized clinical trial by Gazendam and colleagues evaluated a postoperative multimodal opioid-sparing protocol after knee or shoulder arthroscopy [18]. The intervention integrated patient education, scheduled non-opioid analgesics, and restricted rescue opioid prescribing, while the control arm received usual opioid-heavy prescriptions. The opioid-sparing protocol significantly reduced cumulative opioid consumption in the week after surgery, yet pain scores and functional recovery were non-inferior to standard care [18]. This trial demonstrates that re-framing postoperative prescribing can dramatically curtail outpatient opioid exposure without compromising analgesia. Collectively, these four studies suggest that when multimodal analgesia is implemented as a deliberate pathway, combining pharmacologic and organizational changes, perioperative opioid dose can be reduced across diverse surgeries while preserving or improving pain outcomes [11,12,17,18].

Opioid-Free and Opioid-Sparing Anesthesia

Hysteroscopy Lidocaine-Based OFA

Cha et al. randomized women undergoing hysteroscopy to OFA with lidocaine versus a conventional opioid-based anesthetic [13]. The OFA regimen utilized lidocaine infusions as a central component, supplemented with other non-opioid agents, whereas the control group received an opioid-containing balanced anesthetic. The OFA group showed improved early postoperative recovery scores, with similar pain ratings and no excess in PONV or serious adverse events [13]. Although postoperative rescue analgesia still included opioids in both groups, the study supports the feasibility of intraoperative opioid avoidance in short gynecologic procedures when multimodal strategies are used.

Gynecologic Endoscopic Surgery Lidocaine Esketamine OFA

Hu et al. conducted a randomized controlled trial comparing balanced OFA using lidocaine and esketamine with balanced opioid anesthesia using sufentanil in women undergoing laparoscopic gynecologic surgery [14]. The OFA group received bolus and continuous infusions of lidocaine and esketamine during anesthesia, whereas the control group was managed with sufentanil infusions, with similar volatile anesthetic concentrations [14].

The primary outcome, a 48-hour time-weighted average numeric rating scale (NRS) for pain, was similar between groups. Postoperative analgesic consumption over 48 hours, expressed in morphine equivalents, was slightly lower with OFA (approximately 0.79 vs 0.83 mg/kg) but not statistically significant [14]. Extubation time was about 2 minutes longer in the OFA group, but sedation scores, PONV incidence, gastrointestinal recovery, and patient satisfaction were comparable, and no severe adverse events were observed [14]. Thus, OFA with lidocaine–esketamine achieved non-inferior analgesia compared with opioid-based anesthesia, with only modest trade-offs in emergence time.

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Laparoscopic Major Abdominal Surgery – Esketamine Plus Dexmedetomidine

In a recent double-blind randomized trial, Wang et al. evaluated intraoperative esketamine combined with dexmedetomidine (opioid-sparing regimen) versus remifentanil-based anesthesia in patients undergoing laparoscopic major abdominal surgery [15].

The opioid-sparing group had lower pain scores in the post-anesthesia care unit (PACU) and a markedly reduced proportion of patients needing rescue analgesia, while overall anesthetic drug consumption (including propofol and volatile agents) was decreased [15]. Extubation time was longer and dream-like experiences were more frequent in the esketamine–dexmedetomidine group, but no serious hemodynamic instability or long-term sleep disturbance was detected. These findings indicate that an opioid-sparing anesthetic based on esketamine and dexmedetomidine can reduce immediate postoperative pain and rescue opioid use, at the cost of somewhat prolonged recovery and transient neuropsychiatric phenomena.

Major Noncardiac Surgery Dexmedetomidine-Based Balanced OFA

Beloeil et al. randomized adults undergoing major or intermediate noncardiac surgery to balanced OFA with dexmedetomidine versus balanced anesthesia with remifentanil [19]. While postoperative pain scores and opioid consumption were broadly similar between groups, the OFA arm had a higher incidence of bradycardia and hypotension requiring treatment [19].(Nature) Taken together with the gynecologic data, this trial suggests that OFA can match opioid-based anesthesia in terms of analgesia but may shift the risk profile toward hemodynamic adverse events, particularly when dexmedetomidine is used at higher doses.

Intravenous Lidocaine as a Perioperative Adjunct

Popa and colleagues performed a retrospective, single-center analysis of patients undergoing robotic-assisted radical prostatectomy, comparing those who received intraoperative lidocaine infusion to those who did not [16]. Intravenous lidocaine was associated with lower early postoperative pain scores and reduced opioid use, without increased complications, suggesting a potential opioid-sparing benefit in minimally invasive urologic surgery [16].

These findings align with earlier randomized trials and meta-analyses in abdominal surgery, where perioperative lidocaine has been reported to reduce opioid consumption and hasten bowel recovery in some contexts [8,9]. However, more recent randomized work in laparoscopic cholecystectomy has failed to show a clear analgesic or opioid-sparing effect for intraoperative lidocaine alone, underscoring that benefit may be procedure-specific and dependent on dose, timing, and concurrent multimodal components [6,8]. Across the OFA and multimodal trials described above, lidocaine infusions frequently appeared as one element within a broader strategy that also included esketamine, dexmedetomidine, or regional techniques [13–15].

This makes it difficult to isolate the individual contribution of lidocaine but reinforces its role as part of a pharmacologic “cocktail” designed to reduce overall opioid exposure.

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Table 1: Characteristics of included studies (adult perioperative opioid-sparing strategies)

First author, year	Country, setting	Procedure, population	Design	Opioid-sparing strategy (intervention)	Comparator	Key opioid-related outcome	Key pain, recovery outcomes
Geng 2021 [11]	China; single tertiary hospital	Elective laparoscopic gynecologic surgery in otherwise healthy women	Randomized controlled trial	ERAS-style multimodal analgesia pathway with scheduled non-opioid drugs and local anesthetic techniques	Conventional perioperative care with more opioid-centered analgesia	Reduced need for postoperative rescue opioids in first 24 h	Higher quality-of-recovery scores and lower early pain scores without increase in PONV
Geng 2024 [12]	China; oncology center	Open gynecologic oncology laparotomy	Randomized controlled trial	Preemptive multimodal analgesia (combined preoperative oral agents, intraoperative local anesthesia, and scheduled non-opioid postoperative analgesics)	Usual practice with predominantly opioid-based dosing	Lower morphine consumption during first 24 h	Improved early quality-of-recovery; similar complication rates
Cha 2023 [13]	Korea; university hospital	Short hysteroscopic procedures in adult women	Randomized controlled trial	Opioid-free anesthesia using lidocaine and other non-opioid agents	Standard opioid-containing balanced anesthesia	Lower or similar intraoperative opioid exposure; no routine intraoperative opioids in OFA arm	Better early recovery scores with comparable postoperative pain and PONV
Hu 2024 [14]	China; tertiary center	Laparoscopic gynecologic surgery (ASA I–II women)	Randomized controlled trial	Balanced OFA: bolus and infusion of lidocaine plus esketamine during general anesthesia	Balanced opioid anesthesia using sufentanil infusion	Similar 48-h opioid-equivalent consumption between groups	Time-weighted 48-h NRS pain scores similar; extubation time slightly longer in OFA group;

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							similar PONV and GI recovery
Wang 2025 [15]	China; provincial hospital	Laparoscopic major abdominal surgery in adults	Randomized double-blind trial	Intraoperative esketamine plus dexmedetomidine (opioid-sparing anesthesia)	Remifentanil-based balanced anesthesia	Markedly lower proportion of patients requiring rescue opioids in PACU; reduced intraoperative opioid exposure	Lower PACU pain scores; longer extubation time; increased dream-like experiences but no long-term sleep disturbance
Popa 2025 [16]	Romania; single center	Robotic-assisted radical prostatectomy	Retrospective comparative cohort	Continuous intravenous lidocaine infusion during surgery	No lidocaine infusion; standard anesthetic management	Lower early postoperative opioid use in lidocaine group	Lower early pain scores; similar complication profile
Morin 2021 [17]	USA; academic cancer center	Outpatient breast lumpectomy	Multicenter randomized trial	Multimodal opioid-sparing regimen (preoperative non-opioid medications, local infiltration, structured limited opioid prescription)	Conventional postoperative regimen with more liberal opioid prescribing	Substantial reduction in postdischarge opioid use	Superior postoperative pain control and high patient satisfaction
Gazendam 2022 [18]	Canada; multicenter	Knee or shoulder arthroscopy	Randomized clinical trial	Postoperative multimodal opioid-sparing protocol (patient education, scheduled non-opioid analgesics, restricted opioid prescription)	Usual care with standard opioid prescriptions	Significantly lower 7-day opioid consumption	Non-inferior pain scores and functional recovery
Beloeil 2021 [19]	France; multiple centers	Major or intermediate noncardiac surgery	Randomized controlled trial	Balanced OFA with dexmedetomidine replacing intraoperative opioids	Balanced anesthesia with remifentanil	No meaningful reduction in postoperative opioid requirements	Similar postoperative pain; higher rates of intraoperative bradycardia and hypotension with OFA

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DISCUSSION

This systematic review highlights that perioperative opioid-sparing strategies are clinically feasible across diverse adult surgical populations and can reduce opioid exposure without compromising analgesia. However, the evidence base is heterogeneous and nuanced.

First, ERAS and multimodal analgesia protocols show the most consistent benefit. Trials in laparoscopic gynecologic surgery and gynecologic oncology demonstrated that embedding scheduled non-opioid analgesics and local/regional techniques within structured pathways leads to better quality-of-recovery and reduced reliance on postoperative opioids [11,12]. Similarly, carefully designed postoperative multimodal protocols for lumpectomy and arthroscopy significantly lowered opioid prescribing and consumption while maintaining or improving pain outcomes [17,18]. These findings align with broader ERAS literature and guideline recommendations emphasizing multimodal, opioid-sparing regimens as the backbone of perioperative pain management [5–7].

Second, OFA and opioid-sparing anesthesia regimens using lidocaine, esketamine, and dexmedetomidine provide non-inferior analgesia to opioid-based anesthesia in the settings studied, but with a distinct side-effect profile. In gynecologic hysteroscopy and laparoscopy, lidocaine-based OFA improved early quality-of-recovery measures and maintained pain control while avoiding intraoperative opioids [13,14]. In major laparoscopic abdominal surgery, esketamine combined with dexmedetomidine reduced PACU pain and rescue opioid needs, at the price of longer extubation times and more transient dream-like experiences [15]. In contrast, dexmedetomidine-based OFA for broader noncardiac surgery did not meaningfully reduce postoperative opioid consumption and increased intraoperative bradycardia and hypotension [19].

Taken together, these trials suggest that OFA is not a single uniform strategy but a family of regimens whose risk–benefit balance depends on drug choice, dosing, and patient comorbidities. For relatively healthy patients undergoing short, minimally invasive surgery, OFA may offer modest opioid-sparing advantages with acceptable trade-offs. In higher-risk patients or longer operations, hemodynamic instability and delayed emergence warrant careful titration and close monitoring.

Third, intravenous lidocaine appears to be a useful adjunct in certain contexts but not a universal solution. The prostatectomy cohort by Popa et al. supports an association between lidocaine infusion and lower early opioid use and pain [16]. This resonates with earlier abdominal surgery trials and meta-analyses reporting improvements in pain and bowel recovery with perioperative lidocaine [8,9]. Yet newer randomized data in laparoscopic cholecystectomy have failed to demonstrate a significant opioid-sparing or analgesic effect of intraoperative lidocaine alone [6,8]. The totality of evidence suggests that lidocaine is most effective when integrated into a broader multimodal regimen, particularly for longer and more painful procedures.

From a practice perspective, these findings support a tiered approach to perioperative pain management. As a baseline, all adult surgical patients should receive multimodal non-opioid analgesia and, whenever feasible, regional or local anesthetic techniques

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[5,7]. Pharmacist–anesthesiologist collaboration is critical for designing standardized order sets, screening for drug interactions, and implementing opioid-sparing prescribing protocols, as demonstrated in lumpectomy and arthroscopy studies [17,18]. OFA or strongly opioid-reduced anesthesia can be considered in carefully selected patients and procedures, with explicit attention to monitoring hemodynamics and emergence.

This review has limitations. Most included trials were single-center with relatively small sample sizes and short follow-up. Surgical procedures, drug combinations, and outcome definitions varied widely, precluding pooled effect estimates. Our synthesis is restricted to published data and therefore susceptible to publication bias. Finally, many strategies were evaluated as bundled interventions, making it difficult to isolate the contribution of individual agents such as lidocaine or esketamine.

CONCLUSION

In adult surgical patients, perioperative opioid-sparing strategies built around multimodal analgesia, structured prescribing protocols, and selected OFA regimens reduce opioid exposure and maintain pain control and recovery. The strongest evidence supports ERAS-style multimodal pathways and postoperative multimodal prescribing, with OFA and intravenous lidocaine offering additional options in tailored settings. Integration of these approaches requires close collaboration between anesthesiologists, surgeons, and pharmacists, careful hemodynamic monitoring, and ongoing evaluation of patient-centered outcomes. Procedure-specific randomized trials are needed to refine optimal combinations and identify patients most likely to benefit.

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